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. I can switch here.
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 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, and 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 can 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.
I'm going to go into a little bit more detail on this. Up on the top we see that there are actually 3 new novel imaging modalities, three types of PET scans with different radioisotopes. Those have really completely replaced the use of octreoscan, so it's been an exciting time to be in the field. I'd like to also really dispel the myth that Nets are really that rare, 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 yellow is the incidence of Nets the corresponding Y axis is on the left, 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, meaning the number of patients
alive at any
given time and the net prevalence actually
exceeds that of stomach and pancreatic
so I think it's a bigger public health problem.
Many primary care,
general oncologists will see these patients.
Nets are epithelial neoplasms that
are derived from neuroendocrine
cells throughout the body.
As Dan said, I may officially
a card carrying GI oncologist,
but they do in fact happen throughout
the body GI tract most commonly
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
00:05:26.262 --> 00:05:29.191 of this in terms of diagnostics and therapeutics and we’ll talk about that also.

00:05:32.220 --> 00:05:33.730 And just a brief mention, this is a really cursory overview of net biology,

00:05:35.902 --> 00:05:39.630 but I did want to to bring this in large scale.

00:05:41.236 --> 00:05:43.788 Chromosomal alterations are common.

00:05:43.790 --> 00:05:46.894 Tumor mutation burden is low in the net,

00:05:46.900 --> 00:05:49.066 so that’s the lower grade grade 1/2 nor underprint tumors.

00:05:50.510 --> 00:05:53.270 It’s higher in neuroendocrine carcinomas,

00:05:53.270 --> 00:05:55.958 that’s the Grade 3 or poorly differentiated recurrent somatic

00:05:57.256 --> 00:05:58.948 mutations are actually rare.
There have been a number of fairly recent studies. So in pancreatic net, we will say somatic mutations in MN dachsund 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, as 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 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 telangiectasia shown in the picture on the left.

Patients are often misdiagnosed as having rosacea.

They can have diarrhea, bronchospasm.

Valvular fibrosis,
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 WHI 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,

so for one example,

sunitinib is only approved for pancreatic Nets,

not for other primary sites.

And then lastly of these characteristics,

somatostatin receptor,

is our newest characteristic that matters.

This is just a really nice example of

this same patient who had an octreoscan,

so that’s our older imaging tool.

It required patients coming back
two days in a row,

and then our newer gallium 68 dotatate

pet that has much higher resolution.

I’ll just highlight a couple
NOTE Confidence: 0.839235135882353
00:12:26.470 --> 00:12:27.310 of interesting points,
NOTE Confidence: 0.839235135882353
00:12:27.310 --> 00:12:29.242 so the pituitary gland is normally
NOTE Confidence: 0.839235135882353
00:12:29.242 --> 00:12:31.398 a little bit positive on this as is.
NOTE Confidence: 0.839235135882353
00:12:31.400 --> 00:12:34.328 Be or as are the liver has
NOTE Confidence: 0.839235135882353
00:12:34.328 --> 00:12:35.180 some normal background,
NOTE Confidence: 0.839235135882353
00:12:35.180 --> 00:12:36.674 but then spleen and that it’s
NOTE Confidence: 0.839235135882353
00:12:36.674 --> 00:12:37.670 concentrated in the latter.
NOTE Confidence: 0.934096590625
00:12:39.840 --> 00:12:42.324 So just a brief overview of what we have
NOTE Confidence: 0.934096590625
00:12:42.324 --> 00:12:44.919 in terms of tools for hormone control.
NOTE Confidence: 0.934096590625
00:12:44.920 --> 00:12:47.488 So somatostatin analogs are the mainstay
NOTE Confidence: 0.934096590625
00:12:47.488 --> 00:12:50.499 of how we treat functional Nets,
NOTE Confidence: 0.934096590625
00:12:50.500 --> 00:12:51.727 primarily carcinoid syndrome.
NOTE Confidence: 0.934096590625
00:12:51.727 --> 00:12:54.590 There are two approved agents in the
NOTE Confidence: 0.934096590625
00:12:54.652 --> 00:12:57.116 United States, octreotide and lanreotide.
NOTE Confidence: 0.934096590625
00:12:57.116 --> 00:13:00.840 These are both approved for hormone control.
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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 pass rate is a third form. 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, diarrhea, 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.

00:13:50.120 --> 00:13:51.320 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.

00:13:53.950 --> 00:13:55.280 There are a number of tools for tumor control. They fall into four categories, somatostatin analogs, biologics, cytotoxic chemotherapy, and 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
00:14:42.448 --> 00:14:44.488 Cogen the national clinical trial

00:14:44.488 --> 00:14:46.534 network as a fellow and junior faculty it was a great opportunity

00:14:49.056 --> 00:14:50.964 for networking and mentorship.

00:14:50.970 --> 00:14:53.140 Through that I helped to develop this randomized study for patients with progressive, metastatic pancreatic Nets.

00:14:56.891 --> 00:15:01.920 Grade one and two half received 10s Olumide alone and half received capecitabine and Thomas Alameda.

00:15:03.700 --> 00:15:04.137 Together, the maximum duration was 13 cycles

00:15:08.540 --> 00:15:11.675 and the primary endpoint was progression free survival.
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. 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 to one to receive 4 administrations. Ivy of 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
initial publication.

It’s since has been reported actually.

Just ask, oh,

this year it did not officially meet statistical significance,

but was a clinical difference.

So on the basis of this study,

this was FDA approved in January of 2018.

It was really fun to be part of a process of kind of a novel class getting FDA approved,

and then the clinical implementation of that.

I’d also like to sort of 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 those are pursuing that in later phase.

Committees PEN 221 is a peptide drug conjugate with DM.
not have a modest benefit rate.

No PR's, but had an 88% on stable disease rate to do to Mab is a Sonata Staten receptor 2 CD 3 bispecific antibody also just completed a phase one study.

Modest response rates but hadn’t had a 55. Percent stable disease rate.

I’ll just mention I didn’t go into detail in this today, but single agent checkpoint inhibitors do not work in low grade nor consumers. So the idea of trying to use combination approaches is very attractive and then led to 12 dot M.
Tate is an alpha emitter.

PRT alpha emitters are felt to be.

I'm having fewer side effects and have more tumor cell killing.

This just completed a phase one trial.

They just reported some early results, so in their first ten patients there was a response rate of 80%. So we are all very excited about the idea of alpha emitters, and so stay tuned on that.

And then I did a tweet Oriel kind of on this medicine receptors as 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?

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 is the National Cancer Institute.
NOTE Confidence: 0.873074789230769
00:22:52.640 --> 00:22:54.775 Under Consumer task force that I chair,
NOTE Confidence: 0.873074789230769
00:22:54.780 --> 00:22:57.055 I had the opportunity to lead a
NOTE Confidence: 0.873074789230769
00:22:57.055 --> 00:22:58.415 clinical trial planning meeting
NOTE Confidence: 0.873074789230769
00:22:58.415 --> 00:22:59.790 this past year with.
NOTE Confidence: 0.873074789230769
00:22:59.790 --> 00:23:02.190 The objective was to really think
NOTE Confidence: 0.873074789230769
00:23:02.190 --> 00:23:04.500 about treatment in the era of PRT.
NOTE Confidence: 0.873074789230769
00:23:04.500 --> 00:23:06.380 I'll bring you down to the bottom here.
NOTE Confidence: 0.873074789230769
00:23:06.380 --> 00:23:07.960 Our deliverables are in manuscript
NOTE Confidence: 0.873074789230769
00:23:07.960 --> 00:23:09.224 that is in process.
NOTE Confidence: 0.873074789230769
00:23:09.224 --> 00:23:11.748 But really the deliverables are clinical
NOTE Confidence: 0.873074789230769
00:23:11.748 --> 00:23:13.820 trials and so we now out of this.
NOTE Confidence: 0.810262798333333
00:23:13.820 --> 00:23:17.812 Like many month process have a PRT re
NOTE Confidence: 0.810262798333333
00:23:17.812 --> 00:23:20.271 treatment clinical trial started or
NOTE Confidence: 0.810262798333333
00:23:20.271 --> 00:23:21.748 in development I should say and then
NOTE Confidence: 0.810262798333333

41
we have working groups on looking at.

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
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,

00:26:13.000 --> 00:26:16.336 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

NOTE Confidence: 0.929551083571429
00:26:37.454 --> 00:26:40.058 completed a really wonderful JCO oncology
NOTE Confidence: 0.929551083571429
00:26:40.058 --> 00:26:42.270 practice review so please join us we
NOTE Confidence: 0.929551083571429
00:26:42.270 --> 00:26:44.539 have on Thursdays I’d like to highlight it.
NOTE Confidence: 0.929551083571429
00:26:44.540 --> 00:26:46.248 We have a great.
NOTE Confidence: 0.929551083571429
00:26:46.248 --> 00:26:48.383 In our series on Thursday
NOTE Confidence: 0.929551083571429
00:26:48.383 --> 00:26:50.349 afternoons from 4:15 to 5:00,
NOTE Confidence: 0.929551083571429
00:26:50.350 --> 00:26:52.126 and I think I’ll end there.
NOTE Confidence: 0.929551083571429
00:26:52.130 --> 00:26:53.786 So, you know, we’re really excited
NOTE Confidence: 0.929551083571429
00:26:53.786 --> 00:26:54.890 about building this program.
NOTE Confidence: 0.929551083571429
00:26:54.890 --> 00:26:56.546 I think our next step is
NOTE Confidence: 0.929551083571429
00:26:56.546 --> 00:26:58.728 really building on some of the
NOTE Confidence: 0.929551083571429
00:26:58.728 --> 00:27:00.249 translational research opportunities,
NOTE Confidence: 0.929551083571429
00:27:00.250 --> 00:27:00.880 so thanks.
NOTE Confidence: 0.86450185
00:27:02.030 --> 00:27:03.690 Thank you, Pam. Very exciting.
NOTE Confidence: 0.86450185
00:27:03.690 --> 00:27:05.820 Particularly these tremendous
NOTE Confidence: 0.86450185
00:27:05.820 --> 00:27:07.950 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
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, and as I was sharing with you, I think that in this particular field the bar is pretty low.

The 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?

Yes. Had a dominant features of
non STR Nets biologically and clinically compared to those that are somatostatin receptor positive, so that’s another great question.

I would say typically the patients who are noncitizen receptor avid have more aggressive disease. They tend to have lost.

That’s in Edison receptor as they differentiate, so it usually are the grade 3 poorly differentiated in order consumers. I’m as I mentioned, we can see great evolution over time,

so sometimes a patient who may have
00:29:50.200 --> 00:29:51.950 initially been SSTR positive can lose.

NOTE Confidence: 0.92802095

00:29:51.950 --> 00:29:52.190 That

NOTE Confidence: 0.882307798333333

00:29:54.140 --> 00:29:56.858 and another question are there supportive services unique for this population?

NOTE Confidence: 0.882307798333333

00:29:56.860 --> 00:29:59.510 services unique for this population?

NOTE Confidence: 0.633058035

00:30:01.550 --> 00:30:04.928 So so yes, and I actually,

NOTE Confidence: 0.633058035

00:30:04.930 --> 00:30:07.009 I’m really eager to work Terrace Hampton.

NOTE Confidence: 0.633058035

00:30:07.010 --> 00:30:08.270 I have talked some about this,

NOTE Confidence: 0.633058035

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,

NOTE Confidence: 0.633058035

00:30:10.106 --> 00:30:12.139 I think, I think,

NOTE Confidence: 0.633058035

00:30:12.139 --> 00:30:14.383 the chronicity of their survivorship issues, I think,

NOTE Confidence: 0.633058035

00:30:14.390 --> 00:30:15.990 is a really unique aspect that we need to pay more attention to.

NOTE Confidence: 0.633058035

00:30:15.990 --> 00:30:17.220 we need to pay more attention to.

NOTE Confidence: 0.633058035

00:30:17.220 --> 00:30:20.126 we need to pay more attention to.

NOTE Confidence: 0.633058035

00:30:20.130 --> 00:30:22.178 So hopefully we’ll have

NOTE Confidence: 0.633058035

00:30:22.178 --> 00:30:23.714 more dedicated services.
And 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 condition 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 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, is a neuroendocrine tumor with the virus association, which makes it interesting to me.
So I'm very interested in hearing what Kelly has to say.

OK, it looks good.

Great thank you.

So, again, another neuroendocrine tumor and again another instance where it really was a here at Yale.

Seeing more and more of a disease process and really relying on our skin cancer, spore and multidisciplinary networks actually build a relatively new program for a rare disease.

So I have no disclosures, so today we'll talk about an update on the incidence, the management, 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 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 know what the cell of origin is, there’s been some hypothesis that this may be from a pre pro fiesel which 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 about when we look at Merkel cell and the ones that I’m showing you here, one is an intransit picture on the right, and the other ones which are seeing we measure Merkel cells in centimeters versus Melanoma.
We really measure that in millimeters or fractions of millimeters, so this expanding rapidly of a non pigmented mass really should open the thought that this could be a Merkel cell. It's more likely to be found in patients with immunosupression older patients and again can be associated with UV exposure and about if you one looks about 90% of each patient will have more than or equal to three of these characteristics. He immunohistological diagnosis is always based upon the primary skin lesion and generally speaking, most patients will present about 50%
00:35:00.830 --> 00:35:03.626 of the time with localized disease,

NOTE Confidence: 0.828741832857143

00:35:03.630 --> 00:35:05.202 35% with nodal disease,

NOTE Confidence: 0.828741832857143

00:35:05.202 --> 00:35:07.374 and about 15% of patients at

NOTE Confidence: 0.828741832857143

00:35:07.374 --> 00:35:09.104 the time of presentation with

NOTE Confidence: 0.828741832857143

00:35:09.104 --> 00:35:11.850 metastatic disease and up to 15%

NOTE Confidence: 0.828741832857143

00:35:11.850 --> 00:35:13.638 can present with an unknown primary.

NOTE Confidence: 0.88831801

00:35:16.000 --> 00:35:19.570 So as far as management for

NOTE Confidence: 0.88831801

00:35:19.570 --> 00:35:21.819 localized or Merkel cell carcinoma,

NOTE Confidence: 0.88831801

00:35:21.819 --> 00:35:23.937 it really is a surgical disease.

NOTE Confidence: 0.88831801

00:35:23.940 --> 00:35:26.268 So we recommend that we do a wide

NOTE Confidence: 0.88831801

00:35:26.268 --> 00:35:28.408 local excision with one to two

NOTE Confidence: 0.88831801

00:35:28.408 --> 00:35:29.896 centimeter margins when possible,

NOTE Confidence: 0.88831801

00:35:29.900 --> 00:35:32.455 you should perform a Sentinel node biopsy,

NOTE Confidence: 0.88831801

00:35:32.460 --> 00:35:34.992 again, with the caveat being the

NOTE Confidence: 0.88831801

00:35:34.992 --> 00:35:37.329 demographic population who can be high

NOTE Confidence: 0.88831801

63
00:35:37.329 --> 00:35:39.633 risk and elderly and may not be the
NOTE Confidence: 0.88831801
00:35:39.704 --> 00:35:42.319 best candidates for general anesthesia.
NOTE Confidence: 0.88831801
00:35:42.320 --> 00:35:43.610 Again, adjuvant radiation,
NOTE Confidence: 0.88831801
00:35:43.610 --> 00:35:46.190 which is very different than Melanoma.
NOTE Confidence: 0.88831801
00:35:46.190 --> 00:35:47.950 Merkel cells are exquisitely
NOTE Confidence: 0.88831801
00:35:47.950 --> 00:35:49.270 sensitive to radiotherapy,
NOTE Confidence: 0.88831801
00:35:49.270 --> 00:35:50.950 and again are much larger.
NOTE Confidence: 0.88831801
00:35:50.950 --> 00:35:53.365 The only times when we really don’t
NOTE Confidence: 0.88831801
00:35:53.365 --> 00:35:55.363 consider radiation again for a given
NOTE Confidence: 0.88831801
00:35:55.363 --> 00:35:57.163 patient would be very small tumors,
NOTE Confidence: 0.88831801
00:35:57.170 --> 00:36:00.346 no lymphovascular invasion in
NOTE Confidence: 0.88831801
00:36:00.346 --> 00:36:02.368 the setting of a widely margin.
NOTE Confidence: 0.88831801
00:36:02.370 --> 00:36:03.088 Negative resection.
NOTE Confidence: 0.88831801
00:36:03.088 --> 00:36:05.601 There are times two that if a
NOTE Confidence: 0.88831801
00:36:05.601 --> 00:36:07.658 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,
00:37:10.890 --> 00:37:12.885 is particularly in head and neck cancers,
00:37:12.890 --> 00:37:15.249 where if you thought that your nodal
00:37:15.249 --> 00:37:17.314 mapping was poor or inaccurate that
00:37:17.314 --> 00:37:19.624 you could offer that to a patient
00:37:19.630 --> 00:37:21.770 adjutant therapy currently for Merkel
00:37:21.770 --> 00:37:24.416 still is just under investigation and
00:37:24.416 --> 00:37:26.200 actively ongoing clinical trials,
00:37:26.200 --> 00:37:27.248 including the stamp trial,
00:37:27.248 --> 00:37:28.820 which we have open at Yale.
00:37:31.230 --> 00:37:33.690 So for metastatic Merkel cell carcinoma
00:37:33.690 --> 00:37:35.984 used to be chemotherapy, first line
00:37:35.984 --> 00:37:37.946 with the topside and platinum agents.
00:37:37.950 --> 00:37:40.986 Those had very short lived responses,
00:37:40.990 --> 00:37:44.668 lots of toxicity, so we’re abandoned
00:37:44.668 --> 00:37:47.986 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 distinct pathophysiology underlying the tumorigenesis.

00:38:40.120 --> 00:38:40.915 Interestingly, as well, depending on where you live, for example, the US and Europe,

00:38:43.840 --> 00:38:46.213 about 20% of Merkel cell carcinomas are what we call what we think to be UV related,

00:38:46.213 --> 00:38:51.910 very different.

00:38:51.910 --> 00:38:55.816 In the United States and Europe, 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
again about this polyomavirus.

It’s really endemic if you look 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 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,

Again, we don't know what the cell of origin is.

However, what we know is that there's Burley mutations,

particularly in RB one,

and those become founder
00:40:00.618 --> 00:40:03.208 mutations in P53 and RB-1.
NOTE Confidence: 0.873954812222222

00:40:03.210 --> 00:40:05.884 And when we look at the metastases
NOTE Confidence: 0.873954812222222

00:40:05.890 --> 00:40:08.686 later in patients on autopsy study,
NOTE Confidence: 0.873954812222222

00:40:08.690 --> 00:40:10.390 we'll see that those are
NOTE Confidence: 0.873954812222222

00:40:10.390 --> 00:40:11.410 really clonal nature.
NOTE Confidence: 0.873954812222222

00:40:11.410 --> 00:40:12.102 However,
NOTE Confidence: 0.873954812222222

00:40:12.102 --> 00:40:14.870 for virally mediated polyomavirus
NOTE Confidence: 0.873954812222222

00:40:14.870 --> 00:40:16.946 associated Merkel cell,
NOTE Confidence: 0.873954812222222

00:40:16.950 --> 00:40:19.426 what you see is actually a critical
NOTE Confidence: 0.873954812222222

00:40:19.426 --> 00:40:21.066 event where there's viral integration
NOTE Confidence: 0.873954812222222

00:40:21.066 --> 00:40:23.122 and there's a small and a large
NOTE Confidence: 0.873954812222222

00:40:23.122 --> 00:40:24.646 T cell antigen and Merkel cell
NOTE Confidence: 0.873954812222222

00:40:24.701 --> 00:40:26.729 and what happens is that actually
NOTE Confidence: 0.873954812222222

00:40:26.729 --> 00:40:28.081 gets incorporate actually very
NOTE Confidence: 0.873954812222222

00:40:28.090 --> 00:40:30.850 close to where the the RB 1 gene
NOTE Confidence: 0.873954812222222

00:40:30.850 --> 00:40:33.487 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 a 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?
00:42:14.330 --> 00:42:16.178 Are we more aware of the diagnosis
NOTE Confidence: 0.894604984615385
00:42:16.178 --> 00:42:18.364 and so that will affect equally affect
NOTE Confidence: 0.894604984615385
00:42:18.364 --> 00:42:20.735 people across all ages and then the
NOTE Confidence: 0.894604984615385
00:42:20.735 --> 00:42:22.595 last thing is really really important
NOTE Confidence: 0.894604984615385
00:42:22.595 --> 00:42:24.718 is the birth cohort and that really
NOTE Confidence: 0.894604984615385
00:42:24.718 --> 00:42:27.290 says are there real changes in risk factors?
NOTE Confidence: 0.894604984615385
00:42:27.290 --> 00:42:29.546 Is there something actually changing in
NOTE Confidence: 0.894604984615385
00:42:29.546 --> 00:42:31.433 the environment that’s explaining the
NOTE Confidence: 0.894604984615385
00:42:31.433 --> 00:42:34.377 increase in incidence that we’re seeing?
NOTE Confidence: 0.894604984615385
00:42:34.349 --> 00:42:36.610 In Merkel cell,
NOTE Confidence: 0.894604984615385
00:42:34.349 --> 00:42:36.610 we thought that this was a really
NOTE Confidence: 0.894604984615385
00:42:36.680 --> 00:42:38.660 important analysis to be done.
NOTE Confidence: 0.894604984615385
00:42:38.660 --> 00:42:41.068 Even though this is a rare disease,
NOTE Confidence: 0.894604984615385
00:42:41.070 --> 00:42:43.464 so we were able to do is we looked
NOTE Confidence: 0.894604984615385
00:42:43.464 --> 00:42:45.622 and use SEER data and we’re able
NOTE Confidence: 0.894604984615385
00:42:45.622 --> 00:42:48.123 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.
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,
00:43:52.842 --> 00:43:54.884 if you look at panel C&D,
NOTE Confidence: 0.894604984615385
00:43:54.884 --> 00:43:58.340 when we look at the birth cohort effect now,
NOTE Confidence: 0.894604984615385
00:43:58.340 --> 00:44:00.488 compared by age and having looking
NOTE Confidence: 0.894604984615385
00:44:00.488 --> 00:44:02.660 at the age adjusted incidence,
NOTE Confidence: 0.894604984615385
00:44:02.660 --> 00:44:05.168 they’re still seeing actually an important
NOTE Confidence: 0.894604984615385
00:44:05.168 --> 00:44:07.750 association due to the birth cohort,
NOTE Confidence: 0.894604984615385
00:44:07.750 --> 00:44:09.180 which really points to that.
NOTE Confidence: 0.894604984615385
00:44:09.180 --> 00:44:09.830 Despite that,
NOTE Confidence: 0.894604984615385
00:44:09.830 --> 00:44:12.430 the that we’re better and more aware of
NOTE Confidence: 0.914520824482759
00:44:12.500 --> 00:44:14.414 diagnosing Merkel cell and that we
NOTE Confidence: 0.914520824482759
00:44:14.414 --> 00:44:16.904 know that this is a disease that’s
NOTE Confidence: 0.914520824482759
00:44:16.904 --> 00:44:19.196 more prevalent in the aging population,
NOTE Confidence: 0.914520824482759
00:44:19.200 --> 00:44:21.546 there does appear to be something
NOTE Confidence: 0.914520824482759
00:44:21.546 --> 00:44:23.256 that has changed. Overtime,
NOTE Confidence: 0.914520824482759
00:44:23.256 --> 00:44:25.936 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 on 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.

And once again, this is work.
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,

trends looks at surgical resection rates.

The rates in which you’re appropriately staging patients,

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. There were many papers that were being published as retrospective series and they were solely using overall survival as their outcome measure. We thought, you know, this doesn’t really sound right. 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, right? 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 careful, 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, well, 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
dspecific survival really should.

Sorry guys,
should really actually match
up and hear the disease.
Specific survival and those
factors for overall survival
are actually quite discordant.
The things when we look at disease specific survival,
the thing that stood out the most was actually patients who were active smokers.
With the hazard ratio up to 14,
which actually hadn’t been previously described,
but subsequently there’s been one or two papers which have also echoed this finding.
But really,
some discrepancy and again,
our institutional cohort is limited because we don’t have thousands of patients,
we only have hundreds.
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 with the utilization, 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, building upon our strengths in our
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 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, they’re probably.

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 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 re look at. Look at that specifically, but there’s certain thing that’s driving that in a different way. To have that earlier and again, these younger patients that we’re seeing them in interesting, they’re not immunocompromised.
00:55:46.400 --> 00:55:48.540 is there a specific tissue
NOTE Confidence: 0.652937554
00:55:48.540 --> 00:55:50.680 or reservoir for the virus?
NOTE Confidence: 0.652937554
00:55:50.680 --> 00:55:52.390 Among many people who have it.
NOTE Confidence: 0.935801606
00:55:53.050 --> 00:55:57.790 It’s just on the skin. It’s good.
NOTE Confidence: 0.935801606
00:55:57.790 --> 00:55:59.666 There’s some plot, and there may be
NOTE Confidence: 0.935801606
00:55:59.666 --> 00:56:01.308 some reservoir also in the GI tract,
NOTE Confidence: 0.935801606
00:56:01.310 --> 00:56:04.068 but usually it’s a conventional skin flora.
NOTE Confidence: 0.817917780526316
00:56:06.600 --> 00:56:07.896 Brenda emails asked overtime.
NOTE Confidence: 0.817917780526316
00:56:07.896 --> 00:56:10.224 Is there a difference in the proportion
NOTE Confidence: 0.817917780526316
00:56:10.224 --> 00:56:12.808 of cases at a UV versus virus associated?
NOTE Confidence: 0.809017882
00:56:14.390 --> 00:56:15.880 So from our own cohort,
NOTE Confidence: 0.809017882
00:56:15.880 --> 00:56:17.995 unfortunately we’re not able to
NOTE Confidence: 0.809017882
00:56:17.995 --> 00:56:20.110 answer that question we’re creating,
NOTE Confidence: 0.809017882
00:56:20.110 --> 00:56:21.154 hopefully a TMI.
NOTE Confidence: 0.809017882
00:56:21.154 --> 00:56:23.242 We’re trying to get that together
NOTE Confidence: 0.809017882
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.