So our first speaker is Pam Kuntz, who is associate professor of medical oncology here, director of the Center for GI Cancer. As the chief of GI Medical Oncology and the Vice Chief of Diversity, she received her medical degree from Dartmouth and Residency and Fellowship Training at Stanford, where she joined the faculty and she joined us now. She is an international leader.
in the clinical care of patients with neuroendocrine tumors conducting important clinical trials in this area. And as well as translational science for patients with this rare diagnosis, she’s also a vocal advocate for women and underrepresented groups in medicine. And recently, the women leader in oncology named her the 2021 Women oncologist of the Year, so we’re very happy to hear, and we’ll hear about GI neuroendocrine tumors. I suspect from Pam. Thank you. Thanks, Dan.
There has that looks OK all right excellent.

So thanks so much for the opportunity to speak today.

I will in fact be talking about neuroendocrine tumors and establishing the Yale and neuroendocrine tumor program.

I'd like to highlight this is broadly part of the Center for GI cancers.

We have a new Twitter handle and email which is here.

These are my disclosures.

I'm going to go over a brief outline of epidemiology, nomenclature, and some key characteristics of Nets that impact treatment.
We’ll talk some about treatments, some clinical trials in which I’ve been involved over the last few years, and why we should create a Net program at Yale, and then we’ll finish with some future clinical and research opportunities. I like starting with a little bit of history, and I think this one is especially important, so. Neuroendocrine tumors were recognized in the late 1800s and early 1900s. The term carcinoid, which means cancer like, has been attributed to doctor or Bender for a German pathologist.
He felt that these had five key characteristics that they were small, multifocal had undifferentiated cellular formations, well defined borders, no metastatic potential, and we're slow growing and harmless, though this was a very important contribution to the field we now know that these tumors are in fact metastasize. They are in fact cancers, and unfortunately this really held back the field. In fact,
for many many years these were not incorporated or included in cancer registries, and therefore it made epidemiologic and other studies very difficult. So we fast forward to the 1980s when we developed streptozotocin and octreotide for the treatment of neuroendocrine tumors and hormone hypersecretion. And then there was really a desert of therapeutic and diagnostic advances for almost 30 years. And then you can see an explosion of research starting in 2011 with a number of FDA approvals.
00:03:11.480 --> 00:03:13.175 for everolimus and student Neb
00:03:13.175 --> 00:03:15.110 and pancreatic Nets and so on.
00:03:15.110 --> 00:03:16.538 I'm going to go into a little
00:03:16.538 --> 00:03:17.559 bit more detail on this.
00:03:17.560 --> 00:03:20.683 Up on the top we see that there are
00:03:20.683 --> 00:03:23.558 actually 3 new novel imaging modalities,
00:03:23.560 --> 00:03:25.672 three types of PET scans with
00:03:25.672 --> 00:03:26.376 different radioisotopes.
00:03:26.380 --> 00:03:27.864 Those have really completely
00:03:27.864 --> 00:03:29.719 replaced the use of octreoscan,
00:03:29.720 --> 00:03:32.096 so it's been an exciting time
00:03:32.096 --> 00:03:34.350 to be in the field.
00:03:34.350 --> 00:03:36.975 I'd like to also really dispel the
00:03:36.975 --> 00:03:39.789 myth that Nets are really that rare,
00:03:39.790 --> 00:03:42.160 so they are in fact low,
have a low incidence rate,
so that's the number of patients diagnosed per year,
and we can see that in this figure from a seer epidemiologic study in
so at present we have about 7 to
8 diagnosis per 100,000 patients
in the United States.
However, in the figure on the right.
I like to also describe that these are a higher prevalent cancer
than was previously recognized.
The prevalence,
00:04:14.748 --> 00:04:15.900 alive at any
going time and the net prevalence actually
00:04:15.969 --> 00:04:18.630 exceeds that of stomach and pancreatic
00:04:21.508 --> 00:04:23.892 adenocarcinoma combined, so I think
00:04:23.892 --> 00:04:25.476 it’s a bigger public health problem.
00:04:25.480 --> 00:04:27.436 Many primary care,
00:04:27.436 --> 00:04:31.348 general oncologists will see these patients.
00:04:31.350 --> 00:04:33.370 Nets are epithelial neoplasms that
00:04:33.370 --> 00:04:34.986 are derived from neuroendocrine
00:04:34.986 --> 00:04:36.569 cells throughout the body.
00:04:36.570 --> 00:04:38.562 As Dan said, I may officially
00:04:38.562 --> 00:04:40.730 a card carrying GI oncologist,
00:04:40.730 --> 00:04:43.021 but they do in fact happen throughout
00:04:43.021 --> 00:04:45.247 the body GI tract most commonly
00:04:45.247 --> 00:04:47.349 followed by lungs and then other.
And I actually see Nets of almost every primary site. I just saw a base of Skull net last week, so most grow slowly in comparison with their adenocarcinoma counterparts. The majority are sporadic with only the minority associated with inherited. Familial syndromes such as M1 MEN 2, von Hippel, Lindau and Neurofibroma Fibromatosis on pathognomonic for this disease or the presence of somatostatin receptors on the surface of the cells. There are five types and over 80% of Nets over express somatostatin receptor type 2 and we can take great advantage
of this in terms of diagnostics and therapeutics and we’ll talk about that also.

And just a brief mention, this is a really cursory overview of net biology, but I did want to bring this in large scale.

Chromosomal alterations are common.

Tumor mutation burden is low in the net, so that’s the lower grade grade 1/2 nor underprint tumors.

It’s higher in neuroendocrine carcinomas, that’s the Grade 3 or poorly differentiated recurrent somatic mutations are actually rare.
There have been a number of fairly recent studies. So in pancreatic net, we will say somatic mutations in MN dachshund fate Terex we see mtor pathway gene mutations, mute YH, check two and bracket two and there are proposed or hypothesized at least four different molecular subtypes of pancreatic Nets and in small bowels we will see mutations in CDKN 1B. Tumor grade progression does occur in pancreatic Nets, and we have seen clonal evolution patterns as well.
There was a very elegant study done by friends and colleagues. Doctors Nature Raj and Diane Reidy Lagunes at memorial that demonstrated this, and then germline alterations are also more common than previously thought. So in the Scarpa Nature Paper from 2017, 17% of quote sporadic pancreatic Nets actually had germline mutations. In terms of the diagnostic work up, the mainstay of imaging is cross sectional, so either a multiphasic CT and that is key when you order a net CT. So you have to order it as multiphysics specifically with an arterial phase.
and or MRI somatostatin receptor imaging complements the cross sectional imaging octreoscan has been completely replaced by the gallium 60 Dota T ate or Copper 64 Dota Tate Pets. We still occasionally will use FTG. But that’s really only for high grade, poorly differentiated disease. And as you can see in the figure on the left, this is a cross section through the liver with two hypervascular liver lesions shown in the arterial phase of the CT scan. So that’s really important, these can be missed if that arterial phase is not done. We also tissue diagnosis is important.
We try to find the primary site as there are some differences in FDA approvals by primary site and then key minimum data elements on pathology include WHN grade Ki 67 mitotic index and degree of differentiation. Tumor markers are not all that helpful for Nets. In fact, Crimina, which has historically been used pretty widely, is in fact falling out of favor. I don’t use it anywhere. 24 hour urine 5. HIA, which is a metabolite of serotonin.
is useful for those patients in whom it’s elevated, and then they’re all also other specific peptides. Any means which will speak about. So I like to think of six key patient characteristics that impact treatment will go over these briefly hormone status stage and burden of disease grade and differentiation pace of growth, primary site and somatostatin receptor status on these all yield potential status on these all yield potential clinical and research questions. So I think it also helps frame the rest of the conversation today. So in terms of hormone status,
we divide patients into functional and non functional. Functional refers to patients having symptoms from a measurable hormone. Carcinoid syndrome is the classic example, so this happens in about 10% of small intestine Nets and this is due to production of serotonin. Patients may have flushing and venous telangectasia shown in the picture on the left. Patients are often misdiagnosed as having rosacea. They can have diarrhea, bronchospasm.
as seen in that second picture

which is fibrosis of the pulmonary

and tricuspid valves?

Pancreatic Nets can also secrete

hormones in about 40 percent.

40% of the time.

Most commonly insulin,

followed by gastrin,

Glucagon and wezo intestinal polypeptide,

and the symptoms are defined

by the hormones to create it.

And then nonfunctional Nets are patients

who are asymptomatic or have symptoms

that are not from hormone access.

Stage and burden of disease.

It’s important to think about.
Do they have localized or metastatic disease, liver, dominant, or widely metastatic or low volume or high volume and aren’t new dodo pets really are the best tool to help us determine extent of disease? So as you can see on the left, this is a localized pancreatic net with you can see the pancreatic net here in the middle liver dominant disease with a liver really filled with with tumor metastatic disease. And then widely metastatic disease, and this is these are actually bone lesions
throughout the axial skeleton. I'm a JCC.

Staging follows other solid tumors, but the key point I want to make from this slide is that NETs were actually only added to the AJC staging as of 2010, so relatively new.

Grade and differentiation is important, I just have highlighted the two most recent WHO classification for thoracic and digestive NETs. They are, I'd say loosely related, but there are some nuances and suffice it to say that the nomenclature and evolution of the WHO classification and what we call these tumors is complicated and has changed a lot overtime.
I’d like to just bring you to this right column of the 2019. Adjusted WHL classification so we now have well differentiated grade 1/2 and three Nets, and then a poorly differentiated carcinoma so that word carcinoma implies that it is grade 3 and has a Ki 67 greater than 20%. So piece of growth matters also, so I may need a patient who has had stable disease for many years, or I may meet a patient who has rapidly progressive metastatic disease and that matters in terms of how I select therapy. Primary site matters, as I’d mentioned some of our FDA approvals.
are really dependent on primary site,
NOTE Confidence: 0.839235135882353
so for one example,
NOTE Confidence: 0.839235135882353
sunitinib is only approved
NOTE Confidence: 0.839235135882353
for pancreatic Nets,
NOTE Confidence: 0.839235135882353
not for other primary sites.
NOTE Confidence: 0.839235135882353
And then lastly of these characteristics,
NOTE Confidence: 0.839235135882353
somatostatin receptor,
NOTE Confidence: 0.839235135882353
is our newest characteristic that matters.
NOTE Confidence: 0.839235135882353
This is just a really nice example of
NOTE Confidence: 0.839235135882353
this same patient who had an octreoscan,
NOTE Confidence: 0.839235135882353
so that's our older imaging tool.
NOTE Confidence: 0.839235135882353
It required patients coming back
NOTE Confidence: 0.839235135882353
to the facility two days in a row,
NOTE Confidence: 0.839235135882353
and then our newer gallium 68 dotatate
NOTE Confidence: 0.839235135882353
pet that has much higher resolution.
NOTE Confidence: 0.839235135882353
I'll just highlight a couple
of interesting points, so the pituitary gland is normally a little bit positive on this as is. Be or as are the liver has some normal background, but then spleen and that it’s concentrated in the latter. So just a brief overview of what we have in terms of tools for hormone control. So somatostatin analogs are the mainstay of how we treat functional Nets, primarily carcinoid syndrome. There are two approved agents in the United States, octreotide and lanreotide. These are both approved for hormone control.
They have the same affinity for somatostatin receptors 2 and five. The main difference is that octreotide has come in both a short and a long acting form. It is an intramuscular injection whereas lanreotide only has a long acting, 4 minutes, a deep subq injection. It's approved in the US, in Europe for cushions. And then on the right is actually a new agent that is a was approved a few years ago on the basis of improving diarrhea for patients with carcinoid syndrome, telotristat blocks, TPH. It’s the rate limiting enzyme in the
00:13:41.040 --> 00:13:43.855 conversion of tryptophan to serotonin.

00:13:43.860 --> 00:13:45.666 So I participated in this clinical trial when I was at Stanford and it reduces on average bound movements, about two per day.

You may not think that is clinically important, but it often helps get patients out of the house, so it’s again and it’s oral.

There are a number of tools for tumor control. They fall into four categories, somatostatin analogs, biologics, cytotoxic chemotherapy.
and PRRT,

which is peptide receptor radionuclide therapy.

I am going to focus today just talking about two of these, so we’re going to talk about tempos Olamide and capecitabine on the basis of a large randomized trial that I lead through the NC, and also the crescendo dictate, which is our sort of first and only so far. On peptide receptor radiotherapy for this disease. So this was a study and I think if there are any trainees on that, I started getting involved with E
NOTE Confidence: 0.934096590625
00:14:42.448 --> 00:14:44.488 Cogen the national clinical trial
NOTE Confidence: 0.934096590625
00:14:44.488 --> 00:14:46.534 network as a fellow and junior
NOTE Confidence: 0.934096590625
00:14:46.534 --> 00:14:49.056 faculty it was a great opportunity
NOTE Confidence: 0.934096590625
00:14:49.056 --> 00:14:50.964 for networking and mentorship.
NOTE Confidence: 0.934096590625
00:14:50.970 --> 00:14:53.140 Through that I helped to develop this
NOTE Confidence: 0.934096590625
00:14:53.140 --> 00:14:55.056 randomized study for patients with
NOTE Confidence: 0.934096590625
00:14:55.056 --> 00:14:56.891 progressive, metastatic pancreatic Nets.
NOTE Confidence: 0.934096590625
00:14:56.891 --> 00:14:59.520 Grade one and two half received
NOTE Confidence: 0.934096590625
00:14:59.520 --> 00:15:01.920 10s Olumide alone and half received
NOTE Confidence: 0.934096590625
00:15:01.920 --> 00:15:03.699 capecitabine and Thomas Alameda.
NOTE Confidence: 0.934096590625
00:15:03.700 --> 00:15:04.137 Together,
NOTE Confidence: 0.934096590625
00:15:04.137 --> 00:15:06.759 the maximum duration was 13 cycles
NOTE Confidence: 0.934096590625
00:15:06.759 --> 00:15:08.540 to about one year,
NOTE Confidence: 0.934096590625
00:15:08.540 --> 00:15:11.675 and the primary endpoint was
NOTE Confidence: 0.934096590625
00:15:11.675 --> 00:15:13.556 progression free survival.
NOTE Confidence: 0.934096590625
So this study indicated a benefit of the combination arm with a median progression free survival of 22.7 months versus 14.4 months with a hazard ratio of .58.

And the overall survival also showed a statistically significant difference. The median in the Thames Olumide alone arm was 38 months and it was not reached in the combination arm.

And then in terms of response rate, this is actually a combination that yields one of the highest response rates of any available agent, so the response rate for the combination arm was 33% and the single agent arm 27.8%.
These were not powered to determine a difference between the arms, but I think another important takeaway is that both agents yield approximately a 30% record rate.

So moving on to talk about Sonata Staten receptors also just a brief history. Somatostatin was sequenced in 1963. It’s a naturally occurring peptide, but has a very short half life, so analogs were later developed in order to be clinically practical. There are two Nobel prizes on this list. The first is in the 1970s for doctors Gilman and Shelly on
the discovery of somatostatin.
And then later in 2012, doctors could Belka and Lefkowicz were awarded the Nobel Prize for their discovery of G protein coupled receptors to which somatostatin receptors belong.
So I’d like to introduce you next to the concept of theranostics, and this is really important as we think about developing our yield or under consumer program.
So imagine you have a group of patients you’d like to determine whether they have a specific target. You have a diagnostic imaging tool that actually helps select...
who in fact has that target, and then you have a targeted therapy that goes to that target. So Theranostics is using the same target for both therapy and diagnostics. I like to think of this using a lock and key analogy, so the lock is that target, or the somatostatin receptor in the case of Nets, the key is the peptide or octreotide in our case, and the reporting unit is the payload or the radioisotope.
So the diagnostics for Nets.

I walked you through this a little bit, but it actually dates back to the 1980s, and using I won I won 23, labeled octreotide, but then it’s been through this entire evolution of Indian 111 which is Indian 111 octreotide. And so that’s the octreoscan that was approved in 1994 and then in the 2000s we’ve had gallium 68, dotatate pet gallium 68 Doda talk pet and copper 64 dodat 8. So that and there is. I put the reference in here. There’s a great article that’s an
appropriate use criteria for these somatostatin receptor imaging modalities. Therapy is similarly we can think about the lock and key. I use this analogy quite a bit when I talk to patients. So for peptide receptor radionuclide therapy there has also been an evolution first using Indian 111 in the 2000s using yttrium 90 and then later in the 2000s. Evaluation of lutetium 177 dooda tape. It was this clinical trial that I had the opportunity to lead while I was at Stanford and this was an
international multicenter randomized trial.

Get randomized patients with midgut or small intestine narendran tumors 2

to one to receive 4 administrations.

Ivy of this this radioisotope

lutetium dotatate at 200 millicurie

versus high dose octreotide.

This was a positive study,

so the primary endpoint was

progression free survival.

It showed a hazard ratio of .21 and

this is one of our in the median.

PFS was not reached at the time of the study,

but is approximately 2 1/2 years.

The overall survival had not

been reached at the time of this
00:19:34.329 --> 00:19:35.007 initial publication.
00:19:35.010 --> 00:19:36.828 It’s since has been reported actually.
00:19:36.830 --> 00:19:37.682 Just ask, oh,
00:19:37.682 --> 00:19:39.386 this year it did not officially
00:19:39.386 --> 00:19:41.149 meet statistical significance,
00:19:41.150 --> 00:19:42.910 but was a clinical difference.
00:19:42.910 --> 00:19:43.762 Of one year.
00:19:43.762 --> 00:19:45.750 So on the basis of this study,
00:19:45.750 --> 00:19:48.110 this was FDA approved in January of 2018.
00:19:48.110 --> 00:19:50.238 It was really fun to be part of
00:19:50.238 --> 00:19:54.264 a process of kind of a novel
00:19:54.270 --> 00:19:57.966 and then the clinical implementation of that.
00:19:57.970 --> 00:20:00.064 I’d also like to sort of
00:20:00.064 --> 00:20:02.060 postulate that’s not a statin.
Receptors are a perfect target. I'll just mention for other agents that are in very early phase studies. But Letitia Satureia tide is acineta antagonist so that Ludo date is actually an agonist. This was an early phase study that actually had quite a bit of grade 4K metalogic toxicity. They that led to some dose reductions and are pursuing that in later phase.

Committees PEN 221 is a peptide drug conjugate with DM, one that also just recently completed a small phase two trial and did...
00:20:38.907 --> 00:20:41.469 not have a modest benefit rate.

00:20:41.470 --> 00:20:45.646 No PR's, but had an 88% on stable disease rate to do to Mab is a Sonata Staten.

00:20:45.646 --> 00:20:51.503 receptor 2 CD 3 bispecific antibody also just completed a phase one study.

00:20:51.503 --> 00:20:54.790 Modest response rates but hadn’t had a 55.

00:20:54.790 --> 00:21:00.550 Percent stable disease rate.

00:21:00.550 --> 00:21:00.998 Of note.

00:21:00.998 --> 00:21:02.342 I’ll just mention I didn’t go into detail in this today, single agent checkpoint inhibitors do not work in low grade nor consumers.

00:21:10.722 --> 00:21:12.263 combination approaches is very attractive and then led to 12 dot M.
00:21:14.870 --> 00:21:16.710 Tate is an alpha emitter.
NOTE Confidence: 0.873074789230769
00:21:16.710 --> 00:21:19.650 PRT alpha emitters are felt to be.
NOTE Confidence: 0.873074789230769
00:21:19.650 --> 00:21:21.714 I'm have fewer side effects and
NOTE Confidence: 0.873074789230769
00:21:21.714 --> 00:21:23.690 have more tumor cell killing.
NOTE Confidence: 0.873074789230769
00:21:23.690 --> 00:21:25.335 This just completed a phase or in
NOTE Confidence: 0.873074789230769
00:21:25.335 --> 00:21:26.990 the middle of a phase one trial.
NOTE Confidence: 0.873074789230769
00:21:26.990 --> 00:21:28.878 They just reported some.
NOTE Confidence: 0.873074789230769
00:21:28.878 --> 00:21:29.704 Early results,
NOTE Confidence: 0.873074789230769
00:21:29.704 --> 00:21:31.828 so in their first ten patients
NOTE Confidence: 0.873074789230769
00:21:31.828 --> 00:21:34.429 there was a response rate of 80%.
NOTE Confidence: 0.873074789230769
00:21:34.430 --> 00:21:36.614 So we are all very excited about
NOTE Confidence: 0.873074789230769
00:21:36.614 --> 00:21:38.689 the idea of alpha emitters,
NOTE Confidence: 0.873074789230769
00:21:38.690 --> 00:21:40.778 and so stay tuned on that.
NOTE Confidence: 0.873074789230769
00:21:40.780 --> 00:21:43.356 And then I did a tweet Oriel kind
NOTE Confidence: 0.873074789230769
00:21:43.356 --> 00:21:45.975 of on this medicine receptors as
NOTE Confidence: 0.873074789230769
00:21:45.975 --> 00:21:48.801 part of a Twitter tumor board.
So what do we know about Nets as we start thinking about translational research questions? Well, we know there are chronic cancer. We know somatostatin receptors are unique target. Somatic mutations are rare. Tumor mutation burden is low and germline mutations are more common than was once appreciated and existing biomarkers or imperfect and we have a number of treatments that yield stability. Hodo dictates those progression and shrinks tumors in the optimal sequence of therapies is unknown and sequence of therapies is unknown and.
most patients receive therapies. From this experience years of toxicity.

So how can we optimize PRT? How could we take better advantage of this? Meta Staten receptor? Can we identify resistance mechanisms and overcome them? And how can we develop predictive and prognostic biomarkers so the bar is low in the field? Needs your help, so this is part of my plea to the Cancer Center community to help me start thinking about translational questions as we develop teams for research. So one such team that I’m part of
NOTE Confidence: 0.873074789230769
00:22:49.946 --> 00:22:52.636 Under Consumer task force that I chair, I had the opportunity to lead a clinical trial planning meeting this past year with. The objective was to really think about treatment in the era of PRT. Our deliverables are in manuscript that is in process. But really the deliverables are clinical trials and so we now out of this. Like many month process have a PRT re...
we have working groups on looking at.

PR T plus DNA damage repair PR T plus

IO PR T and liver directed therapy

ended in some dosimetry studies.

So why build a net program at Yale?

I hope I’ve shown you that there is

a real renaissance in net research

in terms of increased publications

The volume of net patients at

YCC is increasing.

There’s significant downstream

revenue of patients who have a high

prevalent disease and are in our

health care systems for a long time.

We have the multidisciplinary
expertise for metal, concert, junk, and endocrine and IR, a nuke Med.

Our clinical trial portfolio is growing. There is philanthropic interest.

I’d like to specifically thank the Alan and Cheryl Lipson fund for a generous and multi year gift that we have recently received. And really the timing is right. I think that with my arrival to Yale and really a convergence of all of this expertise, it’s very exciting and we have identified Nets as one of our four key programs in the Center for GI cancers.
So I have just a few minutes remaining.
I'm going to kind of try to breeze through this, but our Yale NET program is cold.
By myself, dark crime.
We are adding Doctor Mary McCoy and we have currently a monthly Net support group and I'm sort of the anchor medical oncologist.
And we are planning a PRT clinic.
Some efforts around a nutrition education and a new theranostics program that Doctor Abovyan will be leading that will really have benefits beyond neuroendocrine to include Neuro and Gu.
As I've mentioned,
we have clinical trials.

We just opened our first one and actually our first patient is enrolling on the net are two clinical trial this week.

We have a biorepository enriched with net cases and we have a number of transitional team brands, one of which we just submitted last week.

On looking at sex differences in neuroendocrine tumors.

It’s a randomized phase three trial for patients with advanced, well differentiated GI in order well differentiated GI in order consumers that are slightly
higher grade than the number one,
and it’s randomized loot 8 versus octreotide.
I have a whole list of my wish
list of other clinical trials.
These are all NC TN trials that are in
queue to hopefully open in the next year.
This is a new alpha emitter as I’d
mentioned where there’s a lot of
excitement about this and I serve on
the steering committee for this study.
So a shout out to the bio GI tumor
biorepository led by Doctor John Kunstmann.
It’s been established for almost a decade,
and I’d like to highlight that it’s
really enriched fernette cases,
so we have 106 net tissue samples,
00:26:06.310 --> 00:26:09.054 70 of which are fresh frozen and you

00:26:09.054 --> 00:26:10.836 can see the breakdown of diseases

00:26:10.836 --> 00:26:11.430 and they’re

00:26:11.487 --> 00:26:12.999 all associated with plasma,

00:26:12.999 --> 00:26:15.593 so a great opportunity for collaboration.

00:26:16.340 --> 00:26:18.118 And then lastly, in terms of education,

00:26:18.120 --> 00:26:19.520 we launched our Patient

00:26:19.520 --> 00:26:20.920 Education initiative in November.

00:26:20.920 --> 00:26:23.136 We have a CMU series planned and a

00:26:23.136 --> 00:26:25.400 number of trainees already involved.

00:26:25.400 --> 00:26:27.367 Carolyn Gordons of Pgy 2 who’s helping

00:26:27.367 --> 00:26:30.239 to do a review paper on sex differences

00:26:30.239 --> 00:26:32.199 and or under commute classrooms.

00:26:32.200 --> 00:26:34.528 They shall shrikumar is helping with

00:26:34.528 --> 00:26:37.454 a pathology project in jamies Ang just

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completed a really wonderful JCO oncology practice review so please join us we have on Thursdays I’d like to highlight it. We have a great. In our series on Thursday afternoons from 4:15 to 5:00, and I think I’ll end there. So, you know, we’re really excited about building this program. I think our next step is really building on some of the translational research opportunities, so thanks.

Thank you, Pam. Very exciting. Particularly these tremendous advances in therapy.
Those are very impressive capital.

Higher plots.

So are there questions while we’re waiting I-1 quick one.

There’s a huge increase since the 1970s.

Is that just better diagnosis or is it incidents actually increasing?

So that’s a great question.

I think that the diagnostics or have clearly improved.

I think that we’re seeing incidentally discovered GI Nets through colonoscopies.

to specifically rectal and colon,

but I think that it probably goes beyond that,
and so some hypotheses have been
are there environmental risks
that we have not yet picked up on.
So I think some of its diagnostics,
but some of it’s something
we don’t yet understand.
And you may have said this, but I missed it.
Do you sometimes have patience with
different primaries and different sites?
That would be really infrequent,
but can happen with some of our
inherited syndromes, but usually
they have a single primary site.
Are there other questions in
the chat or raise your hand?
Well, I have another question we
talk about briefly before we started.

Has anyone looked for viruses in these tumors? I’m asking ’cause as we’ll hear the next one, there is a virus involvement.

So Dan, good question and not to my knowledge, the clinical science interestingly was way ahead of some of the basic understandings of the molecular biology, and in fact we knew that M Tor inhibitors worked clinically before.
We knew that there were entire pathway mutations, somatic mutations. So I think there are a lot of really great questions we still need to ask in this field.

Well, it's great that we have such a strong program here. Oh, thank you for doing that.

I'm seeing whether questions we'll move on to our second speaker, so there's one quick. There is one question. I'm sorry.

It just came in from Jeremy Jaycox. Do you see that?
NOTE Confidence: 0.92802095
00:29:21.405 --> 00:29:23.040 non STR Nets biologically and
NOTE Confidence: 0.92802095
00:29:23.104 --> 00:29:25.344 clinically compared to those that
NOTE Confidence: 0.92802095
00:29:25.344 --> 00:29:27.136 are somatostatin receptor positive,
NOTE Confidence: 0.92802095
00:29:27.140 --> 00:29:29.330 so that’s another great question.
NOTE Confidence: 0.92802095
00:29:29.330 --> 00:29:31.826 I would say typically the patients
NOTE Confidence: 0.92802095
00:29:31.826 --> 00:29:34.022 who are noncitizen receptor avid
NOTE Confidence: 0.92802095
00:29:34.022 --> 00:29:35.850 have more aggressive disease.
NOTE Confidence: 0.92802095
00:29:35.850 --> 00:29:37.290 They tend to have lost.
NOTE Confidence: 0.92802095
00:29:37.290 --> 00:29:39.198 That’s in Edison receptor
NOTE Confidence: 0.92802095
00:29:39.198 --> 00:29:40.629 as they differentiate,
NOTE Confidence: 0.92802095
00:29:40.630 --> 00:29:43.326 so it usually are the grade 3 poorly
NOTE Confidence: 0.92802095
00:29:43.326 --> 00:29:45.069 differentiated in order consumers.
NOTE Confidence: 0.92802095
00:29:45.070 --> 00:29:46.226 I’m as I mentioned,
NOTE Confidence: 0.92802095
00:29:46.226 --> 00:29:48.310 we can see great evolution over time,
NOTE Confidence: 0.92802095
00:29:48.310 --> 00:29:50.200 so sometimes a patient who may have
NOTE Confidence: 0.92802095
initially been SSTR positive can lose.
00:29:54.140 --> 00:29:56.858 and another question are there supportive services unique for this population?
00:30:01.550 --> 00:30:04.928 So so yes, and I actually, I'm really eager to work Terrace Hampton.
00:30:07.010 --> 00:30:08.270 I have talked some about this,
00:30:08.270 --> 00:30:10.106 but I think particularly for the grade one and two under consumers defined as a more chronic cancer,
00:30:10.106 --> 00:30:12.139 the chronicity of their survivorship issues, I think, is a really unique aspect that we need to pay more attention to.
00:30:14.390 --> 00:30:15.990 the chronicity of their survivorship issues, I think. I think particularly for the grade one and two under consumers defined as a more chronic cancer,
00:30:14.383 --> 00:30:15.990 the chronicity of their survivorship issues, I think. I think particularly for the grade one and two under consumers defined as a more chronic cancer,
00:30:12.139 --> 00:30:14.383 defined as a more chronic cancer,
00:30:10.106 --> 00:30:12.139 grade one and two under consumers defined as a more chronic cancer,
And finally, what about differentiation therapy? Isaac Kim has a question on that point, yes, so in fact one wish list for 2022 is to actually bring together a multidisciplinary group of people to examine new under condition citation across specialties. So bringing GUGI thoracic folks together to release. Think about this as a team or underground differentiation. It can be an end differentiation for many cancer types and I think. We know very little about that.
OK terrific, thank you for other people.

Have questions.

You should contact Pam directly.

Our second speaker today.

Get my little sheet out.

Is is Kelly Olino from partement surgery?

She’s an assistant professor and

received her medical training at Johns Hopkins and also residency there.

Then a fellowship at Memorial Sloan Kettering.

She came to Yale from the University of Texas Medical Branch and while in Texas,

she was recognized as a Texas Rising Star,

a Lone Star, a Provost,

scholar and recipient of the
Society for Surgical Oncology
Clinical Investigation Award.
Interested in terminology including Melanoma.
And her clinical specialties include
treatment of patients with Melanoma,
Merkel cell cancer which will hear
about today and other other cancers
and also interested in developing.
Clinical trials,
including immune therapy for
these diseases and like what
we just heard about merkle’s,
a neuroendocrine tumor
with the virus association,
which makes it interesting to me.
00:31:59.830 --> 00:32:00.870 So I’m very interested in
NOTE Confidence: 0.843998448571428
00:32:00.870 --> 00:32:02.120 hearing what Kelly has to say.
NOTE Confidence: 0.923697
00:32:05.360 --> 00:32:06.108 OK, it looks good.
NOTE Confidence: 0.902238968
00:32:07.110 --> 00:32:09.246 Great thank you.
NOTE Confidence: 0.902238968
00:32:09.246 --> 00:32:11.736 So, again, another neuroendocrine
NOTE Confidence: 0.902238968
00:32:11.736 --> 00:32:14.401 tumor and again another instance
NOTE Confidence: 0.902238968
00:32:14.401 --> 00:32:17.507 where it really was a here at Yale.
NOTE Confidence: 0.902238968
00:32:17.510 --> 00:32:20.022 Seeing more and more of a disease process
NOTE Confidence: 0.902238968
00:32:20.022 --> 00:32:22.347 and really relying on our skin cancer,
NOTE Confidence: 0.902238968
00:32:22.350 --> 00:32:24.782 spore and multidisciplinary networks
NOTE Confidence: 0.902238968
00:32:24.782 --> 00:32:27.822 actually build a relatively new
NOTE Confidence: 0.902238968
00:32:27.822 --> 00:32:30.030 program for a rare disease.
NOTE Confidence: 0.902238968
00:32:30.030 --> 00:32:32.460 So I have no disclosures,
NOTE Confidence: 0.902238968
00:32:32.460 --> 00:32:34.427 so today we’ll talk about an update
NOTE Confidence: 0.902238968
00:32:34.427 --> 00:32:35.940 on the incidence, the management,
NOTE Confidence: 0.902238968
00:32:35.940 --> 00:32:38.285 and the treatment of Merkel cell carcinoma.
And then we’ll go into specifically some more recent work that we’ve done looking at our vast experience and benchmarking that against national guidelines, and then briefly I’ll mention some of the new research again supported through the score and through the the great relationships that we have through our skin cancer program.

So. Merkel cell was first described as a true bickler carcinoma of the skin, and it wasn’t until 1978 that it was first coined to even be a neuroendocrine tumor.
However, at that time, thought to be derived from Merkel cells, which is actually not the case. It wasn’t until 2008 that there was the discovery of a Merkel cell polyoma virus which is fairly endemic, as even being a causative factor in. In addition to UV radiation for this disease. And to be quite as we still don’t even know what the cell of origin is, there’s been some hypothesis that this may be from a pre pro fiesel which would fit somewhat with the increased incidence in patients with lymphoma. Other work is focused on dermal stem cells as well as dermal fibroblasts,
but it’s still a work in progress.

As opposed to Melanoma, where we speak about the ABC’s we use our vowels for Merkel cell.

So it’s the AEIOU’s and these are known to be asymptomatic.

They’re not painful.

The big thing with these and how they behave differently is their rate of growth.

When we look at Merkel cell and the ones that I’m showing you here, one is an intransit picture on the right, one is a metastatic picture on the left, and the ones in between are in transit.

Seeing we measure Merkel cells in centimeters versus Melanoma.
00:34:21.425 --> 00:34:23.000 We really measure that in.
NOTE Confidence: 0.6860527

00:34:23.000 --> 00:34:25.540 Millimeters or fractions of millimeters,
NOTE Confidence: 0.6860527

00:34:25.540 --> 00:34:28.222 so this expanding rapidly of a of a non
NOTE Confidence: 0.6860527

00:34:28.222 --> 00:34:30.235 pigmented mass really should open the
NOTE Confidence: 0.6860527

00:34:30.235 --> 00:34:32.798 thought that this could be a Merkel cell.
NOTE Confidence: 0.6860527

00:34:32.800 --> 00:34:35.264 It’s more likely to be found in
NOTE Confidence: 0.6860527

00:34:35.264 --> 00:34:36.880 patients with immunosupression older
NOTE Confidence: 0.6860527

00:34:36.880 --> 00:34:40.240 patients and again can be associated
NOTE Confidence: 0.6860527

00:34:40.240 --> 00:34:43.252 with UV exposure and about if you
NOTE Confidence: 0.6860527

00:34:43.252 --> 00:34:45.436 one looks about 90% of each patient
NOTE Confidence: 0.6860527

00:34:45.436 --> 00:34:47.410 will have more than or equal to
NOTE Confidence: 0.6860527

00:34:47.470 --> 00:34:49.330 three of these characteristics.
NOTE Confidence: 0.828741832857143

00:34:52.090 --> 00:34:53.425 He immunohistological diagnosis
NOTE Confidence: 0.828741832857143

00:34:53.425 --> 00:34:56.095 is always based upon the primary
NOTE Confidence: 0.828741832857143

00:34:56.095 --> 00:35:08.548 skin lesion and generally speaking,
NOTE Confidence: 0.828741832857143

00:35:08.550 --> 00:35:08.830 most patients will present about 50%
of the time with localized disease, 35% with nodal disease,
and about 15% of patients at the time of presentation with metastatic disease and up to 15% can present with an unknown primary.
So as far as management for localized or Merkel cell carcinoma, it really is a surgical disease. So we recommend that we do a wide local excision with one to two centimeter margins when possible, you should perform a Sentinel node biopsy, again, with the caveat being the demographic population who can be high
risk and elderly and may not be the best candidates for general anesthesia. Again, adjuvant radiation, which is very different than Melanoma. Merkel cells are exquisitely sensitive to radiotherapy, and again are much larger. The only times when we really don’t consider radiation again for a given patient would be very small tumors, less than a centimeter, no lymphovascular invasion in the setting of a widely margin. Negative resection. There are times two that if a primary is unable to be respected.
For example, very poor surgical candidate. You could have just local palliative radiation. Similar to Melanoma Sentinel, nodes are important prognostic value. Now, in the case of a clinically positive lymph node, so a patient presents with a lymph node that you can feel. In that case, the recommendation is that we still perform a therapeutic lymph node dissection, and it’s controversial whether or not additional adjuvant radiation therapy is needed in that context.
If someone undergoes a Sentinel lymph node procedure, if it’s positive again, the options are to go further. Surgical treatment. Or to actually undergo radiotherapy again, there’s lots of series that are all retrospective in nature as we have no prospective data looking at this. And again, even if you’re a central node, negative patient, again, fairly controversial radiotherapy. We typically would use here at Yale. There are some centers that still use that, and that really is, for instance,
is particularly in head and neck cancers, where if you thought that your nodal mapping was poor or inaccurate that you could offer that to a patient adjutant therapy currently for Merkel still is just under investigation and actively ongoing clinical trials, including the stamp trial, which we have open at Yale. So for metastatic Merkel cell carcinoma used to be chemotherapy, first line with the topside and platinum agents. Those had very short lived responses, lots of toxicity, so we’re abandoned beginning with two clinical trials that
were completed and published both initially in 2016 and then updated in 2019 and 2020. Looking at pembrolizumab as frontline for metastatic disease with 50% overall response rates, which was. Which is fantastic compared to what we saw historically with chemotherapy and then with PDL. One agents have a limo map with 33% just looking at the overall response rates and this again continues to grow and expand with additional clinical trials focused on immune therapy. So Merkel cell carcinoma is very interesting because of.

The end product of your disease
00:38:31.054 --> 00:38:32.570 looks exactly the same.

00:38:32.570 --> 00:38:35.360 However, there are two completely

00:38:35.360 --> 00:38:36.760 distinct pathophysiology

00:38:36.760 --> 00:38:40.120 underlying the tumorigenesis.

00:38:40.120 --> 00:38:40.915 Interestingly, as well,

00:38:40.915 --> 00:38:42.240 depending on where you live,

00:38:42.240 --> 00:38:43.836 for example, the US and Europe,

00:38:43.840 --> 00:38:46.213 about 20% of Merkel cell carcinomas are

00:38:46.213 --> 00:38:49.314 what we call what we think to be UV related,

00:38:49.320 --> 00:38:51.910 very different.

00:38:51.910 --> 00:38:52.778 Then Australia.

00:38:52.778 --> 00:38:55.816 In in the United States and Europe,

00:38:55.820 --> 00:38:58.790 again we see much more prevalent

00:38:58.790 --> 00:39:00.770 Merkel cell polyomavirus related

00:39:00.847 --> 00:39:02.406 disease and was interested
It's really endemic if you one looks from China to South America, it wouldn't were to swab patients. You know, usually this polyomaviruses found during childhood 60-80% of people will be colonized if you take out a squamous cell or basal cell cancer. And if you look for Merkel cell polyomavirus, you'll see that in up to 25% of those samples. Even though it’s not related to that Physiology, at least that we think. And again, any infection with a polyomaviruses really
asymptomatic and we have patients come in.

They’re very, very concerned that they’re going to give this to their spouse or their partner.

But again, this is not something that that’s really of concern as far as being contagious,

there’s Burley mutations, particularly in RB one,

and those become founder
mutations in P53 and RB-1.

And when we look at the metastases later in patients on autopsy study, we'll see that those are really clonal nature.

However, for virally mediated polyomavirus associated Merkel cell, what you see is actually a critical event where there's viral integration and there's a small and a large T cell antigen and Merkel cell and what happens is that actually gets incorporate actually very close to where the RB gene is and what happens is that.
Along T cell antigen as you look downstream that becomes truncated, it becomes a trophic factor and actually drives further growth of the tumor. Now, the things that are interesting in the UV associated Merkel cell carcinoma. This is very high in neoantigen burden as well as a high overall tumor mutational burden compared to that of the viral one. However, that has a viral T cell antigen expression, and interestingly, the responses to immune therapy are
exactly the same regardless of the etiology.

Why is this important?

You know such a rare cancer is that it's actually growing and you know similar to the the question that was just asked of Doctor Kuntzman Dr. Kunz. We were actually really curious as to why we were seeing this. So this is a multidisciplinary effort really headed by Dan Jacobs, who is now a first year, head and neck. Surgical resident and this was done with myself or medical oncology group. Ben Judson from otolaryngology and Doctor Zhang from the School of Public Health. Really trying to answer the
question so how we underwent this analysis is doing something called an age period cohort analysis, again similar to what’s happening with neuroendocrine tumors and a lot of other cancers. Even thyroid cancer. When we’re seeing increasing incidence, you want to say is this related to aging of the population which is? Really important for Merkel cell or as it related to the calendar period of diagnosis and the calendar period effect really is looking at well, are we better at detecting this?
Are we more aware of the diagnosis and so that will affect equally affect people across all ages and then the last thing is really really important is the birth cohort and that really says are there real changes in risk factors? Is there something actually changing in the environment that’s explaining the increase in incidence that we’re seeing? In Merkel cell, we thought that this was a really important analysis to be done. Even though this is a rare disease, so we were able to do is we looked and use SEER data and we’re able to get it over 3700 patients again.
We saw what one would expect. Again, this is usually a male dominated disease, almost exquisite, almost exclusively found in Caucasians this year. Registry data becomes a little tricky 'cause it just turns out by chance that the areas that are actually involved in this year registry happen to be some of the higher volume. Tertiary referral centres from Merkel cell in the country so you know that that data was a little difficult to interpret,
but again, we saw you know, head and neck primarily again just what we would expect to see localized regional disease. But the APC analysis itself. What you can see here in panel A is what you would expect. So if we look at by the calendar period of diagnosis, right so that the the time that we’ve diagnosed and we look at age older patients, particularly with improving diagnostics, were seen in more age adjusted incidence rates happening. And we see that in men and women. More interestingly,
if you look at panel C&D,

when we look at the birth cohort effect now,

compared by age and having looking

at the age adjusted incidence,

they’re still seeing actually an important

association due to the birth cohort,

which really points to that.

Despite that,

we’re better and more aware of diagnosing Merkel cell and that we know that this is a disease that’s more prevalent in the aging population,

that’s an environmental risk factor,
although we don’t know what that is.

So and again, this is just part of the conclusions of that paper.

Once again, just saying that the effect of how good we are at diagnosing this is really leveling out, yet the incidence is still going up. And that’s not just explained by that.

The aging of the population.

So the second thing that I wanted to show again is some original work again put together by our multidisciplinary team here at Yale.

Looking at our near 20 year experience taking care of this disease.
Put together.
The registry really brought together by Andrew Esposito who’s one of our general surgery residents as well as Dan Jacobs who had worked on the other APC cohort analysis paper. And they really built this up. And then with the support of our Yale spore program, is also now the registry, being maintained by Ray Bowman, who who is a wonderful and really helps us with even our Melanoma program. So again, when we look at just our. 20 year Yale experience.
What we see are similar clinical pathologic features to what one would find at other centers when we look at the cause of death. What we see is only about 36% of our patients that we see are actually dying from Merkel cell. We see them recurring at rates that are similar to other centers. We do have a little bit more of an enriched in transit population, which may be due to how things are referred to us all. Even when we see patients who presented with de Novo disease, I do see more intransit disease.
than what I would expect if one were to compare that to Melanoma, and I think that Merkel cell does have very different biologic behavior. Again, when we look at our final pathologic stage again. We’re seeing similar presentation as to what we would be seeing around the country at high volume centers. So the trends in treatment again with newer approvals, there’s been very quick adoption of increasing frequency of immunotherapy for systemic therapy for patients who
are eligible with the concomitant decrease in chemotherapy.

The radiation therapy. Again, some of this, I think, is that we’re having more patients who have better systemic treatment options. And some of the earlier patients who are seen because I think of improved recognition amongst the dermatologic community in the state. So I think that that explains a little bit of this decrease in the radiation receipt. But again, if we look at our initial nodal management. We’re right on par with where
we would expect our group to be. And our management is following yet again, national Trends 1 looks at surgical resection rates. The rates in which you’re appropriately staging patients, nodal basins and those patients who are receiving non-surgical management. Again, what we’re seeing here. And this is the data that we had pulled from SEER is. We’re very much on target with where we would expect our program to be, and in aligned with what’s going on or across the nation in high volume centers.
But one thing that started to bother me, the more that I learned about Merkel cell, we thought it was a great opportunity when we were looking at our institutional series was there's many, many, many papers that were being published as retrospective series and they were really solely using overall survival as their outcome measure. We said, you know, this doesn't really sound right. We think there's competing causes of mortality. We had done our APC cohort analysis.
We know that age was driving a lot of this, so we said which you know no one had looked just for this specific disease before as we said. Does this make any sense? Should people be writing retrospective papers using things like the NCDB which doesn’t have disease specific survival in it and writing you know how we should be managing a rare cancer? And the answer you know as you can see here nicely illustrated is we really shouldn’t. So if one looks at by age.
if we break this down.

Patients who are 64, which is young for Merkel cell up until about two years or so, right? Those patients and even up to three years. Those patients are actually dying from their Merkel cell. When we get to the more extremes of care, your patients beginning at age 65 to 74, but particularly those about 75. Many of those patients, and again, we’re talking about patients who are immunosuppressed. They’re actually not dying from Merkel cell, so it just makes us pause and say,
you know, we just need to be very, particularly on these retrospective data. How we’re looking at it. So again, because we had our own cohort where we could look at recurrence disease, specific survival and overall survival. We said, we said, let’s take a look at that in our own cohort and what things that we saw that were associated with overall survival. Again, what you would expect age
female sex was protective.
If you are immunocompromised again, you know it makes sense that your mortality would be affected by that. It more advanced disease.
If you’ve had in transit disease, but usually if it’s really related to the disease.
One of the things that your overall and then your disease specific survival really should.
Sorry guys, should really actually match up and hear the disease. Specific survival and those factors for overall survival
NOTE Confidence: 0.886165911666667
00:50:23.576 --> 00:50:25.670 are actually quite discordant.
NOTE Confidence: 0.886165911666667
00:50:25.670 --> 00:50:27.728 The things when we look at
NOTE Confidence: 0.886165911666667
00:50:27.728 --> 00:50:28.757 disease specific survival,
NOTE Confidence: 0.886165911666667
00:50:28.760 --> 00:50:31.024 the thing that stood out the most was
NOTE Confidence: 0.886165911666667
00:50:31.024 --> 00:50:32.887 actually patients who were active smokers.
NOTE Confidence: 0.886165911666667
00:50:32.890 --> 00:50:35.515 With the hazard ratio up to 14,
NOTE Confidence: 0.886165911666667
00:50:35.520 --> 00:50:36.884 which actually hadn’t been
NOTE Confidence: 0.886165911666667
00:50:36.884 --> 00:50:37.566 but subsequently there’s been one or two
NOTE Confidence: 0.886165911666667
00:50:39.782 --> 00:50:42.158 papers which have also echoed this finding.
NOTE Confidence: 0.886165911666667
00:50:42.160 --> 00:50:43.216 But really,
NOTE Confidence: 0.886165911666667
00:50:43.216 --> 00:50:45.328 some discrepancy and again,
NOTE Confidence: 0.886165911666667
00:50:45.330 --> 00:50:48.780 our institutional cohort is limited
NOTE Confidence: 0.886165911666667
00:50:48.780 --> 00:50:50.530 because we don’t have thousands of patients,
NOTE Confidence: 0.886165911666667
00:50:50.530 --> 00:50:52.522 we only have hundreds.
NOTE Confidence: 0.886165911666667
But again, it really made us almost add an editorial to the paper itself, which then was published in the Annals of Surgical Oncology. So the overall conclusions are the surgical and the medical management continue to evolve particularly of immune therapy. For our paper. What we found was that there was little consistency between factors associated with overall and disease specific survival for Merkel cell carcinoma patients. And, as I mentioned,
competing risk for mortality, particularly these older or immunosuppressed Merkel cell patients makes the use of overall survival poor surrogate for therapeutic outcomes, particularly these retrospective analysis. And there are hundreds of papers that I think that this statement applies to. So moving forward, I think that as a Community it would for these rare diseases we really need to get more work together for more prospective data.

And then just finally and then I'll pause for questions I just wanted to
just briefly highlight just one segue into some of the translational research. Again, that’s been aided with the skin cancer score. So again, we have we talk about a similar disease with two separate ideologies, almost similar to some of what we see now with HPV related tumors. You can have squamous cell tumors of the head and neck, summer virally, associated summer, non virally associated in UV. So a lot of work that’s been done in other fields and now seeing that there’s response to immune therapy really allows you to look at things scientifically in a very,
very interesting way where you can see viral associated non viral associated.
And see what are the resistance patterns that can develop in both and. We had looked at this again. You know, again, immune therapy being used. But again when we’re looking at resistance, there’s work that’s been headed by Jeffy, Shizuka and Jessica Way, and now Alex Frey, who’s a surgical resident in Jeff’s lab, is really looking at novel ways that we can take fresh tissue. Again,
Melanoma program with the score and really looking at these different conditions and then getting really great data, even unlimited samples, and. And this is work that that Jeff has has been doing with myself and others, and really pushing forward again. But all of our data is too preliminary to kind of show in a setting like this, but I'd like to say that maybe a year or two from now that we may have new targets or new ways that we could look at things ex vivo to make better targeted treatment for these patients. So again,
thank you everyone for your time, and I'll pause for questions.

Well, thank you Kelly. Very interesting.

I'll start with a question.

While people are gathering their own questions.

Is there any prospect for a vaccine against Merkel cell virus?

I know it's a relatively rare disease which is going to make that difficult, but with new technology, maybe not so crazy.

So it's a great question.
So for the polyoma virus itself, it doesn’t make sense to make a virus, but you know it sounds like you’ve been listening into Jeff and his research meetings. You know with some of the new technologies that we’ve seen with COVID vaccination and so forth, there may be a role for development because there are T cell antigens with this similar to something like HPV where there may be ways that you can do combination of a vaccination. Approach almost similar to wait Akiko Iwasawa’s doing with the cervical cancer.
So I think that that would be a great field. And if there's any experts that want to work with Jeff and I just give me an email.

OK, great so there are some questions in the chat. Do you want to? Can you read them or do you want me to read them? Uhm? Insights into the differences in biology in the younger patients. So the patients I I worry about patients particularly who are less than 60 years old, and if those patients who are less than 40 years old, you almost want to double check that you have the right diagnosis.
So as you’re seeing from part of that analysis that we looked at between mortality and overall survival. Again, anecdotally, I think that the disease is more aggressive. I think we may see more metastatic disease. You don’t have to relook at. Look at that specifically, but there’s something different. To have that earlier and again, these younger patients that we’re seeing them in interesting, they’re not immunocompromised.
is there a specific tissue or reservoir for the virus? Among many people who have it. It’s just on the skin. It’s good. There’s some plot, and there may be some reservoir also in the GI tract, but usually it’s a conventional skin flora. Unfortunately we’re not able to answer that question we’re creating, hopefully a TMI. We’re trying to get that together.
because there wasn’t a difference in how patients were treated.

They historically at Yale.

The immunohistochemistry stain for the polyoma virus in Merkel cells wasn’t done, but we’re very close to having all of that put together to start looking at that clinically.

And like I said retrospectively, we’re hoping to be able to look at that.

And or HIV patients that increase risk. Of this tumor, not if they’re well controlled, so more are CML patients.

I worry about those, and then probably just general Immunosenescence is
probably important post transplant.

We don’t see their higher risk for Merkel, but you know.

Again, it’s a rare tumor, so we don’t see this as much as we see horrible, poorly differentiated cutaneous squamous cells.

You know, that’s usually what we’re worrying and battling more with these patients, but we do see it more often in the transplant patients.

Perfect. Are there other questions?

If not, I’ll thank you very much. You’re very interesting.
talk actually to both speakers,
and we’ve learned a lot about
neuroendocrine tumors today. Thank you.