So I think we can get started.

So hello everyone,

I am Antonio Mora, chief of neurology and today is my pleasure to introduce our wonderful speakers, both of whom from our very own Cancer Center. The first speaker is Doctor Merrick, Goshen, who is a professor of surgery within oncology and Deputy Chief Medical Officer for surgical services at Smilow Cancer Hospital. Doctor Goshen earned his medical
degree from Case Western Reserve University School of Medicine. And he also pursued an MBA at MIT. As well as a fellowship in breast surgical ecology at Northwestern Memorial Hospital, doctor Goshen is an innovator in tailoring surgery and therapy for women with early stage breast cancer. With funding support from the breast Cancer Research Foundation and National Institutes of Health. He is the principal investigator. Several phase two trials aiming to reduce the need for second surgeries or re excisions in women with breast cancer, one of which uses innovative image
NOTE Confidence: 0.960656157142857
00:01:08.710 --> 00:01:10.959 guided operating room capabilities to
NOTE Confidence: 0.960656157142857
00:01:10.959 --> 00:01:13.227 capture and remove all residual tumor
NOTE Confidence: 0.960656157142857
00:01:13.227 --> 00:01:15.610 utilizing MRI and mass spectrometry,
NOTE Confidence: 0.960656157142857
00:01:15.610 --> 00:01:18.418 which is used at Yale’s hybrid
NOTE Confidence: 0.960656157142857
00:01:18.418 --> 00:01:19.354 operating room.
NOTE Confidence: 0.960656157142857
00:01:19.360 --> 00:01:20.844 Prior to joining nail,
NOTE Confidence: 0.960656157142857
00:01:20.844 --> 00:01:23.632 doctor Gosh spent 17 years in Boston
NOTE Confidence: 0.960656157142857
00:01:23.632 --> 00:01:26.428 at the Dana Farber Cancer Institute,
NOTE Confidence: 0.960656157142857
00:01:26.430 --> 00:01:28.818 where he was the inaugural and
NOTE Confidence: 0.960656157142857
00:01:28.818 --> 00:01:31.320 incumbent Dr Abdul Mohsin and Susannah
NOTE Confidence: 0.960656157142857
00:01:31.320 --> 00:01:33.415 out to hearing the distinguished
NOTE Confidence: 0.960656157142857
00:01:33.415 --> 00:01:35.530 chair in Surg conology.
NOTE Confidence: 0.960656157142857
00:01:35.530 --> 00:01:37.510 He also served as the director
NOTE Confidence: 0.960656157142857
00:01:37.510 --> 00:01:39.287 of the Breast Surgical Quality
NOTE Confidence: 0.960656157142857
00:01:39.287 --> 00:01:41.257 Fellowship at the Dana Farber.
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And was an associate professor of surgery at Harvard Medical School. So without further ado. Doctor Goshen, the foresters. Thank you so much for that kind introduction and I'm excited to be here. I know we have one hour and we're going to try to go through two talks, so I will do my best to stay on time. And although you know in the introduction you talk about, reducing the need for surgery and minimizing surgery. One interest of mine early on when I finished or was in training and
fellowship was the role of surgery in stage four breast cancer. I'll kind of go through how the pendulum has really swung in actually two directions, so historically stage four breast cancer as a medium survival. This is really older data before more modern targeted therapies of less than two years, and really treatment has been chemotherapy endocrine therapy more recently targeted or molecular therapy. There has been some radiation to sites of metastatic disease, and you know, interestingly, when people started looking at
whether local regional therapy.

That number was actually fairly high, 35 to 60% of women were undergoing local regional therapy in the United States when really it should have been reserved for palliation at the time. And then there was a question of whether there is any survival benefit in doing this. This is United States data, certainly most women fortunately present with localized or regional disease on stage four, breast cancer in the United States and this is very different when you look outside of EU.
Is only about four to 6% of the population. You know, when I was taking my surgery boards, I would have really failed the room if I had suggested that treatment. It was generally accepted that local therapy did not prolong survival and there was some earlier data suggesting that there may be some stimulation of metastatic growth. However, we know that there are diseases in the stage for setting where...
Resection of the primary and or metastatic tumor site could improve survival or does improve survival. For example, in colorectal disease, potentially with metastatic disease to the liver or in renal cell carcinoma, there are good reasons to leave the primary alone, and there may be reasons to resect the primary tumor. For example, it is very easy to measure disease as opposed to getting scans when you leave the primary tumor alone. There is morbidity associated with resection in even in
a breast cancer surgery,
certainly with mastectomy and more complex closures and reconstructions.
With sometimes are required,
there was some early data suggesting sources of cytokines or angiogenesis.
Inhibitors which restrain growth could be released with metastasis.
And really you know a question on whether there is a survival benefit in this setting or not.
We did use surgery in the palliation of symptoms.
Certainly fear of uncontrolled local disease.
There was suggestion of reducing
the shedding of metastatic cells

and you know could it.

Potentially if you respect the

site provide more effective.

Systemic therapy. Again,

there was data and ovarian cancer,

renal cell cancer and colorectal

setting about surgical debulking

there was data and ovarian cancer,

renal cell cancer and colorectal

cancer setting about surgical debulking

and surgical removal of disease,

and again, this was work that I started

and again, this was work that I started

about 2/2 and a half decades ago.

So I say challenging the

standard so Seema Khan,

who was one of my attendings

who was one of my attendings

presented in 2002 in a in a
not a major surgical society or.

On Koleji society was called Central Surgical Society, looking at the National Cancer Database for women with stage four disease. You know about 4% of patients in EU? S presented with stage four breast cancer. This is again in the 1990s median age or mean age of 62, which is really in line with our average age of breast cancer in the United States and you know, she looked at 16,000 women over a year cohort period of time.
And first you know the thing that was surprising to us and to her and to others was that almost 60% of women underwent local therapy. About 60% underwent mastectomy, about 40% underwent breast conservation and you know, you can see what the negative margin rates were at the time. Not surprisingly, those that either did not undergo surgery or underwent mastectomy had larger burden of disease in terms of tumor size and you know she was the first to really present that. You know, if you didn’t do surgery,
Sir survival was twenty months. If he did, breast conservation was 27 months, and if you did a mastectomy, 32 months and again suggesting that potentially there is a survival benefit in the surgical cohort. You know those that had bone or soft tissue disease tended to do better. Certainly if you had fewer sites of metastatic disease, your outcomes were better giving chemo and or endocrine or combination of therapy ended up being of benefit and this is something that seem Doctor.
Khan has spent a lot of time on as well and we’ll get to the modern era is on margin positive ITI and whether that would influence outcome. So independent predictors of survival. Or the use of systemic therapy? Certainly the location of metastatic disease. The burden of disease and the type of surgical resection that was done. And really for four or five years, this presented as central Surgical and published in surgery really didn’t get much attention until 2006 to 2009. So guilty barbiere at MD Anderson decided to look at their stage four breast cancers. The mean Age was a little bit...
00:07:49.214 --> 00:07:50.410 younger in their cohort.
00:07:50.410 --> 00:07:51.622 They were, you know,
00:07:51.622 --> 00:07:52.834 somewhat surprised at about.
00:07:52.840 --> 00:07:55.540 40% of their patients underwent surgery,
00:07:55.540 --> 00:07:57.424 have had breast conservation,
00:07:57.424 --> 00:08:00.108 have had mastectomies, and you know what?
00:08:00.108 --> 00:08:01.693 We would probably expect is
00:08:01.693 --> 00:08:03.689 that the patients were younger,
00:08:03.690 --> 00:08:05.538 less likely to have nodal involvement,
00:08:05.540 --> 00:08:09.040 fewer sites of metastatic disease
00:08:09.040 --> 00:08:11.770 in their cohort.
00:08:11.770 --> 00:08:14.044 And when they looked at their
00:08:14.044 --> 00:08:15.560 follow-up for 32 months,
00:08:15.560 --> 00:08:18.158 there was a trend towards better
00:08:18.158 --> 00:08:21.049 overall survival in the surgery group.
And there was a benefit in terms of metastatic progression free survival.

Then in the GPIO and there was an accompanying editorial by Monica Morrow in 2006, which I think was something about this.

There were 300 patients with metastatic disease, with the Geneva Tumor Cancer Registry on the use of local therapy and again little over half the patients didn’t have surgery, the patients didn’t have surgery, but 127 patients did. Most were mastectomies.

They describe breast conservation as tumor,
ectomy’s negative margins and about half and.

Nodal surgery in about 1/4 of patients, and this is just kind of a the diagram breaking down in a schematic or graph form those that ended up undergoing surgery versus not were younger. Lower burden of disease in terms of the size of tumor and nodal disease, more likely again to have a single site of metastatic disease or less likely to have visceral metastasis more likely to undergo radiation. And then you can see what the use of chemotherapy and endocrine therapy was the same.
And again, this is, you know, leads the thought of potential selection bias. If you were able to resect the tumor and get clear margins, there was a survival benefit as opposed to those that did not undergo surgery or that have positive margins. And then Fields Group looked at the Washington University data over almost a decade, again about half of patients underwent surgery. This is a much longer median. Follow up of 142 months and again there was a survival benefit for surgery versus not.
And there is a theme in. In all this there was a 250 institution review over almost a two decade period of time. This was published in the Annals of Surgery, but Blanchard again. About 60% had surgery in the stage four setting and survival was 27 months versus 17 months. So, as I alluded to, there is selection bias, potentially younger woman with smaller tumors, less knodel involvement, fewer sites of metastatic disease, and this is kind of the differences.
between the studies from Seema Khan and Repeate and guilty Barbie era.

And from the wash you and the other data again.

Younger women with smaller tumors, less nodal involvement, and fewer sites of metastatic disease had surgery. And certainly there have been a lot of attempts statistically and in terms of matching to be able to look at whether that difference continued or not. So this was a work that a previous resident of mine decided.
Mass general data and you know again, very similar to what everyone else did. You know we had a pretty small cohort of patients a little bit more modern era treatment. About 40% of our patients had surgery in the stage for setting, and I found that actually pretty surprising to see it was that high. But we were actually the first group to look at whether the timing of diagnosis or surgery made a difference or not.
About 25 out of those 61 patients had surgery before stage 4 diagnosis. I'll go over why this is probably potentially important and after stage 4 diagnosis this is kind of hard to read, but again, those in the surgery group in terms of sites of metastatic disease versus those that did not undergo surgery. And again, if you underwent surgery, you're more likely to get radiation therapy. So our median survival from the surgery group was 3.52 years
and in the nose surgery group, just like everyone else. 2.36 years.

However, the timing of diagnosis of stage four disease before after surgery, if it was done afterwards, that survival was four years versus before a 2.4 years.

So you know, we you know our group looked into this and could this be an example of the Will Rogers phenomenon? Honestly two decades ago, if you ask me. But that was I didn’t know the example that that Will Rogers uses,
that when the Okies left the state of Oklahoma for the state of California, they raised the average IQ of both states.

So I'll let you guys ponder that as we move on.

So this was the first paper to suggest that maybe it's there is no survival benefit in surgery and it's really the timing of surgery in relationship to the diagnosis of stage four disease. This shows the difference between surgery and not.

But when we looked at the timing, that difference went away.

So then I asked another colleague of mine that we recruited Laura Dominici.
We looked at the NCCN database of stage four breast cancer. Again a little bit more modern, era 1000 patients, a much larger group. And then we did a match analysis of 236 non surgery patients to 54 patients with that had surgery followed by drug therapy and again that survival benefit that was being seen in the surgery group versus non surgery actually disappeared. Survival is 3 1/2 versus 3.4 years. We matched her age, number of sites of metastatic disease.
ER, her two sites of metastatic disease, and again I and my there was a very few of us who actually came out strongly against surgery in the stage for setting. And all I’ve been talking about is retrospective data, and obviously, you know with this you know anything in the world of oncology. Want prospective data? So the world of prospective data came from really a couple of brilliant folks. One is Raj Way bad way. Who’s runs the breast service at Tata Memorial in Mumbai, India? They ran the first randomized trial of
surgical removal of primary tumor with lymph node.
Surgery in the metastatic setting there.
Endpoints where primary endpoint was looking at removal of the primary tumor and actually nodes on overall survival and progression survival,
and we're going to go over a couple of the randomized trials that have been done.
That again, the Tata Group and Roger Broadway,
there's a first looked at 350 patients.
They were randomizing early to surgery,
will go over to next to the Turkish Medical Federation,
which drug therapy first, followed by surgery and finally. We’re going to get to the E kog trial in the United States that I helped with with semakan drug therapy first followed by surgery. So the group in India looked at randomizing woman with stage four breast cancer to local regional therapy to none. They underwent local regional therapy and then if indicated anti estrogen and then if indicated anti estrogen therapy in the no local regional therapy, they were followed by when indicated anti estrogen therapy. Note it’s important to know that there were in the time of her two positive.
Breast cancer.

None of the patients receive anti her two therapy,
so that’s a criticism of the trial.

But again this was done.

You know, deck started decades ago where you know anti her two therapy was just.

You know getting approved in the United States and certainly in resource limited countries.

It’s not something that was, you know,
automatically approved and paid for.

This is the matching.
They matched the you know their patient population very well and looking at overall survival. There was actually no difference between the two groups. They tried breaking it down by menopausal status numbers, the sites of metastatic disease, a number of sites of metastatic disease, like with that were done like the previous trials, and you can see really no difference. Interestingly, distant progression free survival was actually lower in the local therapy group as opposed
00:16:42.193 --> 00:16:44.060 to those that did not.

00:16:44.060 --> 00:16:44.596 And again,

00:16:44.596 --> 00:16:47.070 this is different than what will get to this.

00:16:47.070 --> 00:16:49.604 The Turkish and the US trial they

00:16:49.604 --> 00:16:52.195 were diagnosed with stage four breast

00:16:52.195 --> 00:16:54.107 cancer underwent surgery first,

00:16:54.110 --> 00:16:57.780 then followed by Agilent therapy.

00:16:57.780 --> 00:16:58.902 So Attila Saran,

00:16:58.902 --> 00:17:01.146 who’s add Pittsburgh but helped run

00:17:01.146 --> 00:17:03.696 on behalf of the Turkish Federation

00:17:03.696 --> 00:17:05.801 of Society of Breast Disease.

00:17:05.810 --> 00:17:07.830 On randomized trial of evaluating

00:17:07.830 --> 00:17:09.446 resection of primary breast

00:17:09.446 --> 00:17:11.549 tumor with women with stage four,

00:17:11.550 --> 00:17:12.546 breast cancer,
and these were actually simultaneous same day presentations at the San Antonio Breast Conference.

Their early presentation in 2013 is actually ends up being different than what they ended up publishing.

Their primary goal is assessment. Early surgical treatment of the primary tumor and stage four disease effects overall survival.

They also looked at progression free survival, quality, life, and morbidity different than the Tata group stage four breast cancer.

That presentation was randomized
NOTE Confidence: 0.795473466666667
00:17:43.828 --> 00:17:45.574 as systemic therapy.
NOTE Confidence: 0.795473466666667
00:17:45.580 --> 00:17:48.742 Then local therapy for local progression
NOTE Confidence: 0.795473466666667
00:17:48.742 --> 00:17:50.850 versus initial local therapy.
NOTE Confidence: 0.795473466666667
00:17:50.850 --> 00:17:51.510 Uh,
NOTE Confidence: 0.795473466666667
00:17:51.510 --> 00:17:54.150 then a systemic therapy
NOTE Confidence: 0.914044793333333
00:17:54.150 --> 00:17:56.676 and then looking at overall survival
NOTE Confidence: 0.914044793333333
00:17:56.680 --> 00:17:58.708 chemotherapy was given to all patients
NOTE Confidence: 0.914044793333333
00:17:58.708 --> 00:18:00.830 either immediately or after randomization.
NOTE Confidence: 0.914044793333333
00:18:00.830 --> 00:18:03.745 All hormone receptor positive patients
NOTE Confidence: 0.914044793333333
00:18:03.745 --> 00:18:06.077 received anti estrogen therapy
NOTE Confidence: 0.914044793333333
00:18:06.077 --> 00:18:08.210 different than the Tata Group.
NOTE Confidence: 0.914044793333333
00:18:08.210 --> 00:18:11.098 The her two positive,
NOTE Confidence: 0.914044793333333
00:18:11.098 --> 00:18:15.160 overexpressed received trastuzumab therapy.
NOTE Confidence: 0.914044793333333
00:18:15.160 --> 00:18:17.720 Most patients if they underwent
NOTE Confidence: 0.914044793333333
00:18:17.720 --> 00:18:19.802 local therapy, underwent mastectomy.
NOTE Confidence: 0.914044793333333
Radiation was given to some patients with sites of metastatic disease. And early on, looking at the difference between surgery and those that just received systemic therapy, there was no statistical difference. Overall, when they broke it down by numbers of sites of metastatic disease, and if there was just a single site versus multiple sites in the Solitaire or oligo metastatic setting, there was a suggestion, potentially of survival benefit and this is what they ended up presenting at San Antonio in 2013. This wasn’t actually published.
until five or six years later, and we'll go over that. While the Tata group, pretty rapidly published in Lancet on Koleji, so they had suggested the Atilius Group surrounds group in the Turkish Federation that there was no statistically difference or difference in overall survival in early follow-up. Potentially those with limited numbers of sites of metastatic disease, and I know that’s of interest of people here at Yale and. Around the country of maybe not.
Group behaves differently than others with metastatic breast cancer. These are the randomized trials that were or were underway, and their primary endpoints are either survival or time to progression. So we’ve seen what happened in India, what happened in Turkey? We’re going to talk about the COG in the next one that will actually report out will be the Japanese jade COG 10710 seventeen trial. So this kind of circles back to you know.
NOTE Confidence: 0.914044793333333
00:20:08.640 --> 00:20:10.548 fellow of SEMA Konzum and watched
NOTE Confidence: 0.914044793333333
00:20:10.548 --> 00:20:13.346 the work that she did in the central
NOTE Confidence: 0.914044793333333
00:20:13.346 --> 00:20:15.206 surgical challenging the standards
NOTE Confidence: 0.914044793333333
00:20:15.206 --> 00:20:17.416 of and providing local therapy.
NOTE Confidence: 0.914044793333333
00:20:17.420 --> 00:20:19.030 A suggestion that local therapy
NOTE Confidence: 0.914044793333333
00:20:19.030 --> 00:20:20.318 would be of survival.
NOTE Confidence: 0.914044793333333
00:20:20.320 --> 00:20:22.792 But then watching the retrospective data
NOTE Confidence: 0.914044793333333
00:20:22.792 --> 00:20:25.448 come out, then the prospective data,
NOTE Confidence: 0.914044793333333
00:20:25.448 --> 00:20:27.276 and then the usdata.
NOTE Confidence: 0.914044793333333
00:20:27.280 --> 00:20:30.196 So I was the KVB rap,
NOTE Confidence: 0.914044793333333
00:20:30.200 --> 00:20:32.168 which is now part of alliance.
NOTE Confidence: 0.914044793333333
00:20:32.170 --> 00:20:35.057 For E card 22108,
NOTE Confidence: 0.914044793333333
00:20:35.057 --> 00:20:37.993 this was presented at 2020 in San Antonio.
NOTE Confidence: 0.914044793333333
00:20:38.000 --> 00:20:39.904 The publication honestly will be coming out,
NOTE Confidence: 0.914044793333333
00:20:39.910 --> 00:20:41.170 hopefully in the next month,
NOTE Confidence: 0.914044793333333
but until then you know it isn’t published presented,
but it will be published very soon,
so we know that from the Tata Group that there was no survival with early local regional recurrence and then again I said that Alisa ran in 2018, presented that there was no difference also in.
Come in local regional therapy in terms of survival but with longer follow-up. Their group actually suggested that there was an overall survival benefit. There is a lot of issues with this paper and publication and I, II and others wrote an editorial that...
00:21:20.306 --> 00:21:23.239 was simultaneously published with this,

00:21:23.240 --> 00:21:25.416 but and we can discuss this in the

00:21:25.416 --> 00:21:27.937 in in the question answer session.

00:21:29.350 --> 00:21:30.700 there was a survival benefit,

00:21:30.700 --> 00:21:34.131 so there’s conflicting data equals 2108.

00:21:37.017 --> 00:21:39.478 Started in 2011 with its last

00:21:39.478 --> 00:21:41.808 2013 because of slow accrual,

00:21:45.144 --> 00:21:47.046 goal and the and the randomization,

00:21:47.050 --> 00:21:48.666 but basically in EU,

00:21:50.690 --> 00:21:52.722 four denovo breast cancer.

00:21:52.722 --> 00:21:54.754 Optimal systemic therapy including
obviously anti her two therapy
if there was no progression of
distant disease followed by 4 to 8
months of optimal systemic therapy.
They either continued down the route of systemic.
Therapy versus local early local regional therapy.
And again, this is something that Doctor Khan focuses a lot on.
Is the complete resection with free margins.
Overall survival, just like I showed you with all the randomized trials.
This is the breakdown in terms of the patient cohorts.
For those that were registered,
not randomized and randomized,
again anti her two therapy was given
when they were her two positive,
certainly anti estrogen therapy
when he R and or PR positive.
the dropout,
which is really not surprising
as those that had more,
as those that had more,
you know,
advanced local disease was ended up
being higher in the initial systemic
therapy as opposed to or the group
that was stable or responding.
Uhm, median age a little bit
younger than CMAS earlier study.
Looking at the NCDB database by about six or seven years. When you looked at those that were randomized, early local therapy 109 received surgery, 87 achieved surgical free margins and local regional therapy was at 74 of those patients. The reasons why no surgery, some ended up refusing some progress, was at 74 of those patients. The reasons why no surgery, was at 74 of those patients. Finally, we were able in the US to go back to what SEMA started in saying that there was a survival benefit.
Now we come to the point of having randomized data from the US and suggested that there is no overall survival benefit for women with stage four breast cancer. This is with a median follow-up of 53 months progression free survival. Similarly, no difference, something that you know we saw a suggestion of in the Tata Group. Is that potentially and there are certain subtypes of breast cancer that actually operating may actually be a more of a detriment to not operating, so it’s not necessarily been equivalent,
but potentially worse, and maybe that's seen in the triple negative breast cancer. One thing again that you know will be focused on a little bit in the paper is that there is some benefit in terms of local regional progression free survival. That's how useful that is of an endpoint is worth discussing. So kind of coming to conclusion is that early local therapy does not improve survival in patients with denovo metastatic breast cancer that there was actually a higher local regional progression when
local regional therapy was used, the primary site. Again, there is a suggestion of progression free, you know, some local regional therapy response in the stage. Four breast cancer setting, and again the JAYCOB trial. Is still pending and at least in my, in my conclusions were that like in in almost two and a half decades, we went. The pendulum was swung from, you know, surgery to surgery to maybe surgery or no surgery to hopefully now no surgery. You know, outside of palliation, although there is interest in,
00:25:33.570 --> 00:25:35.598 you know in the those with
NOTE Confidence: 0.869006688888889
00:25:35.598 --> 00:25:36.950 limited numbers of metastatic
NOTE Confidence: 0.869006688888889
00:25:37.015 --> 00:25:39.010 site or oligo metastatic disease.
NOTE Confidence: 0.869006688888889
00:25:39.010 --> 00:25:41.341 I don’t think the randomized data from
NOTE Confidence: 0.869006688888889
00:25:41.341 --> 00:25:43.852 Tata or the Turkish group supports this
NOTE Confidence: 0.869006688888889
00:25:43.852 --> 00:25:46.559 and the card data that was presented
NOTE Confidence: 0.869006688888889
00:25:46.559 --> 00:25:48.949 ASCO doesn’t support this either.
NOTE Confidence: 0.869006688888889
00:25:48.950 --> 00:25:50.235 Over the publication is still
NOTE Confidence: 0.869006688888889
00:25:50.235 --> 00:25:53.423 pending and once that’s out then you
NOTE Confidence: 0.869006688888889
00:25:53.430 --> 00:25:54.195 guys can make your own judgment.
NOTE Confidence: 0.869006688888889
00:25:54.195 --> 00:25:56.390 I’d like to thank you for the provision
NOTE Confidence: 0.869006688888889
00:25:56.390 --> 00:25:59.134 of the podium and look forward to talking.
NOTE Confidence: 0.902277358
00:26:01.410 --> 00:26:02.930 Thank you very much, Mary.
NOTE Confidence: 0.902277358
00:26:02.930 --> 00:26:06.745 Uh, we have a few questions here,
NOTE Confidence: 0.902277358
00:26:06.750 --> 00:26:08.808 so for everyone, if you have questions,
please post them in the chat.

So let me read some of the questions here.

A question from Doctor Caring, Addison.

She points out that there is a national trend toward doing more local therapy for metastatic disease, which is calling a metastasis sectomy I guess.

So, does this data provide some warning for adoption of this trend outside of research studies?

Honestly, I think it does,

at least in breast cancer, that we really, we may have antidotes of when it works,
and you know when we looked at our data institutionally. Or many others did as well. You know you have to really be careful for selection bias is that you know are unintended, but certainly part of this and I am really outside of the clinical trial or research. Sending as Doctor Edelson suggested. Really not a big fan of even certainly not local therapy, but even metastatic disease in that setting as well. And I know this is different than some other solid tumor types, but in the world of breast cancer,
there was retrospective data.

There was conflict on that,

then we waited for prospective data.

There was conflict on that on.

It's not US data or European data.

Finally we get the us data and we're,

on the border of getting the

publication out on that as well.

And then I thought.

Another question from Doctor Peters.

So did the EKACH trial allow

any number of metastasis?

It seems like the general

thought was that this may be
00:27:54.019 --> 00:27:56.090 helpful in low volume disease, so
NOTE Confidence: 0.902180804444445
00:27:56.570 --> 00:27:59.085 it did allow for multiple
NOTE Confidence: 0.902180804444445
00:27:59.085 --> 00:28:01.097 sites of metastatic disease.
NOTE Confidence: 0.902180804444445
00:28:01.100 --> 00:28:03.844 I think the only real from what I
NOTE Confidence: 0.902180804444445
00:28:03.844 --> 00:28:06.247 remember and I actually enrolled a
NOTE Confidence: 0.902180804444445
00:28:06.247 --> 00:28:08.707 couple of patients to this trial.
NOTE Confidence: 0.902180804444445
00:28:08.710 --> 00:28:11.638 Patients that couldn’t wear those with
NOTE Confidence: 0.902180804444445
00:28:11.638 --> 00:28:14.041 like leptomeningeal disease that were
NOTE Confidence: 0.902180804444445
00:28:14.041 --> 00:28:16.687 excluded and maybe a handful of others.
NOTE Confidence: 0.902180804444445
00:28:16.690 --> 00:28:18.538 And again, I think this points to the,
NOTE Confidence: 0.902180804444445
00:28:18.540 --> 00:28:21.812 you know is low volume or oligo metastatic
NOTE Confidence: 0.902180804444445
00:28:21.812 --> 00:28:23.884 disease different than those with
NOTE Confidence: 0.902180804444445
00:28:23.884 --> 00:28:26.248 higher volumes or burden of disease.
NOTE Confidence: 0.902180804444445
00:28:26.250 --> 00:28:28.450 And again a lot of people try to
NOTE Confidence: 0.902180804444445
00:28:28.450 --> 00:28:29.702 address those selection biases
NOTE Confidence: 0.902180804444445
00:28:29.702 --> 00:28:31.628 of like you know you know,
00:28:31.630 --> 00:28:33.979 is visceral Mets or lung Mets going to be
different than soft tissue or bone Mets?

00:28:33.979 --> 00:28:35.829 I again outside of the research setting I am.

00:28:35.830 --> 00:28:39.277 Really cautious of this.

00:28:39.280 --> 00:28:40.856 I’m glad that in my two decades

00:28:40.856 --> 00:28:43.685 hopefully away from from

00:28:43.685 --> 00:28:45.600 study cancer presented stage four,

00:28:45.600 --> 00:28:47.392 since in this modern era discovery

00:28:47.392 --> 00:28:49.184 the patients as having received

00:28:49.860 --> 00:28:54.066 Thank you and Doctor David Rim.

00:28:54.070 --> 00:28:56.646 It’s asking is it even possible to

00:28:56.646 --> 00:28:58.529 study cancer presented stage four,

00:28:58.530 --> 00:29:00.570 in this modern era discovery

00:29:00.570 --> 00:29:03.170 of the the patients as having received

00:29:03.170 --> 00:29:05.394 below is the standard of care.

00:29:05.394 --> 00:29:08.556
Any comment meaning

NOTE Confidence: 0.731204395714286

maybe. I don’t understand the question 100,

NOTE Confidence: 0.731204395714286

so the. Bing diagnosis stage four is

NOTE Confidence: 0.731204395714286

below the standard of care. Well, I mean,

NOTE Confidence: 0.731204395714286

we’re obviously in the United States I.

NOTE Confidence: 0.731204395714286

I would say that you know,

NOTE Confidence: 0.731204395714286

because we have such a well screened

NOTE Confidence: 0.731204395714286

population that that number is

NOTE Confidence: 0.731204395714286

relatively low, but it still is about,

NOTE Confidence: 0.731204395714286

you know again, 4 to 6% depending

NOTE Confidence: 0.731204395714286

on whether you look at Sierra,

NOTE Confidence: 0.731204395714286

NCDB or whatever data set.

NOTE Confidence: 0.731204395714286

But I really like thinking of things

NOTE Confidence: 0.731204395714286

well outside of EU S borders and

NOTE Confidence: 0.731204395714286

certainly in Sub Saharan Africa or

NOTE Confidence: 0.731204395714286

Asia and many other parts of the world.
You know there are a lot of women who are presenting with stage four breast cancer and are a lot more patients presenting with stage four breast cancer. And you know, should different options be considered in that setting? You know it was nice that at least and you know in the work on stage four, breast cancer and local regional therapy that we had counterparts in India in Turkey, in Japan and others that were looking at this. And it wasn’t just run by EU and Europeans in terms of.
OK, and that well, how about the? Role of the Disney Cetera Cimnetti and the different phenotypes and molecular phenotypes and treatment available and how what does that do to despair? Diamond?

In other words, I was wondering if you know if you have a great treatment, is it good to have surgery or not? Or maybe if you guys have a great treatment it doesn’t matter? Yeah, so that’s such a great question and you get those you know. You know, there’s this young patient, you know she’s got like. A couple of sites that maybe liver disease. You get anti her two therapy.
Everything disappears.

You know maybe she has a little bit of a lump or mass in the breast but you get the story. You know she has young kids and a family and you know, let's just, you know it's easy. Just take it out, you know I, I really think that's you know the you know she's going to likely do well anyways, whether I do the lumpectomy or mastectomy, whether I do the lumpectomy or mastectomy, remove the lymph nodes, yes or no. And again, there's this, you know, making.
00:31:29.518 --> 00:31:31.312 doing a benefit in terms of
NOTE Confidence: 0.871062266666667
00:31:31.312 --> 00:31:32.750 keeping them alive longer.
NOTE Confidence: 0.871062266666667
00:31:32.750 --> 00:31:34.090 And certainly you know,
NOTE Confidence: 0.871062266666667
00:31:34.090 --> 00:31:35.765 breast surgery may not be,
NOTE Confidence: 0.871062266666667
00:31:35.770 --> 00:31:37.226 you know, as morbid as you know,
NOTE Confidence: 0.871062266666667
00:31:37.230 --> 00:31:39.090 very large thoracic and
NOTE Confidence: 0.871062266666667
00:31:39.090 --> 00:31:40.485 intra abdominal surgeries,
NOTE Confidence: 0.871062266666667
00:31:40.490 --> 00:31:42.008 but you know in this society
NOTE Confidence: 0.871062266666667
00:31:42.008 --> 00:31:44.382 we put a lot of emphasis on on
NOTE Confidence: 0.871062266666667
00:31:44.382 --> 00:31:45.997 breasts in the breast cancer.
NOTE Confidence: 0.871062266666667
00:31:46.000 --> 00:31:47.827 And, you know, removal of the breast.
NOTE Confidence: 0.871062266666667
00:31:47.830 --> 00:31:49.503 And then the question becomes in the
NOTE Confidence: 0.871062266666667
00:31:49.503 --> 00:31:51.290 stage for setting if you do a mastectomy.
NOTE Confidence: 0.871062266666667
00:31:51.290 --> 00:31:52.318 How about doing reconstruction
NOTE Confidence: 0.871062266666667
00:31:52.318 --> 00:31:54.210 yes or no and kind of where?
NOTE Confidence: 0.871062266666667
00:31:54.210 --> 00:31:55.002 Where does that end?
Or why don’t you move the opposite?
The rest as well, and you know,
I’ve had those discussions
time and time again,
and you know,
I would hope we’re making some of these
decisions based on data and the science,
and not what like you know,
feels good or or maybe the right
ting to say at that moment.
So I do think heterogeneity does
make a difference,
but I think it’s probably
going to do well regardless of
what I do with my scalp.
Thank you and Doctor Lustberg is pointing out that they are very aggressive tumors that present biological stage for particularly in younger women. So it’s not necessarily substandard care. That’s great, that’s a great comment. Yes, wonderful thank you so much. So I mean there’s interest of time. We’re going to move on to the next talk for the next talk. We have our very own doctor Anita Hutner Dr Hutner is an associate professor of pathology, who specialize in identifying diseases and cancers in the brain.
She has received her medical degree from the University of Ehrlinger Nurburg in Germany. And a completely fellowship at Harvard Medical School at the Brig and her residency here at the Ionia Haven Hospital. So in addition to her specialty in neuropathology, Dr Hutton has stated molecular diagnostic pathology, so in her research, Dr Hutner uses stem cells to try to recreate the brain disorders founding diseases like epilepsy and Alzheimer’s disease and hopes to find better treatments for brain tumors.
So today, Doctor Hutner will talk to us about a very important update in the WHL classification of brain tumors that will pretty much append the way we are calling these diseases and classifying disease and enrolling the patients in clinical trials. So we’re very fortunate to have her here to educate us on that hardener. Thank you, Antonio. Thank you for this kind introduction. Thank you, Antonio. It’s a it’s a real pleasure to be here and have the opportunity to share with you some insights into the upcoming 2021 W
2 classification of CNS tumors.

It’s now the 5th and I’ll talk more about that.

Uhm, in general, you might wonder, well, why shall we even deal with brain tumors? Yeah, they’re relatively rare compared to let’s say breast, lung and other entities.

Yes, well they are relatively rare compared to let’s say breast,

and when you look at the numbers in a bit more detail, you realize that. a bit more detail, you realize that.

Yes, well they are relatively rare compared to let’s say breast,

lung and other entities.

UM, the outcome is rather devastating,

so roughly estimated.

We will find about 24,000
patients with malignant glioma.
The 85 year survival rate is rather low, it’s 36% anti survivability.
With a clear blastoma is really low, so it’s it begs for innovation.
The costs of treating patients with brain tumors or tremendous.
When you look at the survival rates, the five years or survival rates.
Right now, nine out of 10 surviving.
Patients with breast cancer.

Similarly, nine out of 10 survive when you look at patients with brain cancer.

Now you’re down to two per ten surviving.

And then with glioblastoma, you’re down to one pretend so you can see even in 2021 the field is begging for innovation and new approaches to handle this absolutely devastating disease.

And so we this year there is a new W classification of brain tumors coming out, which is dramatically significantly different from before,
and so I felt. Since we have a very large and active neuro clinical neuroscience community here, it would be good to discuss a few of those new changes because they will affect how we all practice and interact, and so for today I thought I'll show you a few. Some of the general changes and recommendations, then go into tumor specific changes and at the end I'd like to conclude with one of our own cases and methadone analysis. For brain tumors, which is now also recommended.
And so.

Why is it overall so important to accurately classify tumor samples well?

The multiple aspects personalized, individualized patient care.

It contributes to prognosis.

AIDS in therapeutic guidance.

It’s click current critical for clinical trial enrollment and interpretation of clinical trials data.

The enrollment in experimental studies and here also data and analysis.

Interpretation the evaluation of population based disease trends.
Are aided by accurate classification and also you know affected is allocation of resources by governments and health insurers to support health care and so.

UW now publishes periodic revisions of tumor classifications, and these have therefore very diverse and important effects on many aspects actually of individual and population health, however, and David Luiz emphasize this at the last meeting.

All classifications are somewhat imperfect. They are imperfect representations, and represent of.
Come off in this state and the representative state of understanding at a particular time. And the interpretations. Of a limited number of experts and so. You see their limitations, their works in progress, yet they’re still extremely needed. Just to shed light on the 5th. So the when you look at how the classification emerged, the first one was published in 17-9. The first edition then evolved over the years that the time gaps are at times quite considerable from.
The period from 2007 to 2016 covered an almost 10-year time span. In addition, the 2016 edition was a more or less a revised edition of the 4th edition, which received the 2007 version, and here for the first time. Definitions were now based on the combination of morphologic and genetic characteristics. This was a huge shift in the field. And I feel that was celebrated by one. By some there’s a paper in Kansas, L. Which caused the fall of the optical wall freedom from the tyranny of the microscope and the molecular...
changes stand could demonstrate this improves humor risk stratification.

Uhm, the from 2016 to now to 2021. Again, you know time passed and but now with the advents in molecular technology. Information is gathered as lightspeed and so in order to bridge these gaps between WTO classifications, the Consortium was formed. They see impact now consortium, which is a consortium to inform molecular and practical approaches to CNS tumor taxonomy. The goal here is to.
Publish new developments in molecular diagnostics and inform the clinical world so this could be implemented along the way and there wouldn’t be a long gap until new changes were implemented. If you wonder what the now stands for, it means not officially who, because this consortium was established in 2016 and basically the authors of all these impact papers are also authors and editors of the new double classification. So it’s a very homogeneous group that works on this the expert editorial group.
is composed of international group. Unfortunately the Blue Book is not yet published there. I was told by David Lewis there are production issues related to the pandemic. However, in the meantime I review paper, came out in neuro Oncology which is available and can be. Teen and so I quickly would like to go through a few general changes before I go into too much specific changes and. The significant change is really related to the report structure, and here we have now a so-called integrated
histo molecular classification system. It's already in place at Yale, and this is what one of our reports looks like and so you have four layers there. Two is the histopathological diagnosis, which would be here. For example, glioblastoma layers 3 then defines the grade would be here for and then layer 4 forms the molecular information, which would be a list of molecular data here and in order to make sense out of this different components. A layer one is added which forms the integrated diagnosis and this is the combined tissue based

00:42:31.220 --> 00:42:33.135 And so this is continuously

00:42:33.135 --> 00:42:35.050 expanding with the addition of

00:42:35.121 --> 00:42:37.266 additional newer markers and the

00:42:37.266 --> 00:42:39.411 integrated diagnosis is really a

00:42:39.484 --> 00:42:42.230 collaborative, team based effort where we,

00:42:42.230 --> 00:42:45.235 as neuropathologists from surface as

00:42:45.235 --> 00:42:49.200 central role for the integration component.

00:42:49.200 --> 00:42:51.370 We closely work with neurosurgery,

00:42:51.370 --> 00:42:53.872 neurology, neuro oncology,

00:42:53.872 --> 00:42:57.208 genetics, and new radiology,

00:42:57.210 --> 00:42:59.814 and then integrate from

00:42:59.814 --> 00:43:01.767 this integrated diagnosis.

00:43:01.770 --> 00:43:05.032 Which then is used by neurooncology in

00:43:05.032 --> 00:43:07.559 radiation oncology foot for treatment.
So it’s a very intimately integrated process. A few words to just a few nomenclature issues, so when a diagnosis cannot be made and the term Nos is used, meaning not not otherwise specified, this just means that molecular information is not available and there could be multiple reasons it’s either not available or not. The test was not performed or simply was not successful, whereas the NEC term. Not elsewhere classified, just indicates that the test was successfully performed. However, the test results simply do not fit into a known category,
so further on.

Now, in this new version, we're now distinguishing our grading from other classifications by adding the Hoos TNS grade, because this is meant to emphasize that the way the neuro grades tumors is different from how it's done and you and your breast, for example.

Further from the now we research, this might sound trivial using Arabic numerals instead of Roman numerals. And lastly, now is also grading within tumor types,
and this is a bit more substantial.
This is meant to provide more flexibility in using grade relative to tumor type.
It should emphasize biological similarities within tumor types rather than just approximate clinical behavior,
and it should. It conforms with who grading in non CNS tumor types.
For example, we used to say astrocytoma IDH Mutant who’s seen as great.
Two or three or form when you have before, you could say, for example,
I had a trim anaplastic astrocytoma who creates three.
This is now obsolete.

Now it’s replaced and the nomenclature now would indicate that you have to say astrocytoma, IDH Mutant, who CNS great three. I think it will take a bit of time to get used to this overtime and the term glioblastoma now is exclusively served for the adult IDH wild type tumors, so the stratification is really based on IDH status and so on. The humerus specific changes now go into this, so when you look at the 2016 WO list of
tumors it has a wide range of entities. Terms like Mr Citic astrocytoma or here to use sarcoma epithelioid, do you blastoma? All these have been removed. Everything has been streamlined and reduced to three main groups, and these are the adult type diffuse gliomas, pediatric type diffuse, low grade glioma, Sandy Patrick type diffuse, and these are exclusively present in pediatric patients but they’re often or more readily seen in pediatric patients. We now when we look at this more closely so the astrocytoma now.
We’re talking now specifically about diffuse gliomas. There now is, it is the idea. Mutant status matters most, and the certification is based on astrocytoma IDH mutant and then the grading is based on grade 2-3 and four for the OLIGODENDROGLIOMAS. Again, IDH mutant status is very relevant. In addition to that, the 1P19 Q correlation status again, the DCNS grade goes up to two to three. And a glass stoma is exclusively reserved for IDH wild type tumors. And these are automatically
who create 4 tumors.

D pediatric type diffuse Low

Bradley almost are now in.

Now include diffuse astrocytomas

with milk and milk LA mutations

The polymorphous low grade

neuroepithelial tumor of the young

and then diffuse low grade lumas

The polymorphous low grade

with MAP kinase alterations so you

see it’s very different group of

tumors that’s now front and center

stage within a diffuse cleoma group,

and then lastly high.

Correctly,

Omar Group includes H3K27 and altered 2 must,
00:47:55.550 --> 00:47:59.360 a new entity DH3G34 Mutant Group is now included.

00:47:59.360 --> 00:48:01.680 And also a new group deep diffuse pediatric type hydrate guma. Which is H3 wild type in wild type.

00:48:01.680 --> 00:48:06.916 And also a new group deep diffuse pediatric type hydrate guma. Which is H3 wild type in wild type.

00:48:06.916 --> 00:48:09.970 pediatric type hydrate guma. Which is H3 wild type in wild type.

00:48:09.970 --> 00:48:12.884 Which is H3 wild type in wild type.

00:48:12.884 --> 00:48:16.020 Now with a high great great forward and nomenclature is part of it and then the last city infant type hemispherically.

00:48:16.108 --> 00:48:19.188 nomenclature is part of it and then the last city infant type hemispherically.

00:48:19.188 --> 00:48:21.981 last city infant type hemispherically.

00:48:21.981 --> 00:48:25.006 Omaha for the adult type tumor tumors. There were also significant changes,

00:48:25.010 --> 00:48:27.170 There were also significant changes, so the diffusely infiltrative Astro City humor with an IDH mutation is morphologically in general well differentiated, lacks features of anaplasia.

00:48:27.170 --> 00:48:30.245 so the diffusely infiltrative Astro City humor with an IDH mutation is morphologically in general well differentiated, lacks features of anaplasia.

00:48:30.245 --> 00:48:34.200 City humor with an IDH mutation is morphologically in general well differentiated, lacks features of anaplasia.

00:48:34.200 --> 00:48:37.075 is morphologically in general well differentiated, lacks features of anaplasia.

00:48:37.075 --> 00:48:39.486 differentiated, lacks features of anaplasia. My target of activity is not detected.

00:48:39.486 --> 00:48:42.706 My target of activity is not detected
or very low and what is absent and this is diagnostically relevant.

Is microvascular proliferation and necrosis, and also there cannot be a city into a homozygous deletion? For the intermediate type here, formally called anaplastic as just cytoma, this is now the astrocytoma IDH mutant and now who CNS grade three. You have similar features except that now you find focal or dispersed. Anaplasia significant mitotic activity but still no faster proliferation, only crosses and no city can to a deletion rest for the highest grade now. Which is no longer called glioblastoma,
but this is the astrocytoma IDH mutant. Suppose CNS great for you have features of a diffusely infiltrative Astro, and IDH mutation that exhibits microvascular proliferation, necrosis, and in this case also sitting case and to a homozygous deletion or any combination of these features. So overall. Do they drive home? Point is the diagnosis anaplastic astrocytoma IDH mutant and glioblastoma IDH mutant are no longer recommended and the city KN 2A and B homozygous.
deletions are molecular markers of whose

in S grade 4 in an idea mutant astrocytoma.

Uhm, the criteria for Clyde Blastoma now are

limited to exclusively IDH wild type tumors.

And here you find diffuse associated
tumors with microvascular proliferation

or in the past it used to be an end.

Now it's just or you need

or you have a molecular defined tumor.

Third promoter mutation,

EGFR gene F receptor gene,

or if.

Amplification or plus 7 -- 10

chromosome copy number changes.

type diffuse kioma with any of
these features is called a glioblastoma.

Who CNS Grade 4.

So the question arises, how do you, you know, handle you plus two more now. So there are two options.

And this is not necessarily trivial, so the case with diffuse kiyama without microvascular proliferation or necrosis. So without anaplastic features it is logically not really a hit glioblastoma, but it is a glioblastoma when it is IDH, wild type and displays each Fr amplification. Third promote imitation or plus 7 -- 10 E 10. Whereas when you have a true histological glioblastoma where you see morphologic
features of anaplasia like Vasco preparation.

Only crosses, it's not ugly blastoma.

It's then a he still logically blows, not clear plus stoma with IDH mutation would then be an astrocytoma IDH mutant grade four so the term glioblastoma is not used its astrocytoma IDH mutant who created for.

For the pediatric group, then we have the entities I already mentioned.

Now within the FGF receptor category, where you have duplications mutations,
be roughest involved or again into a D pad.

Pediatric type diffuse tactically.

Almost this is a relatively.

Unusual entity in here.

You have some involvement of

PDGF receptor amplifications,

or EGFR amplifications or milk.

Others, when you then go beyond the

diffuse gliomas, you look at Leo,

neuronal, and neuronal tumors.

I just want to point out there

were few additional tumors added,

like the high grade astrocytoma with

pilot features within the glue,

neuronal and neuronal tumors,
and unusual tumor diffuse clonal tumor with oligo dentro cleoma like features and nuclear clusters. Myxoid Cleo neuronal tumors and the multinodular backlighting neuronal tumor. Uhm? Major changes were also seen added to the EPENDYMAL tumors. Appendable tumors are those with a relatively isomorphic appearance which form pseudorosettes around vasculature. They’re linked to the ventricular system mostly, and so this was the original classification in 2016. Now this is abolished and the
classification is now based on location

Histology and genetic alterations.

And here we have location based

Supratentorial intro tutorial spinal and

then lastly a few added two additional

entities to MC so popular in Panama.

And these soccer pending normal.

And when we look at those.

In in greater detail,

the supratentorial ependymoma’s used to

the supratentorial ependymoma’s used to

be known with a real or fusion partner.

This has been changed now the C 11 open

reading frame 95 now is dedicated as

CFTA and has multiple fusion partners.

These are usually hemispheric extra
ventricular tumors in adults and children, and another option is also. Y up, one fused to positive tumor. The interesting to introspect the info tutorial appending moments. Are the posterior fossa pantomima a Group A or B, and these are primarily in infants. Have an extremely poor prognosis. Unknown to have H3K27M metation. Loss whereas here you have our attention of the HTK 27 M in the B once and they have a bit better prognosis. This panel Panama must show often mxi amplification. They are they’re very malignant now.
The mix of popular Panama was upgraded to Grade 2 used to be grade one. There's no additional molecular data to change anything, and similarly for this update pending more marks stays the same, the embryonal tumors. I have seen also significant changes. These are as you can see in the image, very aggressive appearing blue cell tumors with high mitotic rate and here we have now molecular defined and histologically defined tumors in 2016. There were four. Subgroups and demolished the middle.
stomachs were stratified according to pathways which involved wind.

pathway Sonic hedgehog pathway and non wind non Sonic hedgehog.

The wind pathway.

Middle of last time I had a relatively good prognosis, whereas the Sonic hedgehog activated ones with up TP with a P53 mutation in addition, had a very poor prognosis. Now in in 2021 the Sonic Hedgehog Pathway Group went from 2 subgroups to four subgroups, so those on the editorial board that were splitters one rather than the lumpers,
and so we have now more subgroups.

Lastly, whenever you have MC involved or P53, these survival goes down the.

The non wind non the groups now went from.

You know, to eight subgroups, which is now a significant almost hairsplitting.

Attempt and you also have C or wherever you have mic involved.

You have lower survival time.

We will see whether this.

Splitting major plus Thomas

UP will hold over time.

The molecular defined middle class Thomas,
however, demonstrate distinct associations with morphologic patterns, and here for all wind tumors you see the classic type, which is a blue cell tumor. The Sonic Hedgehog group shows this decimal plastic nodular arrangement. And also you have a similar feature called middle class. Tomorrow is extensive nodularity and the group three and four are usually large cell, very anaplastic appearing middle blastomas. So for the middle class stoma. Overall it’s more complex. Now it’s more split.
The tumor types I'm just pointing out a change in red in grading. Uhm, their overall to just summarize the 222 new entities. Within different subtypes, clue Mas que neuronal and ependymal. UM Brian has seen 4 sarcomas, so he added and there are several changes. I will not go through those just to see there is quite a bit of modification. Last feed I just wanted to make close with the case we had and we are out of time. Almost the methylome analysis for brain tumors. In 2018, this paper came out by
the German group on David Capper,

where Metalation based classification of

central nervous system team was really dumb.

Breakthrough in certain ways.

The cancer methylome is really

a combination of SOMATICALLY

acquired in a metalation changes.

And characteristics that reflect

this cell of origin so you can

trace the cell back to its origin.

It also has been shown that this

technology is highly robust and

reproducible even when you use very

small samples and you have only poor

quality material and this profiles

have been widely used to classify
CNS tumors and this Disney plot here shows that there has been really a discovery of several new tumor entities. Secondly, it’s very straightforward to use where you use a paraffin embedded section, microdissected, run the array, and then generate a report which is then based on this. And pattern here and the these new classification recommends DNA methylation studies done explicitly for several tumor types. For example,
the pediatric high grade gliomas, the extra ventricular neurosci, Thomas Appending Momus, and also embryonal tumors. It’s mandatory now for high grade astrocytomas with highlighted features, it’s the only way to really diagnose this tumor. And for the diffuse general tumors with liquid entropy human like features, UM case election should follow cases with ambiguous tumor classification. Which are some I mentioned already. For example, in a young adult with a malignant IDH wild type glioma is suspicious.
That should be looked at by methylome analysis diffuse wildtype lumas without necrosis and so forth. And brown tumors in general. Ependymoma as the higher grade many tumors will benefit from it, and patients with putative tumor syndromes. It also it aids in additional testing in complex cases, and there I wanted to briefly show one of the cases we had at Yale. We are metal lumen. Alesis actually resolved this case. So it was a 9 year old female with a very complex heterogeneous
01:01:49.637 --> 01:01:52.096 tumor with enhancement,
NOTE Confidence: 0.79489987
01:01:52.096 --> 01:01:55.788 cystic degeneration, midline shift.
NOTE Confidence: 0.79489987
01:01:55.790 --> 01:01:58.226 No one was sure was that this
NOTE Confidence: 0.79489987
01:01:58.226 --> 01:02:00.110 is on the benign side of things,
NOTE Confidence: 0.79489987
01:02:00.110 --> 01:02:02.205 or somewhat malignant and so
NOTE Confidence: 0.79489987
01:02:02.205 --> 01:02:04.831 biopsied and or a resection shows
NOTE Confidence: 0.79489987
01:02:04.831 --> 01:02:06.627 a very peculiar picture.
NOTE Confidence: 0.79489987
01:02:06.630 --> 01:02:07.160 Also,
NOTE Confidence: 0.79489987
01:02:07.160 --> 01:02:10.870 where we have fields with embryonal type
NOTE Confidence: 0.79489987
01:02:10.870 --> 01:02:13.760 morphology areas with pseudo rosette forming,
NOTE Confidence: 0.79489987
01:02:13.760 --> 01:02:16.748 this is almost Astro Astro blastoma
NOTE Confidence: 0.79489987
01:02:16.748 --> 01:02:19.818 like fields with sclerosis and there’s
NOTE Confidence: 0.79489987
01:02:19.818 --> 01:02:22.288 more pleasure there is nothing.
NOTE Confidence: 0.79489987
01:02:22.290 --> 01:02:25.854 In our current WTO that would
NOTE Confidence: 0.79489987
01:02:25.854 --> 01:02:29.978 fit this features and so the the
NOTE Confidence: 0.79489987
01:02:29.978 --> 01:02:32.330 immunohistochemistry was not helpful
We ran I enormously wide piano or without any conclusion. UM, lastly sent it to end to end value for DNA methylation studies and here it came back to our surprise as a tumor which matches a neural epithelial tumor with Eminem, one alteration. This was confirmed with a fish he choose. Helped us out and here we have now a probe that confirmed that the emanon arrangement is really, truly the driving factor here, and so the high grade new rapidly tumors M1 is defined as one rearrangement.
01:03:23.708 --> 01:03:26.570 is a very new or relatively
NOTE Confidence: 0.801978871666667
01:03:26.661 --> 01:03:29.217 new entity recently described.
NOTE Confidence: 0.801978871666667
01:03:29.220 --> 01:03:31.638 It has several bank binding partners,
NOTE Confidence: 0.801978871666667
01:03:31.640 --> 01:03:33.605 including Band 2.
NOTE Confidence: 0.801978871666667
01:03:33.605 --> 01:03:38.190 Uhm it be metalation profiling shows it
NOTE Confidence: 0.801978871666667
01:03:38.312 --> 01:03:43.303 really splits off as a separate entity
NOTE Confidence: 0.801978871666667
01:03:43.303 --> 01:03:46.940 is distinctly different from others,
NOTE Confidence: 0.801978871666667
01:03:46.940 --> 01:03:49.607 so most of this high grades CNS.
NOTE Confidence: 0.801978871666667
01:03:49.610 --> 01:03:52.098 Peanuts are grouped clusters
NOTE Confidence: 0.801978871666667
01:03:52.098 --> 01:03:54.586 within the reference group.
NOTE Confidence: 0.801978871666667
01:03:54.590 --> 01:03:58.090 Here, 24% form 4 clusters,
NOTE Confidence: 0.801978871666667
01:03:58.090 --> 01:04:01.888 and the I mean one is one of them.
NOTE Confidence: 0.801978871666667
01:04:01.890 --> 01:04:05.028 And so in general this.
NOTE Confidence: 0.801978871666667
01:04:05.030 --> 01:04:08.789 Worked a sort of false between Astroplus
NOTE Confidence: 0.801978871666667
01:04:08.789 --> 01:04:12.370 stoma, but also somewhat high grade.
NOTE Confidence: 0.801978871666667
01:04:12.370 --> 01:04:13.810 He was unsure morphologically
what to do with it,

but this now really helped us.

You know,

stratified this tumor,

and so it was initially reported

in in a minute you mop.

In other tumors it has been seen in AML.

It’s actually it’s improved survival,

but I think there’s not enough data to

properly judge this rearrangement here.

And so where do we go from here?

Uhm,

the goal is to build and expand

on a molecular neuropathology

service here at Yale.
Embrace new developments.

Embrace state of the art technology

molecular markers and so forth

to improve on the statistics.

The image I showed you at the beginning

of the talk and continue to work very

closely with all our clinical partners.

And here we are.

I’d like to acknowledge and thank a wide

range of colleagues from neurosurgery.

Neurooncology my own group is

fantastic group of neuropathologists

Neuro radiology medical genetics.

Molecular genetic pathology also again

in my department radiation oncology

and then many who work behind the
01:05:32.397 --> 01:05:35.618 scenes and help us along the way.

01:05:35.620 --> 01:05:36.304 And with that,

01:05:36.304 --> 01:05:36.760 thank you,

01:05:36.760 --> 01:05:38.610 I'm sorry I'll reign over.

01:05:40.950 --> 01:05:41.978 Thank you very much.

01:05:44.380 --> 01:05:45.696 Thank you very much. I need to.

01:05:45.700 --> 01:05:48.300 So I think we are running over time.

01:05:48.300 --> 01:05:50.267 So I think questions will need to

01:05:50.267 --> 01:05:51.838 be addressed through email to you.

01:05:51.840 --> 01:05:56.026 So I think this is fantastic and

01:05:56.030 --> 01:05:57.982 I think it is one more example of

01:05:57.982 --> 01:06:00.008 where the oncology field is heading.

01:06:00.010 --> 01:06:01.381 Usually bring tumors,

01:06:01.381 --> 01:06:04.123 lead the way in terms of

01:06:04.123 --> 01:06:05.723 incorporating molecular studies

01:06:05.723 --> 01:06:06.510
and then other diseases follow.

So it seems like we’re getting more complex and more sliced and if even.

Rarer diseases so big challenges ahead, so thank everyone for attending and once again thank you for our wonderful speakers and I hope to see you next week.

Our next grand rounds.

Thank you very much.

Bye bye.