So welcome everyone, my name is Doctor Pamela Koons and I am a GI medical oncologist. I am the director of the Center for Gastrointestinal Cancers at Yale Cancer Center and Smilow Cancer Hospital. This is our kickoff for our spring CME series. For the Center for GI cancers we are starting tonight on neuroendocrine tumors and I will be your host on Thursday, April 21st. We will have a CME on rectal cancer.
hosted by Doctor Michael Cicchini, and on Thursday, May 19th. We will have a CME on gastric cancers hosted by Doctor Jill Lacy. So this evening I have the pleasure of hosting and moderating this talk on neuroendocrine tumors. I will be giving a brief overview of Nets 101 and then we’ll help moderate the Q&A. I’m joined by Doctor Miriam, a boy and an assistant professor of radiology and nuclear medicine, and she will be speaking about the role of molecular imaging and theranostics in care of patients with
Nets and doctor Saj Khan and associate professor of surgery and surgical.
Allergy and Section chief of Hepato Pancreato, biliary and mixed tumors will be joining us this evening and talking about the surgical management of pancreas and small foulness.
So I will just go ahead and get started, so I'm just for our audience. Each of our talks will be about 20 minutes. Please feel free to put questions in the chat or Q&A throughout. We will try to respond with a typed response throughout, but we will also have time at the end.
for a through Q&A and you can ask them.

These are my disclosures, so I’m going to talk briefly about the epidemiology and nomenclature of Nets.

Talk about characteristics that I think really impact treatment selection for patients and then talk about treatment for hormone and tumor control.

I usually like starting with a little bit of history so neuroendocrine tumors and the description of Nets goes back to the late 1800s, and it was really in the early 1900s that Doctor Urban door for a German pathologist coined the term carcinoid.
It meant cancer-like and he described and felt that there were five key characteristics that they were. These tumors were small and multifocal had undifferentiated cellular formations, had well defined borders, no metastatic potential, and were slow growing and harmless, and though he contributed really important early knowledge about this disease, we now know that many of these characteristics are not true. And I think the term carcinoid and cancer-like, unfortunately, really slowed the field in terms of our
recognition that these are in fact cancers.

The term carcinoid is really fallen out of favor and instead we are using the term neuroendocrine tumor and then by which primary site.

So we have seen an explosion of advances, both therapeutics and diagnostics really since 2011. So in the 1980s we had strept Zosyn and Ivy alkylating agent, and octreotide that was initially approved for hormone control, and then since 2011 we have had therapeutic advances in the areas of biologics of everolimus and snib somatostatin analogs of lanreotide.
to look just at for carcinoid.

Syndrome, Ludo date in 2018.

We'll talk about some of the.

Other systemic agents and then also

some of the imaging agents that

are listed above the timeline.

I like also sort of nailing down the

point that Nets are really not that rare,

so they are rare by incidents,

so incidents being the number of

patients diagnosed per year and for

this is based on a large Sears study

conducted in 2017 and the incidence

rate for Nets is about 7 per 100,000

and this is in the yellow line on the
figure compared to the blue line, which is the incidence of all malignant neoplasms which has remained relatively stable. However, the prevalence of neuroendocrine tumors is actually the second highest prevalent GI malignancy. It exceeds stomach and pancreatic adenocarcinoma combined, and that’s likely because this is a more indolent disease and patients live for many years more commonly with the low grade neuroendocrine tumors. Nets are epithelial neoplasms derived from neuroendocrine cells throughout the body,
most commonly found in the GI tract, but also in the lungs and other sites, and most grow slowly in comparison with their adenocarcinoma counterparts. The majority are sporadic and the minority are associated with familial syndromes such as Von Hippel, Lindau and Neurofibromatosis. Pathognomonic for this disease is the fact that somatostatin receptors are present on the cell surface in about 80 to 90%. This is typically with somatostatin.
00:05:14.384 --> 00:05:15.770 receptor type 2.
NOTE Confidence: 0.905978501333333
00:05:15.770 --> 00:05:17.464 The diagnostic work up and I will
NOTE Confidence: 0.905978501333333
00:05:17.464 --> 00:05:19.544 say if you take away one thing from
NOTE Confidence: 0.905978501333333
00:05:19.544 --> 00:05:21.213 this is that the cross sectional
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00:05:21.213 --> 00:05:23.446 imaging is really the mainstay of how
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00:05:23.446 --> 00:05:25.874 we monitor the patients with Nets.
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00:05:25.874 --> 00:05:28.550 Either a multiphasic CT and that
NOTE Confidence: 0.905978501333333
00:05:28.636 --> 00:05:30.826 arterial phase is critical if
NOTE Confidence: 0.905978501333333
00:05:30.826 --> 00:05:33.580 you’re ordering a CT scan or an
NOTE Confidence: 0.905978501333333
00:05:33.580 --> 00:05:34.546 MRI somatostatin receptor.
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00:05:34.546 --> 00:05:36.724 Imaging is important but is not
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00:05:36.724 --> 00:05:38.546 the primary modality with which
NOTE Confidence: 0.905978501333333
00:05:38.546 --> 00:05:39.930 we image these patients.
NOTE Confidence: 0.905978501333333
00:05:39.930 --> 00:05:41.946 These are done commonly at time of
NOTE Confidence: 0.905978501333333
00:05:41.946 --> 00:05:43.540 diagnosis and for patients with
NOTE Confidence: 0.905978501333333
00:05:43.540 --> 00:05:45.538 metastatic disease we may do them.
Annually or every two years, somatostatin receptor imaging is now used with gallium 68, dotatate pet or copper 64, and I’m going to actually.

This will be a little bit of a teaser.

I’m going to let doctor a boy and talk more about somatostatin receptor based imaging.

The tissue diagnosis we like to know the primary site if we can identify it and four key data elements are important when you’re looking at a pathology report. The Who grade Ki 67 mitotic index.
Degree of differentiation.

We'll talk about that in a moment.

And then tumor markers or hormones are important for this disease, but I will say that tumor markers such as chromogranin or neuron specific enolase or pancreas statin often fluctuate and may not actually track with what's happening radiographically.

The field has swung away from using these and I often don't use chroma granite a now because really the gold standard is the imaging.

Hormones, however, such as serotonin or 24 hour urine 5 hiaa,
which is a byproduct or a metabolite of serotonin. Those can be useful and should be tracked over time. So I find that there are really six key characteristics that impact treatment hormone status stage and burden of disease grade and differentiation. Pace of growth, primary site and somatostatin receptor status. I'll spend just a moment on each of these just to really set the stage in terms of how we talk about and think about
treatments for nuts.

So a functional neuroendocrine tumor is defined as a patient who has symptoms from a measurable hormone that’s in either the urine or the blood. Carcinoid syndrome is a classic example of that. 10% of patients with small intestine Nets have carcinoid syndrome, and it’s due to production of peptides and means such as serotonin or five hiaa, and it can cause Flushing Venus telangiectasis as shown in this picture on the left. Bronchospasm, valvular fibrosis, and hypotension.
This is also a picture of a of the pulmonary and tricuspid valves that are very fibrotic. Pancreatic neuroendocrine tumors can also secrete hormones in about 40% of patients, most commonly insulin, followed by gastrin, Glucagon and vaso intestinal polypeptide, and the symptoms are really defined by the hormones secreted and nonfunctional. Nets are defined as patients who are either asymptomatic or have symptoms that are not from hormone access. So stage and grade.
00:08:36.150 --> 00:08:37.650 describe this to patients 'cause
NOTE Confidence: 0.878234082727273
00:08:37.650 --> 00:08:39.537 I think for patients in particular
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00:08:39.537 --> 00:08:41.107 this can be very confusing.
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00:08:41.107 --> 00:08:43.710 So to this audience however,
NOTE Confidence: 0.878234082727273
00:08:43.710 --> 00:08:45.910 stage is very familiar term.
NOTE Confidence: 0.878234082727273
00:08:45.910 --> 00:08:47.870 What's interesting is that
NOTE Confidence: 0.878234082727273
00:08:47.870 --> 00:08:50.320 the AJC staging criteria have
NOTE Confidence: 0.878234082727273
00:08:50.320 --> 00:08:52.907 only included Nets since 2010.
NOTE Confidence: 0.878234082727273
00:08:52.910 --> 00:08:55.182 This is a really nice picture here
NOTE Confidence: 0.878234082727273
00:08:55.182 --> 00:08:57.287 of a localized pancreatic net,
NOTE Confidence: 0.878234082727273
00:08:57.290 --> 00:08:59.971 which will show in the video and
NOTE Confidence: 0.878234082727273
00:08:59.971 --> 00:09:01.919 a metastatic pancreatic net with
NOTE Confidence: 0.878234082727273
00:09:01.919 --> 00:09:03.729 high degree of liver burden.
NOTE Confidence: 0.878234082727273
00:09:03.730 --> 00:09:05.430 As you can see here,
NOTE Confidence: 0.878234082727273
00:09:05.430 --> 00:09:06.828 grade is really what the cells
NOTE Confidence: 0.878234082727273
00:09:06.828 --> 00:09:08.320 look like under the microscope.
00:09:08.320 --> 00:09:09.624 Low grade is slower,
NOTE Confidence: 0.878234082727273
00:09:09.624 --> 00:09:11.580 growing higher grade is faster growing.
NOTE Confidence: 0.878234082727273
00:09:11.580 --> 00:09:14.016 We really base this on the Ki
NOTE Confidence: 0.878234082727273
00:09:14.016 --> 00:09:15.630 67 in mitotic index.
NOTE Confidence: 0.878234082727273
00:09:15.630 --> 00:09:17.842 The 2019 digestive WHO
NOTE Confidence: 0.878234082727273
00:09:17.842 --> 00:09:20.607 classification is the most recent.
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00:09:20.610 --> 00:09:22.706 I’m next to the Red Arrow is a.
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00:09:22.710 --> 00:09:25.188 New change that was made to this
NOTE Confidence: 0.878234082727273
00:09:25.190 --> 00:09:27.310 so we have well differentiated.
NOTE Confidence: 0.878234082727273
00:09:27.310 --> 00:09:30.914 Net grade 1/2 and three and poorly
NOTE Confidence: 0.878234082727273
00:09:30.914 --> 00:09:32.510 differentiated nurkin carcinoma
NOTE Confidence: 0.878234082727273
00:09:32.510 --> 00:09:35.655 grade 3 and that’s divided into
NOTE Confidence: 0.878234082727273
00:09:35.655 --> 00:09:37.650 small cell and large cell.
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00:09:37.650 --> 00:09:39.295 When I didn’t put on this slide
NOTE Confidence: 0.878234082727273
00:09:39.295 --> 00:09:41.158 is kind of the breakdown of the
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Ki 67 in mitotic index, but really the take away from this is that clinically we treat the grade one and two well differentiated Nets very similarly. This well differentiated grade 3 net is a relatively new category. I think that we have to treat based on the individual patients biology bulk of disease. The poorly differentiated nerdacon carcinomas are treated very differently. That will not be the primary topic of. Kind of the subsequent slides on treatment. That’s typically those patients are typically treated with platinum at openside.
So pace of growth, something I was getting to really does inform our treatment selection. We may need a patient with a metastatic low grade net who has very stable disease or slow progression, or may have more rapid progression. Some of those patients may not need treatment initially. Observation may be appropriate, whereas others may have high burden of disease or symptoms from tumor bulk and they may need treatment. Primary site matters, I know this is a GI focused talk.
but Nets can happen in almost any organ in the small intestine. Most commonly that is one of the most common sites we see commonly in the ilium, but we will also see pancreatic Nets and other Nets in the GI tract, and many clinical trials and treatments are really tailored based on primary site. Therefore, FDA approvals are sometimes limited specifically to primary sites. One example of that is synonym for pancreatic Nets. We now know that somatostatin receptor status is critical both for diagnosis and therapy.
Again, I'm going to let Doctor boy and go into this. This is an interesting picture just to show an octreoscan which has now really completely been replaced by gallium dotate. This is the same patient image with an octreoscan and a gallium 68 dotate pet, and you can see that the resolution is far superior with the pet based imaging. So now we're going to launch in the next sort of the final half of my presentation on general treatment categories for nuts. I will go into some of the specifics just so that you have access to this.
If you choose to watch this again, so we have 4 main categories, somatostatin analogs, peptide receptor, radionuclide therapy, biologics, and cytotoxic chemotherapy. I am going to really focus my conversation or presentation tonight on antitumor treatments. Just a brief comment that we know. So not a statin. Analogs were really initially developed for a hormone control and remain as the primary tool that we use for hormone control, but I’m not going to go into just for sake of time. Details on hormone control tonight, so somatostatin receptors.
and theranostics again, I’m going to just use this to talk about some of the therapies. Dr Abovyan will go into this as well, but in terms of my cartoon here, imagine you have a patient in population for whom you would like to select out. Do they have a receptor on the surface of their cells? We do in fact have that. So with the gallium 68 or copper 64 pets, we select out those patients using that imaging, and then we in fact have a targeted therapy that goes to that target.
So that’s theranostics Dr.

Boy and will focus on that.

When I described this to patients, I used the lock and key description or analogy. I think that helps them understand why we use somatostatin analogs, why we use the Dota Tate imaging. So think of the somatostatin receptor as the lock, the Key is the peptide, and then there’s a reporting unit. So for somatostatin analogs, we actually have two trials that demonstrated antitumor effect. The Pro MID study demonstrated the
00:13:31.564 --> 00:13:33.910 effect of octreotide versus placebo,
00:13:33.910 --> 00:13:36.826 and the clarinet study demonstrated the effectiveness of lanreotide versus placebo.
00:13:36.826 --> 00:13:39.370 Both had a primary endpoint of progression and that the clarinet study was progression free survival.
00:13:39.370 --> 00:13:43.142 Both had a primary endpoint of progression and that the clarinet study was progression free survival.
00:13:43.142 --> 00:13:45.046 the permits that it was time to progression and that the clarinet study was progression free survival.
00:13:45.046 --> 00:13:46.657 They both should have benefit over placebo octreotide.
00:13:46.657 --> 00:13:48.342 study was progression free survival.
00:13:48.342 --> 00:13:50.416 over placebo octreotide.
00:13:50.416 --> 00:13:51.540 Is not formally does not have a formal FDA label for antitumor effect.
00:13:51.540 --> 00:13:54.690 It is primarily in hormone control.
00:13:54.690 --> 00:13:57.930 formal FDA label for antitumor effect.
00:13:57.930 --> 00:13:59.766 It is primarily in hormone control.
00:13:59.770 --> 00:14:00.793 but it is.
00:14:00.793 --> 00:14:02.498 These two agents are often used interchangeably.
Landry Tide was FDA approved in 2014 as an antitumor agent. I’d like to put this up because I get asked this a lot. So how do we think about dosing for tumor control? Octreotide LARC is usually used at the 30 milligram I am monthly dose and lanreotide at 120 milligrams deep. Subq. There is no need to overlap with short acting unless it’s a functional tumor. I think there was data years ago that we needed to do a test dose to test for allergy. That’s not generally needed in practice and there is little data to support the routine use. Above standard dose of somatostatin
00:14:42.255 --> 00:14:44.163 analogues for tumor control.

00:14:44.170 --> 00:14:47.217 The side effects include nausha, diarrhea,

00:14:47.217 --> 00:14:50.958 cholelithiasis, and hyperglycemia.

00:14:50.960 --> 00:14:52.500 I’m going to go through these quickly.

00:14:52.500 --> 00:14:54.276 I have them just kind of as placeholders,

00:14:54.280 --> 00:14:56.275 but Doctor Brian will talk about these,

00:14:56.280 --> 00:15:02.075 but we’ve had incredible advances in

00:15:02.075 --> 00:15:04.611 the diagnostics for Nets as well and

00:15:04.611 --> 00:15:07.275 there is a very handy paper and I have

00:15:07.275 --> 00:15:09.440 this here just as a reference on the

00:15:09.440 --> 00:15:12.512 appropriate use criteria for somatostatin

00:15:12.512 --> 00:15:14.284 That’s a great reference.

00:15:14.290 --> 00:15:16.922 And then in the therapy is something that

00:15:16.922 --> 00:15:19.486 also Doctor Boy and will discuss and

00:15:19.486 --> 00:15:27.000
specifically around the Netter one phase, three clinical trial. So I'll mention it just in passing that this was a study I had the opportunity to serve as a key. It's a randomized study that really set the stage for using their Gnostics and and specifically alluded it, and that's it. Was a positive study. I will give that punchline away for Doctor O'Brien.

But moving on to some of the other systemic therapies,
Everolimus is approved for pancreatic, net and non-functional GI and lung nets. This is an inventory inhibitor. There were sister studies Radiant three and Radiant four and. Both of them showed a progression free survival benefit in these patient populations, and they were both approved. So for pancreatic net in 2011 and for GI and lung nets in 2016. And tyrosine kinase inhibitors also have a role in neuroendocrine tumors. Sonett nib was approved on the
basis of this randomized study in patients with well differentiated advanced pancreatic Nets.

So that’s the one that I said we don’t yet have a tyrosine kinase inhibitor approved for small bowel Nets.

This was also approved on the basis of a PFS benefit.

You’ll notice that most neuroendocrine tumor clinical trials have progression free survival as a primary endpoint, and that’s because OS.

Is an impractical endpoint given that patients tend to receive many subsequent therapies after these clinical trials and it be given
the indolence of the disease, it would be too difficult, practically speaking, to use overall survival. So this was approved in 2011. Sir Afatinib is not yet FDA approved. It is under FDA review. At present, this was on the basis of two large studies conducted in China and then a phase one. Two study that has been conducted in the United States. in a more traditionally Western population. But this was positive in both.
pancreatic and extra pancreatic Nets.

And is, I suspect that at some point this spring or summer, we will have a decision from the FDA.

I’d like to mention a study on chemotherapy that I had the opportunity to lead for pancreatic Nets, so this was a study of temozolomide versus capecitabine intimas Olumide for grade one or two metastatic pancreatic Nets. This was a study that ultimately demonstrated that Caped M was superior to temozolomide alone and median progression was about 23 months for the combination versus 14 months.

Free survival was about 23 months for the combination versus 14 months.
00:18:06.392 --> 00:18:08.020 of the initial analysis,

00:18:08.020 --> 00:18:10.799 it appeared as if there was an

00:18:10.799 --> 00:18:12.650 overall survival benefit benefit.

00:18:12.650 --> 00:18:13.538 Stay tuned.

00:18:13.538 --> 00:18:16.202 We have the final analysis submitted

00:18:16.202 --> 00:18:19.918 to ASCO for an updated analysis.

00:18:19.920 --> 00:18:21.691 I think one of the key takeaways

00:18:21.691 --> 00:18:23.984 of this is that we see a higher

00:18:23.984 --> 00:18:25.840 response rate than we’ve seen really

00:18:25.840 --> 00:18:27.760 for any of the other therapies.

00:18:27.760 --> 00:18:29.158 I did not go into that,

00:18:29.160 --> 00:18:32.840 but somatostatin analogues, mtor inhibitors,

00:18:32.840 --> 00:18:35.582 tyrosine kinase inhibitors all have a

00:18:35.582 --> 00:18:39.250 you know 5% or less objective response rate.

00:18:39.250 --> 00:18:41.776 So for patients with pancreatic Nets

NOTE Confidence: 0.953139839166667
who need objective tumor shrinkage, these are actually very good therapies to think about.

So let’s wrap this up. I think I have. Two slides left.

So how do we really think about sequencing that these treatments? It’s very confusing.

We’re actually in a fortunate place now of having a number of therapies, but it gets very difficult to know what order in which we should use them, so this is adapted from Nancy CN guidelines, so I would say commonly a first line treatment is either observation.
or octreotide or lanreotide, but where it gets very confusing as thinking about second line therapies. So I have a handy table to help you think about that, and I’ve put them in. Order of how I generally will think about using them. I often will consider using PR T or Ludo tape or lutathera as the as it’s also called in the second line setting. It has a modest response rate of about 18% along PFS and is well tolerated and we do have to take care if patients GFR is less than 30 but
we are developing more experience with them.

The chemotherapy tamela mining capecitabine has the highest response rate. And should be considered for patients with pancreatic Nets who need an objective response.

It does have higher adverse events for older patients.

I will sometimes consider temozolomide alone.

Forever Elemicin soon if they both have very low response rates, the PFS is about a year best for low volume disease, but I find that the adverse event profile is tough for both of these. Everyone ever really miss in
particular is good for insulinoma
because it can cause hyperglycemia,
but it’s tough and can cause pneumonitis and the hyperglycemia can be difficult for patients with uncontrolled diabetes.
So takeaways I hope you’ve learned that Nets are not that rare. They are deserving of high quality basic,
translational and clinical research efforts. We’ve had incredible advances in the last 10 years.
PRT is really a game changer and I expect the next decade of
clinical trials to be looking at better patient selection, minimizing toxicities and increasing efficacy and multidisciplinary care and team science is really key for this disease so I am going to stop share. I think I’m close to time. I am going to pass the baton to Doctor Abovyan and then Doctor Boyd if you can then pass that baton when you’re done to Doctor Khan and then we will do a Q and a great. Thank you doctor Kuntz. This was fantastic. Sam my screen.

So I’m going to talk about the role of molecular imaging,
and there are Gnostics in the care of patients with neural neoplasms I’m in. I’m at Yale Department of Radiology and I am in a nuclear medicine and new radiology sections. For disclosures, I have a research collaboration with vistage imaging and I do clinical trials with Blue Earth diagnostics. We’re going to start a little bit with standard imaging, CT, and MRI, but we’re not going to focus on this imaging modalities because they’re pretty well understood in the community and just kind of going over the basics of it. For carcinoid tumors, we can do very...
nice chest imaging with CT of the chest.

We can do contrast and noncontrast imaging.

and here is an example of

a lung carcinoid lesion.

For pancreatic neuroendocrine

tumors we can do CT imaging.

Enhance CT imaging,

but we can also do MRI and here you

see actually a patient with pancreatic

tail or entropy neoplasm that is

heterogeneous solid and partially cystic

and you can see that it’s actually

sometimes difficult to evaluate.

We can also do MRI imaging with

abdominal MRI.

You can do it with contrast
and without contrast, and you can evaluate in this particular patient static liver lesions within the. This MRI pretty well and this actually is same patient that progressed in development has to season the liver. But we want to also start imaging beyond standard anatomical imaging with molecular imaging and with standard and understandable imaging we can see a lot of the basics of actually delineate the borders of the tumor and where they’re located, but it’s really hard to say what is
The characteristics of the tumor, we're very good at defining the anatomy and the location and the extent of the disease and location of disease. But not so much in terms of is the same neuroendocrine tumor. If you just look at the lover? Or is this something else? What's really nice is that you can actually use targeted imaging to describe the receptors on the surface of tumors, without having to do a biopsy. And this is an example of a gallium dotatate PET.
which I'll describe this little alphabet. So soup in the next few slides, but what it allows you to do is to visualize semantics. Some of some analog binding to a somatostatin receptor, and being able to see it light up on this Cam. I'm so glad Doctor Kunz mentioned that tree a scam that used to be the standard way of trying to see some exciting receptor receptor expression on tumors. And as you can see, these are not very good images.
and they're very hard to see. And it's very difficult to tell where the tumor is, with pancreatic tail tumor, and you can barely see where this illusion is, and this is actually the same planar imaging, and if we did SPECT, we could localize it to the left upper quadrant, but it would be very difficult to localize it to the pancreas very well. Also, if there were smaller lesions, we wouldn't be able to see it.
And here's an example of a trio scan being lined up right next to door dotate scan gallium. And you can see how many lesions are being missed. An actress can that can be clearly seen on the pet C team.

But going to the dough depart a lot of folks ask me Doda what, what is this Doda and the alphabet soup lutetium dotate gallium dooda talk but there's actually a very nice logic to it. So let's go over that,
because then you will never question what these are. So first, let's talk about labeling in chemistry. When you're thinking about pet radionuclides such as gallium and copper, which are used for imaging and pet, you cannot just attack, give them to the patient, they're actually toxic, so you need to keep them in the cage, and this is a doda cage. so you would kill the gallium 68 in this doda cage, and what's really nice about this cage. It has a couple of. Four different arms and to these arms you
can actually attach your targeting molecule, so in this case it’s actually a tight analog Tate, so you attach this peptide to the doda and you have your radionuclide chelated inside of the Doda. So there’s a very logical name to this. This value attach it through the ARM gallium Doda date. Very simple, right? So now that you understand. This kind of logic it it becomes very easy to understand how we mean these scans and with the labeling you can actually really be able to see this.
So this is a gallium dotate PET CT in a patient with multiple metastases. Some medicine receptor positive liver metastases and you can actually see that there is also a period where did metastasis in the lymph node that’s outside of the liver and here you have kidneys and bladder. So it really helps you evaluate the patients in terms of the appropriate use criteria. I’m so glad Doctor Kunz had a full slide on this in terms of evaluating. Not all patients need to be getting gallium daughter take pets and there’s there. We’re still truly evaluating exactly where
and when we should be doing these scans, but there's several indications that can.

That are appropriate and some of the most indicative are the initial staging after histologic diagnosis of neuroendocrine tumor and localization of primary tumor. Very important point is selection of patients for some meta stat.

This skin is so sensitive for lesions, so you'll be able to see it and then the other very common.
and receptive targeted therapy
Later now what’s really nice about this
therapy and this is where it’s really
revolutionary in medicine is that you
can use this method to image your tumor,
so you have your radionuclide.
You have your cage and you
have your targeting peptide,
but then after you image the tumor,
all you have to do is to pop this one
out and pop lutetium 177 in so you keep.
You keep the targeting the same but.
The radionuclide now is actually emitting
beta particles that can can act as a
therapeutic for neuroendocrine tumors.

So this would be called very logically.

I know you’re thinking about this.

Lu teach to Doda tape.

There you go. Very simple.

So we imaged with gallium dotatate.

And we treat it with lutetium.

So you know this drop whatever we imaged.

That’s exactly where the treatment went.

Now we don’t just have to do lutetium, we can also use other radionuclides.

Such as alpha emitters and here.

At Yale we’re now are approved to
start doing this and it’s very exciting new development to start doing these therapies in patients.

So how do these alpha and beta emitters work? Well for lutetium and this is an image from a website where basically describes the mechanism of lutetium and you administer the drug intravenously. The drug gets taken up into the neuroendocrine tumor sides. The drug binds to the receptors on the tumor sides and gets internalized inside of the cell. Through endocytosis and the radionuclide emits its particles beta particles, or if using that actinium type of therapy.
Luther, it’s really the beta particles because it’s lutetium 177 and that can cause DNA damage. And once you have DNA damage you can that can lead to tumor cell death. And that’s and that’s the main mechanism. So to just kind of overview this again in terms of image guided therapy, you can select patients for whether they are eligible for this kind of therapy with your imaging agent, gallium dotatate. And you can see if the patient expresses this amount of statin receptors in the body, and in this particular patient.
there are multiple metastatic lesion that can take up the targeting.

Molecule, then you bring the patient in and you provide intravenous therapy.

And that is basically the same as the imaging agent, except it has the radionuclide that causes DNA damage.

And what’s really interesting is that lutetium can also emit. Image trace that you can see on gamma camera and you can basically see exactly where lutetium dotatate went. Now it’s not as crisp and beautiful as PET CT,
but you can actually see where this therapy went. And you can actually start doing those symmetry. These images so this kind of technology allows selection of right patient and providing the right drug for the patient and in neuroendocrine tumors that has really changed how we change how we treat patients. So the indications for lutetium dotatate. So these are the GI neuroendocrine tumors and they have to be well differentiated. G1 and G2 tumors. We need to confirm some metastatic.
receptor expression and that can be done with gallium dotatate PET CT. We’re still allowed to use octreoscan and sometimes we will use it if insurance will deny that the pet city, but you really want to be doing this with a pet CT. We also evaluate bone marrow function, renal function, and liver function. Yes, and this is the point where nuclear medicine physicians are starting to become partners with oncologists and surgeons in treatment of these patients. Because we no longer just read the images were actually evaluated. Whether the patient is eligible
for the study and we evaluate,
follow up, and we do those symmetry.
And this is of patient oriented,
patient facing role for nuclear
medicine physicians and radiologists.
Now.
Even though the letter one has established the parameters for
treatment of patients with Sarah,
but we are still,
we’re still figuring out the exact
guidelines for which patients will
benefit most, and they’re still.
There’s a lot of active research
going on in this field,
and it’s very exciting to be part of this field as we’re expanding beyond the netter one. Trial indications. But you’re probably thinking, well, what about FDG? GS News and pretty much every other oncological indication. How about your endocrine tumors? Well, a lot of the well differentiated G1 on your endocrine tumors are actually not hypermetabolic, so we there’s really no role for our DG in the well differentiated once, and there is the spectrum that the tumors will express.
A lot of this medicine receptor will not have as much. Hypermetabolic activity, but the higher grade tumors. Then you’re in different parts. Sonoma is Angie 3 tumors. They will have hypermetabolic activity and there’s still a lot of Gray area in between them as well, because sometimes they look the lower grade tumors will also have hypermetabolic activity, but in nuclear medicine we have this idea that there’s dedifferentiation that happens.
So this is a patient with a well differentiated neuron, different tumor. With multiple somatostatin receptor avid lesions and this is a patient that had dedifferentiation that neural different from which the tumor is now hypermetabolic, or it can actually expect express sounds of medicine receptors, but not as many. So the exact point where we would treat these patients, particularly the ones that have FDG uptake.
Is still not fully evaluated, but hypermetabolic activity within these tumors is seen as a poor prognostic marker. So in terms of PR T treatment, the details for this treatment is we do right now. Standard dose of 200 millicuries every eight weeks and we do 8 cycles. During the therapy we do an amino acid infusion for renal protection and we provide antiemetics for nausea and patients usually will continue somatostatin and lock therapy at this during PR T treatment now.
None of you are thinking well. What if?

How do we treat a patient?

Every single patient with the same dose?

And you’re thinking right,

the whole field of theranostics right

now and treatment PRT treatment

is moving towards personalized

of symmetry and that is becoming

a big talking point with Society

nastix agents are becoming more and

for different cancers

and in prostate cancer will have a
new theranostic agent that's very likely to be FDA approved next month.

And with that targeted therapy, you want to think about it in a couple different ways and just in terms of global way with with their Gnostics, you can image the targets such as location of the tumors and that way you can provide targeted therapy in terms of location of the tumor, because you can see where the drug is and then you can just exchange the radionuclide and and target that therapy. You can also think of targeted therapy in another way where you target as
particular step in the mechanism of.

Therapy, and that is targeting a specific pathway step.

So for FDA approved radiopharmaceuticals there’s really been an explosion in the recent years. So it we really kind of started with a cold see lemon cooling for prostate cancer and gallium dotatate was approved when you’re entering tumors in 2016 and then was followed by Gallium Delta talk and the difference between Tate and talk is in the peptide portion of the targeting agent. And in there they work pretty much the same in terms of ability to
00:38:31.450 --> 00:38:33.222 detect some metastatic receptors.

00:38:33.222 --> 00:38:36.887 We also now have a copper 64 labeled DOTATATE and.

00:38:36.887 --> 00:38:39.908 The therapy for lutetium builder did was.

00:38:39.910 --> 00:38:43.606 He has also been FDA approved for quite a while now and it was basically approved based on the meter one trial,

00:38:43.610 --> 00:38:45.822 which showed improved progression in these patients and I really appreciate Doctor Koontz going over.

00:38:45.822 --> 00:38:48.328 The therapy for lutetium builder did was.

00:38:48.328 --> 00:38:50.700 which showed improved progression in these patients and I really appreciate Doctor Koontz going over.

00:38:50.700 --> 00:38:53.032 which showed improved progression.

00:38:53.032 --> 00:39:00.424 For this so for future directions we have to evaluate PRT efficacy and

00:39:00.430 --> 00:39:04.451 For this so for future directions we have to evaluate PRT efficacy and

00:39:04.451 --> 00:39:10.250 higher grade neuroendocrine neoplasms.

00:39:10.250 --> 00:39:14.186 We’re also working on personalized symmetry,

00:39:14.190 --> 00:39:17.060 so providing the right dose to the
00:39:17.060 --> 00:39:19.302 patient and hopefully see better
NOTE Confidence: 0.814651204
00:39:19.302 --> 00:39:20.706 outcomes in patients,
NOTE Confidence: 0.814651204
00:39:20.710 --> 00:39:23.356 and we need to evaluate indications
NOTE Confidence: 0.814651204
00:39:23.356 --> 00:39:25.930 for re treatment of patients.
NOTE Confidence: 0.814651204
00:39:25.930 --> 00:39:28.000 So after they completed the four
NOTE Confidence: 0.814651204
00:39:28.000 --> 00:39:29.035 cycles of therapy,
NOTE Confidence: 0.814651204
00:39:29.040 --> 00:39:30.990 what are the indications for repeat?
NOTE Confidence: 0.814651204
00:39:30.990 --> 00:39:33.770 Treatment another cycle of therapy
NOTE Confidence: 0.814651204
00:39:33.770 --> 00:39:37.466 and also of the alpha therapeutics.
NOTE Confidence: 0.814651204
00:39:37.470 --> 00:39:43.082 And another thing that we're working
NOTE Confidence: 0.814651204
00:39:39.588 --> 00:40:01.065 on here at Yale is personalized tumor
NOTE Confidence: 0.814651204
00:39:43.082 --> 00:39:48.503 directed analysis with basically doing
NOTE Confidence: 0.814651204
00:39:48.503 --> 00:40:01.065 volumetric assessment of the different
NOTE Confidence: 0.814651204
00:39:51.270 --> 00:39:53.798 metastases and generating growth
NOTE Confidence: 0.814651204
00:39:53.798 --> 00:39:57.590 curves for each individual lesion in
NOTE Confidence: 0.814651204
00:39:57.681 --> 00:40:01.065 the in volumetric form and following.
Physical growth parks and figuring out which lesions are growing and needs targeted therapy through different ways and which ones are not so, so. In conclusion, cross sectional imaging with CT and MRI can diagnose and follow in your Endocrine meal Plaza. And it’s they’re really excellent ways to do imaging for these patients, but. And molecular imaging of somatostatin receptor expression allows for better molecular characterization of new rendering, Neil plasm’s. Gallium Dotatate pet is very sensitive.
for detection of metastatic lesions and allows to evaluate whether patient is eligible for PR T lutetium dotatate therapy is established and allows to treat some medicine receptor tumors expressing some extra. Staten receptor expressing neuron doctrine, neoplasms, and it allows us to visualize the location of the therapy and many advances for personalized therapy are being evaluated right now, so stay tuned to this field ’cause it’s really changing how we’re managing their endocrine schermers. I really want to thank you for your time
00:41:25.626 --> 00:41:28.430 and pass the Bhutan to doctor Sajid Khan.
00:41:41.280 --> 00:41:43.010 You’re on mute. Doctor Khan.
00:41:57.400 --> 00:42:00.375 OK, OK, I think I’m unmuted now.
00:42:00.380 --> 00:42:01.660 I’m is that right?
00:42:01.660 --> 00:42:03.784 OK, yes, OK, alright.
00:42:03.784 --> 00:42:05.794 Thank you Doctor rebellion that
00:42:05.794 --> 00:42:08.300 was just an outstanding talk.
00:42:08.300 --> 00:42:10.360 I learned a lot from that talk and I’m sure
00:42:10.414 --> 00:42:12.478 other people in the audience learned a lot.
00:42:12.480 --> 00:42:16.224 And Doctor Kunz talk was also at standing.
00:42:16.230 --> 00:42:18.118 So, uh, you know, so I’m going to
00:42:18.118 --> 00:42:20.192 spend the next 20 minutes talking to
00:42:20.192 --> 00:42:22.450 you from a slightly different perspective,
00:42:22.450 --> 00:42:25.600 and one that will include the surgical
00:42:25.600 --> 00:42:27.490 management of neuroendocrine tumors.
And since just the surgical management of neuroendocrine tumors is a large topic in and of itself, no, over the next 20 minutes, I'll focus specifically on pancreas and small bowel, and I'd love to ask answer any questions towards the end. First time I have no disclosures.

Looking at it from the end where they looked at. Sear based study of the incidence of neuroendocrine tumors over the course of time and what’s striking about this talk,
and this is kind of the punch line.

One of the points that Romans made is neuroendocrine tumors are not necessarily a rare anymore because the incidence of these is rising and this includes the focus of this talk, which will include pancreas and small bowel. 2 and that’ll be the focus of this talk. I’m sure many people in
the audience know that.

Many of our patients are getting scans.

A cross sectional imaging, and they're often incidental findings.

And oftentimes these are how neuroendocrine tumors are discovered as our other kinds of tumors as well, and I'm sure that's driving the higher incidence that we're seeing over time.

So the interesting thing about neuroendocrine tumors is that the survival for neuroendocrine tumors is, generally speaking, favorable when we and the focus again will be on pancreas.

Neuroendocrine tumors and small
bowl neuroendocrine tumors and the survival is dependent on grade, and we're not going to talk too much about grade three grade 4 door under consumers and much of what we see are grade one and grade tuna under consumers and the survival. Is is usually favorable and that leads to. That the perspective of how these new entrants should be managed and you know, and you know I'm going to give you my perspective as a surgical oncologist. And I think we all have our own perspectives on things. And as a surgical oncologist at
longer progression free survivals,
the longer survivals impact how?
What kind of surgical management we offer to our patients.
So for the talk, we’ll break it up into the remainder of the talk.
Will break it up into three different.
Sessions one will be the pink richner endocrine tumors,
which I’ll talk about first.
I’ll follow that with the small bowel and are under consumers.
And lastly, we talk about metastatic metastatic neuroendocrine tumors as well.
These are common surgical scenarios that maybe some of your patients
have experienced and hopefully this will provide some types.

So in regards to the pancreas

So you know, I think in order to understand if someone needs an operation, one needs to just understand the basics of the neuroendocrine tumors. And you know these are some of the points that are important to a surgical oncologist.

When we see patients who think christner under consumers.

I'm very interested in tumor biology and I could tell that to
rebooting is also from her very elaborate talk and pink Krishna render from rumors arise from the endocrine cells of the pancreas, which are important to understand and they account for 3% of pancreas tumors altogether. So still pancreatic ductal adenocarcinomas and other kinds of tumors comprise majority but 3% of pink christner under consumers comprised of by peanuts. The median age at diagnosis is 60 years and the survival is longer than that anchors adenocarcinoma, so that’s very important point.
to understand is as all of us in the audience have. I'm sure I can understand, and they're obviously people. Some celebrities over the years that we have observed that have been diagnosed with these kinds of tumors. Both adenocarcinoma. The note status is very important, so patients with node negative peanuts tend to have them. Sorry to interrupt you. Your slide is not projecting it maybe. Yep, there you go. Perfect, thanks.
00:47:00.720 --> 00:47:02.796 Sorry, so the survival is very
NOTE Confidence: 0.918569646666667
00:47:02.796 --> 00:47:05.100 important based on the nodal status.
NOTE Confidence: 0.918569646666667
00:47:05.100 --> 00:47:08.614 So patients with no negative peanuts have
NOTE Confidence: 0.918569646666667
00:47:08.614 --> 00:47:12.206 a very favorable survival at 136 months.
NOTE Confidence: 0.918569646666667
00:47:12.206 --> 00:47:14.821 The addition of noteworthy metastasis
NOTE Confidence: 0.918569646666667
00:47:14.821 --> 00:47:17.867 to lymph nodes decreases at survival
NOTE Confidence: 0.918569646666667
00:47:17.867 --> 00:47:20.646 to 77 months and one patient
NOTE Confidence: 0.918569646666667
00:47:20.646 --> 00:47:22.494 present with distant metastases.
NOTE Confidence: 0.918569646666667
00:47:22.500 --> 00:47:25.780 This survival is 24 months and
NOTE Confidence: 0.918569646666667
00:47:25.780 --> 00:47:28.230 you know that’s important to
NOTE Confidence: 0.918569646666667
00:47:28.230 --> 00:47:30.356 understand because 60% of patients
NOTE Confidence: 0.918569646666667
00:47:30.356 --> 00:47:32.266 do present with distant metastases.
NOTE Confidence: 0.918569646666667
00:47:32.270 --> 00:47:34.094 And I think that plays into
NOTE Confidence: 0.918569646666667
00:47:34.094 --> 00:47:35.310 the decision making process.
NOTE Confidence: 0.918569646666667
00:47:35.310 --> 00:47:37.718 So for how to treat the patient
NOTE Confidence: 0.918569646666667
00:47:37.718 --> 00:47:39.642 to optimally and as doctor Kunz
had mentioned during her talk, majority of cases are sporadic and some are familiar. Pink Reisner under consumers are nonfunctioning tumors and and nonfunctioning tumors do not produce clinical symptoms, even though the tumors can’t still produce hormones, but they don’t produce enough hormones that cause clinical symptoms. The nonfunctioning tumors, now in the updated literature, revealed account for about
75% of these tumors.

I think some of this has to do with these smaller new render consumers, the child.

Talk a little bit about that are diagnosed more and more frequently in that number has increased over overtime and then functioning tumors, so functioning tumors are tumors that have hormone hypersecretion that does lead to clinical manifestation. The six types are listed here, which are insulinomas most commonly that we see Glucagon, omas, gastrinomas VIP,
00:48:38.644 --> 00:48:40.984 omas Mathis adenomas and others
00:48:40.984 --> 00:48:43.315 as well functioning tumors tend
00:48:43.315 --> 00:48:45.640 to have better survival than
00:48:45.640 --> 00:48:47.754 nonfunctioning tumors and part of this.
00:48:47.754 --> 00:48:49.234 Probably is patient present symptom
00:48:49.234 --> 00:48:50.663 with symptomatology earlier than
00:48:50.663 --> 00:48:52.453 non functioning tumors and that
00:48:52.453 --> 00:48:54.425 might lead to a better survival
00:48:54.425 --> 00:48:55.930 ultimately because it was diagnosed
00:48:55.930 --> 00:48:57.620 or earlier on in the process.
00:48:59.780 --> 00:49:01.960 So when a surgical oncologist,
00:49:01.960 --> 00:49:03.423 if you come to Yale Surgical and
00:49:03.423 --> 00:49:05.274 I see one of the Yale surgical
00:49:05.274 --> 00:49:06.739 oncologists you know there are
00:49:06.739 --> 00:49:08.335 certain things that we think are
important to guide our principles of sort of surgical management of patients for assessing a patient. For that and our goals for surgery are the first is to maximize local control, so I think that’s a very important point for not just bankers neuroendocrine tumors, but in general for other types of neuroendocrine tumors as well. Another goal is to increase ones. Quality of Life OK, so sometimes that even non functioning tumors can have an adverse effect on the individuals quality of life. So surgery can improve, increase funds, quality of life progression.
Free survival is an important point as well given the behavior of these tumors a lot of times. Generally speaking we aim for R0 resection margins and that’s something we strive for. We’ll talk a little bit more about.
not always the case, but that’s for some of the metastatic tumors. We are usually striving for an artist or section and the other final goal is we try to alleviate clinical symptoms, and this is very important for those with the functioning or underprint tumors. And and with the source of the hormone, hypersecretion is removed. It can substantially alleviate ones clinical symptoms in the completely. Address it altogether. And we also, you know, with our surgeries and a lot of these pancreas cases can be major
NOTE Confidence: 0.75222638
00:50:39.922 --> 00:50:40.978 operations and us.
NOTE Confidence: 0.75222638
00:50:40.978 --> 00:50:44.070 But we do try to limit our short
NOTE Confidence: 0.75222638
00:50:44.070 --> 00:50:45.982 term morbidity and the long term
NOTE Confidence: 0.75222638
00:50:45.982 --> 00:50:47.780 morbidity as well too in the few.
NOTE Confidence: 0.75222638
00:50:47.780 --> 00:50:49.780 See one of the surgical oncologists at Yale.
NOTE Confidence: 0.75222638
00:50:49.780 --> 00:50:51.736 We our role is taking this
NOTE Confidence: 0.75222638
00:50:51.736 --> 00:50:52.388 into consideration.
NOTE Confidence: 0.90576498
00:50:54.800 --> 00:50:57.635 So, so I’m gonna give you some
NOTE Confidence: 0.90576498
00:50:57.635 --> 00:50:59.202 specific surgical scenarios here
NOTE Confidence: 0.90576498
00:50:59.202 --> 00:51:01.897 that may be of some use and you know
NOTE Confidence: 0.90576498
00:51:01.897 --> 00:51:03.931 one scenario includes a patient that
NOTE Confidence: 0.90576498
00:51:03.931 --> 00:51:06.298 presents the localized non metastatic
NOTE Confidence: 0.90576498
00:51:06.298 --> 00:51:07.774 pancreas neuroendocrine tumor.
NOTE Confidence: 0.90576498
00:51:07.780 --> 00:51:08.683 And generally speaking,
NOTE Confidence: 0.90576498
00:51:08.683 --> 00:51:11.438 we respect the for the resection is feasible.
NOTE Confidence: 0.90576498
The meeting survival in the literature is 7.1 years, but the important thing to understand, and is that about half the patients do recur at two almost three years. So recurrence free survival is important to consider here as well, so so many patients to recur.

Another common scenario are these small pink trees that are under 15 years, so these are pink creature under consumers that when we say that there are small, we’re thinking 1.5 to 2 centimeters in the depends on which studies you’re looking at. There’s a good study out of.
the University of Chicago.

There's another good study out of Massachusetts General and then that's where this number of less than two centimeters or 1.5 to 2 centimeters comes up, because given the behavior of neuroendocrine pancreas, sometimes surgery is not necessary for these patients, but I would recommend careful observation and you know each patient is an individual and we need to evaluate every patient should be evaluated individually and but oftentimes patients with
smaller tumors can be observed, you know, and I just want to make a quick comment about that. And that being said, you know if there’s a young patient that’s diagnosed with a 1.8 centimeter neuroendocrine tumor that’s in. They say, for example, one can make a reasonable argument that with a longer life term expectancy, maybe that might not be the person we tried. Decide to observe with the small neuron consumer and we do survey these patients.
And if there are changes to their cross sectional imaging, which is an important point for neuroendocrine tumors, we will consider them per section. Another scenario that sometimes comes up is a locally advanced and metastatic on fund, resectable. Patient in that kind of a scenario, you know, sometimes we consider palliative surgery with some of the options listed here, and that's sometimes a scenario and then limited liver metastases. We're going to talk at the last.
third of this talk a little bit more

about metastatic disease and in some patients with limited liver metastases.

Will will use a asynchronous approach where the primary tumors are addressed and the liver tumors is addressed, or we considered a surgery in a staged fashion.

So for all of these for sections I’m just figured I’d share some patient examples for you to try to put it into some perspective and and the first patient I’d like to present is an 80 year old male who presented with hypoglycemic episodes and he had what’s called the Whipple’s triad,
which we've heard about, and for Pinkerton are under consumers, what we teach our residents is, you know, if you're ones considering a functional.

Increased our hundred tumor work up starts with the biochemical workup and this patient did have a biochemical work up, which indeed was consistent with insulinoma.

After the biochemical work up, then we preceded with the localization studies to identify where this tumor is located and in this patient. Here, this is the frontal images and it shows.
00:54:29.716 --> 00:54:32.440 I don’t think my arrow is projecting here, 
NOTE Confidence: 0.867011257692308
00:54:32.440 --> 00:54:35.611 but there’s a hyper enhancing mass in 
NOTE Confidence: 0.867011257692308
00:54:35.611 --> 00:54:38.579 the head of the pancreas which is seen. 
NOTE Confidence: 0.867011257692308
00:54:38.580 --> 00:54:40.368 And that is sometimes the look 
NOTE Confidence: 0.867011257692308
00:54:40.368 --> 00:54:42.405 of how a neuron tumor shows 
NOTE Confidence: 0.867011257692308
00:54:42.405 --> 00:54:44.350 up on cross sectional imaging, 
NOTE Confidence: 0.867011257692308
00:54:44.350 --> 00:54:46.785 and we performed a pancreaticoduodenectomy 
NOTE Confidence: 0.867011257692308
00:54:46.785 --> 00:54:49.639 with an extended lymphadenectomy on this 
NOTE Confidence: 0.867011257692308
00:54:49.639 --> 00:54:51.775 patient specimen seen on the right, 
NOTE Confidence: 0.867011257692308
00:54:51.780 --> 00:54:55.278 and interestingly, 
NOTE Confidence: 0.867011257692308
00:54:55.278 --> 00:54:58.087 immediately the patients hydroplocemic 
NOTE Confidence: 0.867011257692308
00:54:58.087 --> 00:55:00.137 episodes were completely resolved and 
NOTE Confidence: 0.867011257692308
00:55:00.140 --> 00:55:10.630 provided this gentleman with many, 
NOTE Confidence: 0.867011257692308
00:55:05.880 --> 00:55:08.730 Next, I’d like to transition to 
NOTE Confidence: 0.836767505
00:55:08.730 --> 00:55:10.630 small bowel neuroendocrine tumors.
And these are tumors that are submucosal neoplasms which primarily arise from the jejunum and the ileum. And there they do have neuroendocrine differentiation, just like some of these other tumors that we’re talking about today. They have an ability to secrete functional hormones and a means they are the most common tumor of the small bowel with malignant potential. Which is interesting because this is shifted because when I was in intern almost 20 years ago now we used to not look at small bowel neuronal tumors as
the most common small bowel tumors. We would think more of adenocarcinoma and then more often even benign tumors. But interestingly, now neuroendocrine small bowel tumors are the most common. Nearly a third of these tumors arise relatively close to the ileocecal valve, and that the reason that’s important is our operative decision making takes that into consideration. Many patients present with multifocal disease that’s also very important. When I talk about surgical approaches, and about 35% of patients
00:56:20.665 --> 00:56:22.805 present with distant metastases,
00:56:22.810 --> 00:56:24.820 so surgical resection is a preferred
00:56:24.820 --> 00:56:26.670 frontline treatment for these patients.
00:56:29.060 --> 00:56:30.956 And the reasons for that is number one.
00:56:30.960 --> 00:56:33.408 It can improve survival.
00:56:33.410 --> 00:56:36.134 Number two can reduce the risk
00:56:36.134 --> 00:56:37.950 for developing metastatic disease.
00:56:37.950 --> 00:56:40.831 #3 can alleviate symptoms and
00:56:40.831 --> 00:56:42.658 finally #4 it can prevent or delay
00:56:42.658 --> 00:56:44.489 the onset of symptom development,
00:56:44.490 --> 00:56:46.295 and that’s important as we
00:56:46.295 --> 00:56:48.550 talk a little bit more here.
00:56:48.550 --> 00:56:49.183 So you know.
00:56:49.183 --> 00:56:50.660 So like I thought it would be
00:56:50.712 --> 00:56:52.218 useful to go over some scenarios
that some of your patients may present with into the hospital. And 11 scenario is in east symptomatic prime patient that the patient presents with asymptomatic disease with the 00:57:03.708 primary tumor without distant metastases. So even though these patients present with asymptomatic disease, in retrospect, many of them will have some symptomatology. And they won’t know about it until after they’ve had their surgery. But that symptomatology may have prompted their imaging in the 1st place and the cross sectional imaging Dr Booing can speak to this better than I can.
but oftentimes it shows something such as a mesenteric or small bowel mass, which is hyper enhancing. Speculated or calcified, and interestingly in the operating room, the speculation is something we really appreciate because these tumors in the OR or the mesenteric mass in the OR tend to be fixed, as opposed to something that some freely movable, which is the case with some of the benign small bowel tumors.
and even small biologists.

Another scenario is an asymptomatic primary tumor with distant metastasis.

I'm going to talk a little bit about that.

In the last scenario, because I think that’s going to be an important thing to go over.

And and symptomatically.

You know, sometimes these neuroendocrine tumors present with the bowel obstruction, abdominal pain, bleeding, and the so-called carcinoid syndrome as well.

An approach that is important is expectations for our patients suffer.
Patient knows what to expect in a non-emergent setting prior to undergoing a surgical and conchological section. It goes along way for their satisfaction down the road. That’s something that our group at Yale uses. So we talked to our patients ahead of surgery and one thing that we talked to our patients about is sometimes that because of the multifocality of these tumors, larger areas of small bowel need to be respected. Lead to increased frequency of bowel movements.
We also consider perceptibility. A lot of it comes down to the mesenteric artery and the vein superior mesenteric, artery and vein. That’s something we strongly consider for respectability for these guys into tumors, and indirectly or small bowel resection with a lymphadenectomy.

Sometimes it involves resection of a mesenteric mass, which is how a patient may present, and in the operating room. It’s very important to palpate for synchronous tumors, so so open operations are preferred.
and I just want to spend just a minute talking about that as well too.

So we do a lot of laparoscopic and minimally invasive surgery at Yale. A lot of our operations are done in that manner, and the way I look at laparoscopy and minimally invasive surgeries is that it should be a tool to provide a good oncologic operation. It shouldn’t be the other way around, meaning someone should not get a minimally invasive surgery just for the sake of getting minimally invasive surgery.
but so so for the way we approach these are we usually will do them.

Laparoscopic Lee roulette, metastases and sometimes we could make a very small incision and eviscerate the tumor and palpate the entire small bowel to make sure that they’re synchronous.

Tumors are are not missed, which sometimes is the case with true laparoscopic operations.

For these small bell, any tease we value for distant metastases and sometimes consider a cholecystectomy and a lot of that.

Ends up being a conversation with the
surgical oncologist and medical oncologist, and about this patient may be a candidate for lanreotide in the future which can predispose to the development of gallstones. Uhm? So a few scenarios. So patient presents with an incidental finding on cross sectional imaging. You know our suggestions are the patient should be evaluated by a surgical oncologist per section the patient presents, with an isolated mesenteric mass or small bowel mass, and the reasons we consider surgery.
are again, it could be diagnostic.

Sometimes these tumors are not always new render consumers,

but they usually are when we look at it with our radiologists,

so it’s something to consider.

In, the operation is potentially curative and this is very important.

It can avoid future symptoms of bowel obstruction,

bleeding or ischaemia,

which sometimes happens in these small bells are under primary.

Tumors are left alone,
so that’s an important point to mention and we do see that sometime with the patient that had an arrangement in which was being observed and so and the patient can present with some symptoms down the road. And of course it can avoid reduced risk. Another scenario is an asymptomatic primary with distant metastasis, and again this can be. This would suggest to be evaluated by a surgical oncologist and the reasons for surgery in order
to avoid future complications and metastasis and discomfort. This kind of an approach can still provide a profession free survival advantage. And then, if patients present symptomatically and impatient that’s presenting symptomatically should probably just get to the operating room and be seen by a general surgeon in the local hospital. Because sometimes these patients you know don’t have room to be transferred, and they and acute ballot traction should just usually be managed locally and the reasons for this.
Of course the obvious it alleviates her symptoms. That it can be diagnosed and be potentially cured. And a patient example here is an asymptomatic patient with an asymptomatic small bell NET. This is a 59 year old male who presented with a 4.2 centimeter hyper enhancing mesenteric mass on CT for abdominal pain, which resolved by the time we evaluated him and then this picture shows a CAT scan with a hyper In Sync 4.2 centimeter mass, which we ended up taking to the OR and resecting which is
01:03:03.502 --> 01:03:05.699 showing all the way in the right.
NOTE Confidence: 0.876315255
01:03:05.700 --> 01:03:09.060 And we did an en bloc small bowel
NOTE Confidence: 0.876315255
01:03:09.060 --> 01:03:11.204 resection with the mesenteric mass
NOTE Confidence: 0.876315255
01:03:11.204 --> 01:03:13.700 and the surgical pathology
NOTE Confidence: 0.876315255
01:03:13.774 --> 01:03:15.679 revealed multifocal tumors.
NOTE Confidence: 0.876315255
01:03:15.680 --> 01:03:18.910 Node positive disease without metastasis,
NOTE Confidence: 0.876315255
01:03:18.910 --> 01:03:22.109 and it was a grade one tear.
NOTE Confidence: 0.876315255
01:03:22.110 --> 01:03:22.956 And finally,
NOTE Confidence: 0.876315255
01:03:22.956 --> 01:03:25.494 I'll end this session by submitting
NOTE Confidence: 0.876315255
01:03:25.494 --> 01:03:27.469 metastatic here under consumers.
NOTE Confidence: 0.876315255
01:03:27.470 --> 01:03:28.136 So again,
NOTE Confidence: 0.876315255
01:03:28.136 --> 01:03:29.801 some perspective on things from
NOTE Confidence: 0.876315255
01:03:29.801 --> 01:03:31.384 a surgeon’s perspective that so
NOTE Confidence: 0.876315255
01:03:31.384 --> 01:03:32.980 the reason we find this important
NOTE Confidence: 0.876315255
01:03:32.980 --> 01:03:34.489 is because the third patient,
NOTE Confidence: 0.876315255
01:03:34.490 --> 01:03:36.010 present with cysteine metastasis
in the liver, happens to be the most common site of metastasis. Metastasis is important because it negatively affects revival as, and that’s the case with all cancers, and there’s a increased risk of death compared to an individual that has localized disease. Clinical presentation can include hormonal symptoms, and that’s more often the case for small bowel and any tease. This could be diarrhea,
wheezing and flushing,

and sometimes the patients could have valves are right sided valvular disease which can lead to heart failure.

Increase your under.

Consumers are important.

They’re at their often nonfunctional burden and by respecting ones metastatic neuroendocrine tumors.

The progression free survival improves the patients as a whole and you know
01:04:37.574 --> 01:04:39.842 the literature can show five year overall five year survival up to 74%.
01:04:39.842 --> 01:04:42.316 That's overall survival,
01:04:42.316 --> 01:04:43.324 but the important thing to understand is there's a high risk of recurrence.
01:04:43.324 --> 01:04:45.340 Despite that kind of an approach,
01:04:45.399 --> 01:04:47.254 so even though I'm talking about 5 year old roll survival,
01:04:47.260 --> 01:04:49.078 so even though I'm talking about 5 year old roll survival,
01:04:49.080 --> 01:04:50.310 if 74% the recurrence rate is nearly is over 80%.
01:04:50.310 --> 01:04:52.060 But there is benefit to doing this because it can provide effective symptom control,
01:04:52.060 --> 01:04:54.310 particularly for functioning tumors.
01:04:54.310 --> 01:04:56.560 It could prevent or delay the
sequelae of carcinoid syndromes.

It can improve one’s performance status and pain,

and this is the case more for nonfunctioning tumors and the number has shifted us to the number of the percent of tumor that we’d like to site, or reducing individual.

And there was a time where.

We used to think more along the lines of 90% but more recent literature has suggested that that number might be closer to 70%.

Reduction of the tumor burden, and it’s important if one can have this kind of cytoreduction,
and we usually try to remove the primary tumor in the regional disease in this 70% number that I mentioned. But even if one does not have their primary tumor that’s identified. One can still consider a cytoreductive surgery if greater than 70% of the disease burden that’s clinically present can be addressed. And extrahepatic disease is not a contraindication to the surgical site or reduction. The tools that we use in surgical oncology for Cytoreduction,
on the liver because I’m very biased towards the liver and, uh,
I like operating the liver and then this ends up being the most one
of the most common sites for the most common cited medicine disease.
For any tease, we often will try to do what’s called prank while sparing resections,
because, as I mentioned before, many of these patients were occur and they can have a longer survival,
and they can recur in the liver, so we try to do prank whispering resections.
Impossible understanding that.
Well, if there’s another recurrence down the road,
it can allow the patient for a second liver operation or liver directed therapy down the road. But sometimes we do need to perform major head protect me as given the distribution of the testis is sometimes we consider a microwave ablation where we put a probe into the center of the we put a probe into the center of the we put a probe into the center of the we put a probe into the center of the and if they can do it in the last invasive fashion, that’s always. Investing for the patient and surgical
site or rejection should be attempted when it’s anatomically feasible and it can be performed with a low morbidity. So I’ll end with a patient example, and this is a 62 year old male who, when I had seen him, was five years after the status posted, dissipate protect me for nonfunctioning tankers or under consumer one of his smile. Medical oncologists was surveying him and and identified enlarge. And this doesn’t show everything, but this is a patient that had three tumors when we had seen him,
one in the left lateral liver,

one in the left medial liver,

and then one in the right liver.

And and then we went ahead and we

actually needed to do a major

liver section for the left side,

and apparently sparing resection on the

right side to clear all of the disease.

And and we did a cholecystectomy

in this case as well too,

and the pathology revealed

for neuroendocrine tumors,

which were identified in the liver,

which were well differentiated.

So the surgical manager of papers at
small bowel neuroendocrine tumors, the incidence is rising. Section of primary neuroendocrine tumors. This clinical benefit and we’ve shown that, and I’ve shown that the pancreas for under consumers those non functioning, functioning and for small Val any teas and finally surgical site of reduction for metastatic. Any tease has clinical benefit at greater than 70% of the tumor burden. Which percentage. OK, thank you for your time. Thank you to doctors appointment and con. Those were both great presentations, so I think what we’ll try to do is
01:08:48.810 --> 01:08:50.544 tackle some of the questions that
01:08:50.544 --> 01:08:52.748 have come through the chat and I also
01:08:52.748 --> 01:08:54.538 have some questions for the two of
01:08:54.538 --> 01:08:56.288 you and we can have a conversation.
01:08:56.290 --> 01:09:00.586 So one of the the first questions
01:09:00.586 --> 01:09:03.061 that came through is I think this
01:09:03.061 --> 01:09:04.363 was in reference and Doctor Boy
01:09:04.363 --> 01:09:05.987 and maybe I'll direct this to you.
01:09:05.990 --> 01:09:09.246 Is can the Ludo dictate treatment?
01:09:09.246 --> 01:09:11.640 PR T if it started early I'm
01:09:11.640 --> 01:09:16.440 can we achieve cure from this?
01:09:16.440 --> 01:09:20.340 And particularly if the cancer load is low,
01:09:20.340 --> 01:09:24.674 that's I think aspirational,
01:09:24.674 --> 01:09:27.180 but I will allow you to maybe
01:09:27.180 --> 01:09:28.616 comment some on that.
What are the goals of treatment and in what setting do we typically use it? Yeah, this is a really great question now. The indications for which PRT is being used for right now is for well differentiated tumors, and when we do the therapy majority of the tumors actually do not decrease in size, but it does slow their growth, so there’s significant improvement in progression. Free survival. So no, this is not a cure, but it does improve symptoms and improve survival. In patients. So that’s for the lutetium. We still have a lot of other therapies in in
the pipeline that we’re still evaluating,

but the goal is not cure.

The goal is extension of life

and improvement of symptoms.

Thank you, there was another question that

I think perhaps Doctor Khan can answer.

So and I think you addressed this

a little bit in the course of your

presentation such so is it possible

that we maybe can’t find the primary,

but we do see metastatic disease.

You touched on that a little bit in the

course of your surgical indications,

but maybe you can address that some. Yes,

yeah, so that’s not an uncommon scenario.
Back spoons, and that's very good question. And you know it is all worth it to look for the primary tumor and do a thorough exhaustive look for the primary tumor. However, the primary tumor cannot be found. There is benefit towards some. If a patient has a resectable metastatic disease, which could be said or reduced to over 70%, and the morbidity is not very high. Uh, I would still recommend consideration for surgical cytoreduction because of the improvement in the professional free survival. And I'll just comment this. You know, entity of unknown primaries is
certainly something that we come across, although I will say I think that’s less in the era of gallium 68 PET scans.

I think we are often identifying the primary a little bit more easily with better imaging so, but we do still see that I have a couple of questions actually there.

Some cancers, even lung adenocarcinomas,
had endocrine secretion. How can we treat that? I didn’t personally spend a lot of time talking about how we treat hormone control, but I think for certainly for many patients with neuroendocrine related hormones secretion we the mainstay is really using somatostatin analogs. First they were approved on the basis of controlling hormones, specifically carcinoid syndrome, which is diarrhea and flushing. They are also indicated in some. Other forms of hormones secretion, including gastrinomas and others. But we also try to PSI to reduce or
kind of reduce the bulk of the tumor, either through surgery as Doctor Khan indicated or other systemic treatments that have the ability to shrink the tumor. So cytotoxic chemotherapy can do that. Doctor Khan, I think, spoke about some of the like oblated procedures. We often didn’t talk tonight a lot about liver directed treatments, but I think that when patients have secretion of hormones, we really it’s tricky. Because we need to think about both managing the hormones and managing the tumor itself.
So doctor, can you have any other comments on that? Yeah, I know, I think those are why you know if if if an individual has a patient. If a provider has a patient with, you know neuroendocrine tumor general, but in this specific scenario it's good to have them evaluate in a multidisciplinary fashion. Because surgery. I'm not saying everyone needs surgery and sometimes systemic options are much more effective at controlling these symptoms than surgical options. And and I think that's why you know an active discussion by a
NOTE Confidence: 0.891338747777778
01:13:47.674 --> 01:13:49.018 multidisciplinary tumor board.

NOTE Confidence: 0.891338747777778
01:13:49.020 --> 01:13:51.940 Is it is very beneficial for the patient, but you know if if one is able

NOTE Confidence: 0.891338747777778
01:13:51.940 --> 01:13:53.636 to control you,

NOTE Confidence: 0.891338747777778
01:13:53.636 --> 01:13:54.320 know a high burden of disease like

NOTE Confidence: 0.891338747777778
01:13:55.937 --> 01:13:58.034 I threw the number of 70% out there. That’s that’s for surgical literature.

NOTE Confidence: 0.891338747777778
01:13:58.034 --> 01:14:02.080 But I don’t know if this is true or not, but perhaps that would is true for non-surgical approaches as well too.

NOTE Confidence: 0.891338747777778
01:14:02.080 --> 01:14:04.796 And I think if we’re able to address the source of where the hormones are being separated from,

NOTE Confidence: 0.891338747777778
01:14:04.796 --> 01:14:12.352 we could probably really provide some good clinical abilities to our patients.
Right, right now I agree.

Good doctor Brian.

I have a question that comes up almost in many of my patient interactions and also when I'm teaching trainees this actually just came up yesterday.

How do we interpret SUV on Gallium 68 pet? Should we pay attention to it?

Is it different than how we think about FDG pet?

Oh yeah, that’s a great question. It’s a we can give a whole lecture tracer uptake, so I would I would think too.

I do recommend to, so it’s a.

It’s a general unit of Tracer
update that’s generalized to patient body weight. But the big issue?
Hope we lost Doctor Abovyan there for a moment. So hopefully she will be back. I can text her, we technical issues. Related to the tax, there will be a doctor boy and we lost you for just a minute. Maybe you can repeat the last portion of that. Oh sorry, I was having Internet connectivity issues so so in terms of that SUV is it’s a way to measure tracer uptake normalized to patient body weight. And it is a semi quantitative that measure.
Now there's a whole field of quantitative PET that requires very complex mathematical modeling. And here at EO, under the guidance of Doctor Rich Carson, their leader leaders, they go pet center in quantitative PET imaging and we're still trying to figure out how to apply to clinical practice because it's not used in clinical practice. But as UV is kind of a poor man's approach to try to quantitate so it's a semi quantitative measure, but I would really focus on looking at the CVS within a specific tracer.
SUV values only, compare them between gallium dotate scan. Don’t compare them between gallium dotate and don’t talk or gallium dotate, and if you’re so, if you have a patient that’s being imaged with MTG pad, then you can compare the SUV values. But if you’re patient change significantly so supposedly lost a lot of weight in between the scans, then you have to be really careful and usually in nuclear medicine we do the reports, we do mention the numbers.
'cause everybody wants some. Connotation, well because it’s it’s is a semi quantitative analysis. Thank you, yeah that’s helpful. Doctor Khan I have a question that comes up a lot in tumor board. You know, I think I’d love to hear from you of. Are there situations or or notable situations where you’re like? Gosh, I really wish I saw this patient earlier, like when? When should medical oncologists or surgeons in the community be thinking about surgery?
When should it be on their radar?

I'd say specifically for metastatic disease.

OK, you know the first. Maybe I can also answer one about non metastatic disease. Some you know. I think if one identifies a hypervascular mesenteric mass, I would consider that I wouldn't just sit on it. I would consider sending it to one of the surgical oncology, one of the general surgeon to evaluate for it, because you know, every so often we do see a patient that...
01:17:47.942 --> 01:17:50.557 has had this followed a cross sectional
NOTE Confidence: 0.842575879166667
01:17:50.557 --> 01:17:52.651 imaging and then presents with you
NOTE Confidence: 0.842575879166667
01:17:52.651 --> 01:17:55.014 know some sort of a problem with the.
NOTE Confidence: 0.842575879166667
01:17:55.020 --> 01:17:56.680 Primary small bowel related issue.
NOTE Confidence: 0.842575879166667
01:17:56.680 --> 01:17:59.040 Whether it’s this kimia infarct
NOTE Confidence: 0.842575879166667
01:17:59.040 --> 01:18:00.714 or balance traction and then it
NOTE Confidence: 0.842575879166667
01:18:00.714 --> 01:18:02.840 becomes more of an emerging problem.
NOTE Confidence: 0.842575879166667
01:18:02.840 --> 01:18:04.478 And it’s something that I probably
NOTE Confidence: 0.842575879166667
01:18:04.478 --> 01:18:06.644 could be less of a bigger operation
NOTE Confidence: 0.842575879166667
01:18:06.644 --> 01:18:08.660 for metastatic disease as well too.
NOTE Confidence: 0.842575879166667
01:18:08.660 --> 01:18:09.718 So actually,
NOTE Confidence: 0.842575879166667
01:18:09.718 --> 01:18:13.421 the last patient I presented was being
NOTE Confidence: 0.842575879166667
01:18:13.421 --> 01:18:16.536 followed for awhile because the the
NOTE Confidence: 0.842575879166667
01:18:16.536 --> 01:18:19.605 tumors were were visible and I had
NOTE Confidence: 0.842575879166667
01:18:19.605 --> 01:18:22.090 given a talk on liver metastasis about.
NOTE Confidence: 0.842575879166667
01:18:22.090 --> 01:18:24.136 You know around that time and
then the individual who. Caring for that patient was didn’t realize that surgical options so I think if a patient is known to have a neuroendocrine tumor and perhaps present was the liver metastases, I think it’s worth it for that patient to be seen by GI medical oncologist or surgical oncologist. Because I do think that we can provide a good progression free survival benefit for most patients in that kind of a scenario. If with a good multidisciplinary approach.
Great thank you and doctor Brian.

Maybe I’ll ask you one one more and sort of.

I’d say a really exciting direction and something you and I are partnering on is really thinking about a theranostics program.

Can you speak to how you think the field is changing and how we are likely to see the development of theranostics programs?

Sort of in multiple locations, but maybe the value of that.

What that means and and sort of how nuclear medicine docs are going to be.

Providing direct patient care.

Oh, thank you. Yes,

this is a very exciting field and
I just came back from Society of Nuclear Medicine and Molecular Imaging Therapeutics conference where we met for several days and talked about how different sites across USA are starting the theranostics centers and their layout plans and how they’re going to be treating the patients. We are now going back to senior patients. We’re now we’re now becoming parts of teams with oncologists and surgeons and really practicing together and with radiation oncology as well and
we’re really practicing together as a team in terms of taking care of patients. There’s sites where patient is being seen by their GI oncologist and followed up by a visit with nuclear medicine Doc to discuss PRRT and the specifics of radiation based therapy radionuclide. Therapy and that really helps patients in terms of understanding what they’re going to be undergoing and their side effects and the risks. The nuclear medicine physicians are following up on the patients and are involved in the care. So another thing that’s really helpful is that we’re starting to combine...
chemotherapy with radionuclide therapy and trials and trying to see how we can improve the efficacy of these therapies. And the only way to do it is to work together. So it’s a really exciting team based approach that’s happening across the country and it’s really gonna change radiology and how we care for our patients. Not very exciting, I think. Lots of opportunities for asking for really gonna change radiology and how we care for our patients. One thing we can speak to is really
the importance of multidisciplinary care for the care of these patients. I think the intent was to have three different disciplines represented on this panel tonight and I think we all certainly work together and caring for our patients with Nets. So I think what we can do is I don’t see other. I don’t know if Doctor Boyd or Doctor Khan you had any other burning questions for each other or anything that has come up. If not, I really want to thank the two of you. Certainly for your time and excellent presentations,
I want to thank our audience for their time and listing tonight. This will. This has been recorded so we will make this available to the Community and stay tuned for our future GCM E series in April and May. We will promote those and hope that some of you will listen again. So thank you and have a wonderful evening.