HEIDI MARIE MUNGER CLARY, M.D.: Good morning. before we get started, I wanted to get a quick sense of you in the audience. Raise your hand if you work in neurology, in some area of neurology, currently-- OK, so quite a few. And then how about primary care areas and then other specialties besides neurology or primary care? OK, good, so we've got a good mix of a group.

I have two main goals today. One of which is to convince you why people practicing in any area of medicine you should know about refractory epilepsy and the potential benefit of epilepsy surgery. And then the second component of the talk will cover, quickly, the basics of the presurgical-surgical evaluation and then the wide variety of surgical techniques that we have available.

So with that, this is a slightly more specific outline of the different things that we're going to talk about this morning. So first, what we need to do is talk a little bit about, well, how do we define drug resistant epilepsy or intractable or refractory epilepsy. These terms are used pretty interchangeably.

So the ILAE recently came out with a new precise definition of drug resistant epilepsy. And at this point, that's the preferred term. And that is defined as failure of two anti-epileptic drugs, used in adequate or informative trials to control seizures full. So the goal is full seizure control.

And what is an adequate or informative trial? How do we define that? Well, that means that the medication was an appropriate choice for the type of epilepsy that the patient has, that the patient was able to tolerate a reasonable dose of the medication. So using that, that's how we would characterize patients as having drug resistant or refractory epilepsy.

So then the question becomes, how early might we be able to figure out whether someone has drug resistant epilepsy or not. And to touch on this topic, we'll go back to a very nice study that was published back in 2000 in the *New England Journal of Medicine*, in which a group in the UK followed patients prospectively from the time of initial treatment with medications for seizures and saw how patients did over time, with each subsequent medication trial, saw how many patients became seizure free with each medication trial.

And some of the key result are here. Now, the first medication trial made a very large percentage of the patients seizure free-- 47%. Those who failed that first trial of medication, when a second medication was tried, were much less likely to become seizure free. Only 13% of those who failed the first drug responded to the second medication trial.

And then, for the third medication trial, those who failed the first or second trial, only 4% of those patients became seizure free for a period of a year. So oftentimes, very quickly when patients begin treatment for epilepsy, we can start to get of whether or not they are going to have drug resistant epilepsy.

And the next question is, well, based on this study did we learn anything about what kinds of factors might predict who is going to have drug resistant epilepsy. And there were two risk factors that came out of the study. And the first one-- which this is a little bit small, but in the handouts you can see. The first risk factor was, if the etiology of the epilepsy was thought to be what we call symptomatic cryptogenic, meaning the patient may have had a structural lesion or some kind of known cause of epilepsy, as opposed to having idiopathic epilepsy, which means there just simply a presumed genetic cause. That would include syndrome like childhood absence epilepsy, juvenile absence epilepsy. And this study followed both children and adults.

And then the second risk factor for drug resistant epilepsy was number of seizures prior to the initiation of treatment. And there was a kind of roughly linear relationship between the higher number of seizures before onset of treatment. This bar here is 20 seizures before. And more than half of those patients did not respond to any of the drug trials and the likelihood that they were going to not respond to medications.

And this probably reflects a measure of seizure frequency right at the onset of epilepsy. So patients with higher seizure frequency may be more likely to fail medication treatment. Most of the patients didn't have a large variety of time from start of seizures to initiation of treatment. So number of seizures before was mostly a measure of seizure frequency.

Moving on-- so once patients have drug resistant epilepsy, they've failed at least two good trials of anti-epileptic medications. What do we know about how those patients do with further medication treatment over time? There were two cohort studies done at a couple of major epilepsy centers, University of Pennsylvania and Columbia University, looking at a group of patients followed in those centers of that group.

And the main things that were found in these studies is that there is a small percentage of patients that, over years, with continued medical management, trials of other medications-- a small number of patients will attain at least a one-year period of seizure freedom, at some point. And that's estimated to be between 3% to 5% per year, combining the two studies.

So there is some hope with medication treatment for patients who've failed other medications. But it's a relatively low chance of attaining seizure freedom. Then, those who had a one year period of seizure freedom in these groups, how many of them then went on to have seizure relapse later. And the answer to that question is, almost all of them.

By five years, 81% in the study from Columbia ended up having relapse of seizures over time. So further medication treatment isn't hopeless. But the chances of attaining very sustained seizure freedom are pretty low in this group of patients.

So let's now switch gears a little bit and talk more about what are the impacts of having drug resistant epilepsy, continued seizures, on patients. In other words, why should we care about this problem? And the reason is, there are multiple effects that continued seizures have on patients. One of them is poor quality of life.

So this study that looked at comparative quality of life between patients with epilepsy with varying degree of seizure frequency and then patients with other medical conditions, specifically depression, hypertension, diabetes, and heart disease, and looked at quality of life among those different groups. The medical diseases are in purple. And depression is down here, also in purple.

Each of the points across the x-axis correspond to different dimensions of a quality of life measure, with this first point here being overall quality of life. And what you can see is, that in comparison to the medical disease patients, patients who had epilepsy with continued seizures that involved some kind of loss of awareness had the lowest overall quality of life, compared to all the medical diseases but was a little better than depression. So this has a significant impact on quality of life.

Well, what if the patient only has seizures that do not impair awareness, simple partial seizures. Well, patients of that sort, their quality of life was pretty similar to patients with heart disease, hypertension, diabetes. But it was only those patients who were seizure free, who had noticeably better quality of life than patients with these other chronic diseases.

So epilepsy has a big impact on quality of life. And if the patient is not seizure free, quality of life is significantly impacted. And some of the reasons for that are obvious, once you start thinking about it.

Dr. Wang already mentioned aspects of driving restriction. That can impact life just so dramatically, even if somebody is having say, one seizure a year-- still can't drive. This can lead to employment limitations. There's the stigma associated with seizures, risk of injury due to seizures.

We know that patients who have continued uncontrolled seizures over time have memory decline over time. And then there's the medication side effects. Patients like this will be generally taking more medications, higher doses. And that can effect different aspects, that would lead to poor quality of life.

So what other impacts does the presence of continued seizures have? So there's a condition called sudden unexpected death in epilepsy. Overall, when you look at epilepsy as a whole, the risk of sudden unexpected death compared to the general population is about 20 times higher.

And if you look more specifically at different populations of epilepsy patients, based on severity and frequency of different seizure types, the risk is higher. The more frequently patients have generalized tonic-clonic seizures, the more refractory the group is.

And this is from a review summarizing the results of multiple different observational studies that measured the incidence of SUDEP and in different kinds of groups-- very new onset epilepsy, community epilepsy groups, intractable epilepsy cohorts, and then patients who were surgical candidates or failed epilepsy surgery. And you can see how much higher the rate of SUDEP is, in those patients are more refractory. It can be as high as 1% per year, in that really refractory group. So basically, continued seizures in the setting of drug resistant epilepsy can have major impacts on quality of life, as well as mortality.

So then, now what we'll do is, we'll switch gears and talk a little bit about what's the potential for the impact of surgical therapy. What possible outcomes could occur? And the answer is, that for certain patients who are good surgical candidates, it can make a big difference.

So this is a slide showing some of the results from the first randomized controlled trial of epilepsy surgery, which was published in 2001. This was conducted in Canada. And basically, patients with refractory temporal lobe epilepsy were randomized either to surgery right away, by standard temporal resection-- which we'll talk about that a little bit later-- or to being on a waiting list for one year for surgery, which at that time was the standard of care.

And this shows the result of showing how many patients had absence of seizures impairing awareness in any way. And you see that surgical group, the vast majority of patients were free of those types of seizures. However, the medical group, only 8% of them had that same type of outcome. And I will say, one other thing is, that in this medical group, there was a SUDEP death. And overall, the number needed to treat here is about two.

So I don't know, when you think to own specialty, is there any intervention that you know of that has a number needed to treat that good. So this procedure could have a huge potential to make patients seizure free. And not only seizure free, but this is just a quick snapshot of frequency and a little bit of severity of seizures that patients had in the surgical group, compared to the medical group, over the one year study period. And overall, the frequency and severity of seizures also seem to improve, for some of those who were not completely seizure free.

SPEAKER 2: What time frame are you talking about this was the median with the medicine, with the Canadian study?

HEIDI MARIE MUNGER CLARY, M.D.: So one year of medical treatment versus surgery, right after the evaluation for surgery.

So then what other kind of data is out there? There was actually recently one other randomized controlled trial of a similar type of procedure that was conducted in the United States for temporal lobe epilepsy, called the ERSET trial. But the difference between that and this Weibe study was that they were trying to do surgery early, so within the first two years after someone became medically refractory.

And that trial, unfortunately, was not able to recruit enough participants to meet their recruitment goals, probably because the rate of referral of patients with drug resistant epilepsy that early on, to the tertiary care in epilepsy centers that we're conducting the trial was so low. But despite the fact that they did not actually meet their enrollment criteria, they still had a dramatically positive result. So it ended up being that 15 patients were in the surgical arm, and 23 patients were in the medical arm.

11 of the 15 surgical group patients, at two years, were seizure free. And non in the medical group were seizure free. And a lot of those medical group patients went on to have surgery in the short term after that.

So we have a little other randomized data, but not as much as we were hoping to get from that trial.

SPEAKER 3: Can I ask a question?

HEIDI MARIE MUNGER CLARY, M.D.: Absolutely.

SPEAKER 3: So those medical folks, are they on one drug or two drugs?

HEIDI MARIE MUNGER CLARY, M.D.: Most of them are on multiple medications. And they could have continued typical medical management, adjusting the medications to try to attain better seizure control during the trials.

So far, I've only been talking about temporal lobe epilepsy surgery. So what about patients who have focal epilepsy, but it's not coming from the temporal lobe? Well, this is a study that was conducted in a number of the US academic epilepsy centers, that was observational study, looking at patients who received epilepsy surgery, either for temporal lobe epilepsy or extra temporal lobe epilepsy and following them in terms of seizure outcome, quality of life outcome, and other outcomes over many years after the surgery and starting at the time of their surgical evaluation.

And what you can see is that at up to four years out from surgery, the cumulative probability of having at least a one year remission, in the group that had a medial temporal resection, that up to almost 80%. But those patients who had neocortical resections, a lot of them were not just temporal lobe epilepsy patients. A lot of them still had quite good outcome, when we think back to that medical outcome data we just looked at. And almost 60% of them also attained a one year seizure free period. And quality of life also improved significantly, in the three months since surgery. And that had a sustained improvement over two years.

And then this is just a small reminder-- of course, these aren't the same populations-- but of kind of the difference in what we know about the potential for seizure freedom of a duration one year, with either surgical treatment on the left, medical treatment on the right. Of course, they're slightly different populations, so it's not a perfect comparison.

OK, so what's the problem? Well, despite the fact that we have this kind of data showing that some patients can have a dramatic impact, if they undergo epilepsy surgery. The time to referral of refractory epilepsy patients for a surgical evaluation is extremely long. So in the multicenter epilepsy surgery study, the mean duration of epilepsy at the time of referral or the initiation of the evaluation was 22 years. And that's that kind of time frame has been replicated in many other studies as well.

So the community thought maybe, once the AAN practice parameter promoting epilepsy surgery came out in 2003, perhaps referral patterns would change, and patients would be referred sooner. So the UCLA group took a look at that and looked at a few years before the practice parameter or that randomized control trial we went over in detail and then a few years after the practice parameter and found no difference in the delay to surgical referral, still about 20 years in their center. So this is part of the reason why it's really important, no matter what specialty you're in, to kind of, if you see a patient who has tried a lot of drugs and is still having a lot of seizures, think about referring them to an epilepsy center.

So now, who might be a good candidate for epilepsy surgery? The answer is, it's complicated. But there are a few groups that are particularly good surgical candidates. First of all, there are a lot more techniques and a lot more techniques likely to cause seizure freedom for patients with focal epilepsy, as opposed to generalized epilepsy. And if the patient has a potentially epilepsy-causing lesion, they are much more likely to have a good outcome with epilepsy surgery.

And I've just listed here some of the lesions that have potential for very good outcomes, based on various observational studies. And then, hypothalamic hemartoma, that's something where surgery is really the treatment of choice. Cortical dysplasia, depending on the particular characteristics of the patient, may potentially have a very good surgical outcome. But really, any lesion, surgery is something to consider. And the patient with any sort of lesion might potentially be a good surgical candidate.

And in general, any patient with some sort of drug resistant epilepsy might be a candidate for some type of epilepsy surgery technique. And referral to a comprehensive epilepsy center is really indicated for any patient with drug resistant epilepsy.

So what if you have somebody who perhaps is not clearly a drug resistant at this point? Are there any tools that can help you decide whether they should be referred? This is a neat, web-based tool that was developed based on an evaluation of multiple different case scenarios by a panel of experts in epilepsy surgery, to try to create this tool and help guide people, in terms of referring patients who may not yet have met criteria for drug resistant epilepsy.

And I'm just going to show a few screenshots from that website. It starts out with just giving some general advice about patients who should definitely be referred to a comprehensive epilepsy center. And then it takes you through a series of simple questions, looking at what seizure type does the patient have. How long have they had epilepsy? Seizure frequency, severity, medication trials, side effects, and then the results of their EEG and MRI-- and after you go through those few simple questions for your patient, then it gives you a score and a recommendation about whether that patient would be appropriate to refer for epilepsy surgery.

And this particular scenario that I put in, that wasn't somebody who yet really needed to go to an epilepsy surgery center. So hopefully, that tool may be of some use to some of you in the future.

So then, what is the presurgical evaluation composed of? So we'll take you through a brief tour with a couple quick examples of that. Now, first of all, the overall goal of the epilepsy surgery evaluation is to assess whether using multiple different types of testing modalities to figure out whether they all point to one single area, that might, if it was resected, result in seizure freedom. And we call that the epileptogenic zone.

Now, no one test is perfect at identifying that particular area. So we use multiple modalities to try to approximate it and then come up with the best possible surgical plan for the patient, as an individual. So these are the basic components of a surgical evaluation that I would think that almost any center would do all of these things for any patient who's being evaluated, so brain MRI. video EEG, looking at both-- what happens when the patient has seizures-- recording multiple seizures and looking at where those appear to come from on the scalp EEG; also looking at the detailed video recordings of the seizures to gain some information from the clinical manifestations of that seizure; and then also looking at the EEG findings in between seizures. Additionally, neuropsychological evaluation and a clinical neurological exam would be included in the most basic surgical workup.

So now what we'll do is go through just a couple of quick examples of some of the results you might see these tests and that might be useful in planning an epilepsy surgery. So the MRI, the purpose of that is to figure out, well, do they have an epileptogenic lesion. And patients will often already have this test done at the time that they're referred.

So this is an example of one of the lesions that can lead to the best potential outcome, if the patient undergoes epilepsy surgery. So if we look at-- let's see, look at the hippocampi here on the right and the left. You'll notice a few things.

This one on the left is much smaller than the right. And on the right, you see nice kind of spiraling layers of the hippocampus, not as well seen here on the left. So this is smaller. On the left, the architecture is not as good.

And then, when we look at coronal flare image the left hippocampus is brighter. And so these are the imaging characteristics of mesial temporal sclerosis. So that's one of the key lesions that we know can potentially be associated with a really good outcome from epilepsy surgery. So that's the main purpose of the MRI study.

So then, EEG in between seizures-- what we're looking at there is trying to figure out, in between seizures, are there spikes. And where are they? And we interpret spikes as showing that the underlying cortex there is irritable. And it may potentially be somewhere that a seizure could come from. And this is an example of a left temporal spike.

Not very many of you here are neurologists or epileptologist. But hopefully, you can appreciate how much this stands out. And that comes from a group of cells firing synchronously and then relaxing. And so that's something that we look for. So that a left temporal spike.

So then, moving on, we record the EEG during the seizure and try to identify where does that seizure start. And if you look here, you'll see these rhythmic spikes, just going and going and going. And these happen to be in the left temporal region. And this particular pattern is often seen when somebody is having a seizure that is involving the left hippocampus. So that's just a simple example.

So then, other components of the basic evaluation-- when we look carefully at the video the seizures that the patient has, what we're looking for are clues to what brain regions are active at the time the seizure is going on, which areas are causing those seizure symptoms.

Neuropsych testing is used to determine whether or not there are particular areas of cognitive weakness. And many of the cognitive functions map to specific areas of the brain. And if there's one particular function that's weaker than other functions, oftentimes, that may be a dysfunctional area where seizures come from. So that's one of the things we use neural neuropsychological testing for.

And then, particularly for patients who have temporal lobe epilepsy, the function that they have in terms of verbal memory, for example, how good that is may give us some information about whether or not they may have a decline in their verbal memory, if they were to undergo surgery. So it helps us with prognosis as well, in terms of cognitive outcome. And then, the neurological exam, if they have a focal deficit that localizes to some area, that can provide additional information, as far as where seizures may be coming from or where the epileptogenic zone may be.

Now, at our center, the following three studies are part of our standard workup. And different mixtures of these studies are probably standard at different centers. Sometimes, these techniques are used in particular patients, if they're a little bit more complicated, to find more information. So we'll look at some examples of these studies.

So the PET scan, it's FDG PET. So what the purpose of the PET scan is, it's to look at different areas of the brain and the metabolism, in terms of glucose use, with that radio-tracer glucose, in different areas of the brain. And we aim to do the PET scan when the patient is not having a seizure. The seizure focus often does not use as much glucose or has lower metabolic activity than other areas. And so we're looking for an area of hypometabolism.

And this might look a subtle from the distance. But basically, the way that this is interpreted is, the brighter or hotter colors mean there's more metabolism in a given area. And if you look carefully at these temporal lobes, the left temporal area has a lot less yellow, a lot less of those brighter colors. And that's an example of that type of left temporal hypometabolism that we may see in a patient with left temporal epilepsy.

So then, another study-- also in the nuclear medicine category that we use-- is ictal and interictal spect. And this study reflects the amount of blood flow in different areas of the brain at a given time. We use a technetium-based tracer.

And the idea here is that the seizure focus, when someone is not having a seizure, is potentially a dysfunctional area brain that may not receive as much blood flow as the normal areas of the brain. But during a seizure, the blood flow to the seizure focus is going to be much higher than other areas of the brain, because of all of that activity going on.

And so this is an example of one of my patients. And her ictal and interictal PET. So if we first look at this row here, these are her scans when she was not having a seizure. And if you look and compare this part of the temporal lobe on the left to the right, there's a little bit less of that bright yellow, as well as here. So there's a little bit of reduced blood flow in the left temporal area, when she's not having a seizure.

Now, during her seizure, look at how much more of that yellow and even some orange-- so increased blood flow-- we see in that area. And then our radiologist will do a mathematical subtraction. And that really highlights the areas where the blood flow increased dramatically in the setting of the seizure.

So then for selected-- oh, good. So then one other study that is a standard part of our work-up here-- but the technique isn't available in a lot of epilepsy centers-- is magnetoencephalography. And this is looking at a similar concept to the interictal EEG. Where is the brain irritable? What places might a seizure be able to come from?

But the MEG has a couple of advantages, potentially, over EEG and can sometimes add something a little bit extra. So the first thing is that, if you all recall from Physics, way back in undergrad, for every electrical field, there's a perpendicular magnetic field. And the way that scalp EEG works is, it's really best at picking up brain potentials that are radially oriented, so oriented from inside, towards the scalp in sort of a perpendicular manner to the scalp.

But some epileptic spikes that a patient may have may be oriented in more of a transverse way. And a small percentage of those kinds of spikes may be completely missed by EEG. But because MEG is looking at a field that is oriented perpendicular to that electrical field, MEG may pick up those types of spikes. So that's one of the uses of MEG.

And then one of the other advantages of the MEG technique is that there are ways to try to calculate, based on where we see a spike and how it looks on different electrodes, on and array that's all over the scalp, to try to calculate, where is that source within the brain deep. And that's a very difficult thing and very flawed thing to try to do with EEG, because the electrical signals are distorted significantly by the cranium and the scalp and all of that. But MEG is not affected in the same way by those intervening tissues, so we can do a better job of trying to estimate where is the source.

And so this is an example from a research study where the calculation was done. Let's see if we can get the pointer to work. Here we go.

And based on the calculations, these yellow areas were felt to be the possible locations that the spike was coming from. And then the bottom left panel shows what those spikes looked like on the MEG recording. So that's just one example of how that may be used.

So then there are some additional special studies that we may do for a particular patient. The WADA test involves anesthetizing one side of the brain, testing memory and language function of that other side that's not anesthetized, letting it wear off, and then anesthetizing the other side, testing memory and language. And this is usually used in temporal lobe epilepsy patients, to assess whether there might be a risk of catastrophic memory problem, if a particular hippocampus or the temporal lobe, including those mesial. The hippocampus would be resected.

And it can also give some predictive information about, if you end up respecting a left temporal lobe, including the hippocampus, whether the patient may have a small amount of verbal memory decline, which is usually reported as a word-finding difficulty. Functional MRI may be used to get a map, an idea of where the eloquent functions are, ahead of time, going into surgery. And MEG techniques can also be used to obtain that type of information as well. And sometimes diffusion tensor MRI will be used to map out the white matter tracks associated with some eloquent functions for surgical planning. And then, we're going to talk about these further surgical evaluation techniques in a few slides.

So now what we'll do is take a very quick sort of whirlwind tour of the various different surgical therapies that are out there. So starting with some of the standard techniques-- this diagram shows what the procedure specifically was that was done in the randomized controlled trial of temporal lobe epilepsy surgery, the Wiebe trial from 2001, the one done in Canada.

And basically, what they did is removed a certain portion of the anterior temporal lobe, including laterally. And if it was the non-dominant hemisphere that was being resected, they went to six to 6.5 centimeters back from the front of the temporal lobe. If it was dominant hemisphere, they went two centimeter less back, to preserve language function. And they did take some of the mesial structures.

Now, there are variations on this technique that are done at many epilepsy surgery centers. And this is probably, if not the, one of the most common techniques used for epilepsy surgery across the country. But I think a lot of centers, like in the multi-center epilepsy surgery trial, those centers focused more on also trying to remove all of the mesial structures going all the way back.

And there's some thought that may result in slightly better outcomes. The multi-center epilepsy surgery study had a little bit higher seizure freedom rate. And that may potentially be why, although we don't know that definitively, from randomized controlled trial on that question.

So then there's a variation on this technique, a little bit less invasive so to speak, for patients who have specifically mesial temporal lobe epilepsy. So the seizures seem to be coming from the hippocampus or amygdala or those structures in the medial part of the temporal lobe, not the lateral part of the temporal lobe. And so for patients like that, a selective amygalohippocampectomy is an option. And some centers do this procedure.

The resection is much smaller. This is an example of a post-op patient from a technique that involves going in through the lateral temporal lobe and removing the mesial structures. Whether or not this results in equal rate of seizure freedom to the bigger standard anterior temporal lobectomy is unclear and controversial.

There's a lot of conflicting data. And it hasn't really been compared in a controlled side-by-side way. But there is some evidence that this technique may reduce the chance of post-operative cognitive decline.

So then lesionectomy, this is another one of the more common procedures. And usually, this isn't quite as simple as just removing the lesion only. Oftentimes, we tailor the resection a little bit more than that, to try to give the patient either lower chance of some kind of deficit afterwards or better chance of seizure freedom. So oftentimes, we may do ECoG or electrocorticography in the OR.

And what that is, it's recording from the cortical surface adjacent to the lesion, looking for spikes at that time. And if there are areas where a lot of spikes are coming from, adjacent to that lesion, then that area will also be resected, in addition to the lesion. And then, also in the OR, what can be done are different cortical mapping techniques to map out eloquent functions. And that is composed of using electrical stimulation to stimulate different areas and identify the function.

So an example is, if the concern is that a tumor may be very close to motor area, then the surgeon can stimulate areas. And you can watch, and you'll see a jerk. If it's the primary motor cortex of the hand, a hand jerk will be seen. And so that can be done even without waking the patient up in the OR.

If the concern is that a language area may be near the lesion, then there are also ways to map language in the OR. But the patient would be awake, speaking with a neuropsychologist. And then similar simulation techniques would be used. If a language area is identified, the patient will have some sort of trouble speaking, oftentimes, speech arrest or inability to name things.

And so these are techniques that can be used to reduce the risk of deficits afterwards. And then one other special thing is, that if somebody has on top of the cause of their epilepsy, there may be an additional benefit, if hemosiderin-stained tissue surrounding the cavernoma is removed in addition to the cavernoma.

So then another very common epilepsy surgery technique that's used at our center and pretty much any of the major epilepsy centers is a procedure involving two steps. Number one is putting in intracranial electrodes. And these are examples of grid and strip electrodes, directly on the patient's cortical surface and then bringing the patient out of surgery into the EMU and repeating an evaluation, recording multiple seizures, bringing their medications down. And the goal is to precisely figure out where the seizures are coming from, with this detailed mapping of electrodes.

And that's for patients where the noninvasive evaluation just doesn't provide enough information for us to know exactly what the borders of resection should be. So this is often referred to as a phase two evaluation. And the most common way this is done in US centers is using subdural grids and strips. And there might be a few depth electrodes, very thin, flexible electrodes that go deep into the brain surface.

In Europe, stereo EEG technique is used more commonly. And this is a little bit different. Instead of a big craniotomy to put the grid and strips in, what they do are multiple very small twist drill holes, to insert multiple depth electrodes. And there are few US centers that are starting to adopt this technique. And we're gearing up to start doing this. It can be advantageous, potentially, for patients who have a very deep lesion, for example. And we don't know what the boarders of the resection should be.

So as I mentioned before, the goals of this evaluation are to identify the precise location of the seizure onset. And then we also do cortical stimulation mapping if we're anywhere near eloquent cortex. We can do that in the EMU and stimulate from each of the electrodes, to map out where is the eloquent function of the brain-- 0 where are the seizure onsets-- and then come up with a safe plan to remove as much of the seizure onset as we can without causing deficits.

Now, if it turns out that some eloquent cortex is involved in the seizure onset, then there's one technique that some centers might use. It's called multiple subpial transections. These are just very superficial cuts on the cortical surface meant interrupt the cortical-cortical connections locally in that area of the brain, but without disrupting connections deeper. And usually that doesn't result in a deficit. But it may result in some benefit, in terms of seizure control, although usually doesn't result in complete seizure freedom.

Oh, let's go back one. So another technique used in very special epilepsy populations is hemispherectomy, to me, or hemispherotomy. And this is an effective surgical therapy for refractory epilepsy due to Rasmussen encephalitis It's really the only effective treatment. And it can be used to treat select young children with refractory epilepsy and a lesion spanning a whole hemisphere.

So for example, this is a patient who has hemimegalencephaly and was treated with a hemispherotomy, or what's called a functional hysterectomy. Sometimes those terms are used relatively interchangeably. And the goal of this procedure is to remove some parts of the hemisphere-- like the mesial temporal structures typically are removed-- and then to disconnect the rest of the hemisphere, at least in terms of the cortical components. Deep components may stay connected or do stay connected.

And the reason that this is done, as opposed to removing the whole hemisphere entirely is that there are multiple complications that can result if you remove the whole hemisphere-- superficial siderosis, hydrocephalis. There's all sorts of things. So this technique of leaving that disconnected brain tissue in minimizes those complications. So this is for a very select type of patient.

So then so far, you're saying, well, if somebody doesn't have focal epilepsy, why would you ever send them to an epilepsy surgery center. Well, there are some techniques that could be available to patients who have generalized types of epilepsy. The Vagal Nerve Stimulator is a device that's sort of a pacemaker-like device that is inserted underneath the skin in the left side of the chest wall and then has a wire that goes up to the left vagal nerve and stimulates intermittently.

And the mechanism of action of this is not really fully understood. But this exerts some sort of inhibitory effect in the brain and can result in reduction in seizure frequency. So down here are some of the results from the initial trial that led to approval of this device. And this trial compared patients who had the device implanted and on simulation at a very, very low frequency not expected to produce any effect, versus standard settings. And patients with the standard settings had about 20% to 30% reduction in seizure frequency.

And you see here, number of seizures per day, pre turning on the device. And then, during the stimulation period, the frequency of seizures dropped. This technique doesn't usually result in seizure freedom. And it works about as well as a medication, but it doesn't have the same side effects as a medication.

And there are some patients who can benefit significantly from this technique. So that's an option for some patients, regardless of whether they have focal or generalized epilepsy. The trials were initially done in focal epilepsy. But a lot of centers use it for all types.

And then corpus callosotomy is another standard technique that's used for patients with a very particular type of generalized, usually generalized epilepsy. So Dr. Wang mentioned the Lennox-Gastaut patients and drop attacks. And this is often the patient population that undergoes this particular procedure.

So the idea is, the corpus callosum is the biggest connection between the two hemispheres of the brain. And so the idea behind this is to disrupt bilateral synchrony of seizures that have some kind of bilateral motor manifestations. And that's by interrupted at least the anterior 2/3 of the corpus callosum.

And what this can do-- it doesn't usually make patients totally seizure free. However, there are a large number of patients that may be significantly impacted perhaps even getting rid of the most disabling seizures, those drop attacks or possibly generalized tonic-clonic seizures. And so that is often the group that may benefit quite a bit from corpus callosotomy.

And I've followed some patients who have had dramatic improvements in quality of life, don't have to wear the helmet anymore, et cetera, from this technique. So it can be very useful.

So now we're going to move on to some of the more investigational therapies very quickly. And what's very exciting is that yesterday we had some news about the Responsive Neurostimulator. So this was in the investigational category, but it's going to come into the standard therapy category shortly.

So the RNS or Responsive Neurostimulator is an intracranial stimulator. The way that it works-- so this is what the stimulator device here looks like. It's inserted into a small shelf in the cranium that's made surgically. And then it's connected to one or two four-contact electrodes, that could be either depth electrodes or strip electrodes.

And those electrodes are placed on where the seizure focus is for our patient. So this is a technique that is really best used for patients who have focal epilepsy, who may have more than one focus-- so they're not a candidate for the typical type of receptive epilepsy surgery-- or patients who may have a focus that was identified. But it in eloquent cortex and can't be removed.

And the way that this device works is really neat. So it is both a recording and stimulating device. And these electrodes-- this is an example of the strip electrode, the part there. The electrodes will record the brain waves. And the patient's epileptologist looks at it and starts to recognize patterns that may indicate a higher likelihood of seizure or patterns that happened right before the seizure.

And it trains the device. It sets settings to give a stimulation if those patterns are identified. And over time, those settings are modified. And the goal is to see whether or not, by doing that, you can kind of prevent a seizure from happening as it starts.

And this is something that, at this point, we don't fully understand what the best techniques are, as far as programming the device. But the trial was done while we're all in this learning process of how to do the settings. So in purple here is the treatment group.

Up to here was a period where the treatment group had the simulator on. It was being titrated and programmed. And the other group, the non-simulator group, they had it implanted, but nothing was being done. It wasn't turned on yet.

And you can see that the difference, by the time three months hit, between these two groups, in terms of their mean seizures per month. And then, after three months, stimulation was turned on in the other group. And their seizure frequency started to go down.

Interestingly, even before the device is turned on with either group, there's some reduction in seizure frequency. And we often see that when there's some sort of surgical intervention due to a lesioning effect. But this is really exciting because it's available to a different group of patients who previously weren't able to have epilepsy surgery.

And the thing to keep in mind here-- now, this so far hasn't shown a lot of seizure freedom outcomes. But for the most part, the group of patients who enroll in this trial or ones who don't have traditional epilepsy surgery modalities as an option. So this may add a lot for a group that can't undergo the typical epilepsy resective surgery.

Another exciting technique that is investigational but that we are part of a trial of here at Wake Forest University is the first real minimally invasive epilepsy surgery, which is Visualase Laser Ablation Procedure. And so what this is composed of its very brief surgery through a very small incision, to put a laser probe in the location where the target is. These are usually for patients who have a particular epilepsy-causing lesion, that we can target to ablate.

And then, once that probe is in place, the patient goes to the MRI suite. And then the laser is activated and thermally ablates the tissue. And on MRI, that can be monitored to allow for the desired amount of tissue to be ablated.

Patients just have one stitch or a Bandaid afterwards and usually go home the next day. So this is a technique, that at this point we've had a lot of good outcomes, but we don't have a lot of results published on this technique yet. But it certainly is very appealing to patients.

And just earlier this week, I saw one of our patients who underwent this procedure for refractory left temporal lobe epilepsy more than six months ago. And he's seizure free and doing wonderfully. So this is something that might become really widely used in the future.

And then finally, there's two quick things we'll go through. So deep brain stimulation of the bilateral anterior nucleus of the thalamus is another technique that was studied here in the US for patients with medically refractory focal epilepsy. And it had overall kind of similar results to the RNS trial.

It actually was never approved by the FDA here, despite a committee recommending its approval. But it is approved in Europe and Canada. So although this was studied in focal epilepsy patients, the reason why I still mention it here is, down the road, it may be something like that people will start trying to do in generalized epilepsy patients-- not available in the US but available to patients in other areas of the world.

And then finally, gamma knife radiosurgery-- this, I don't think, is going to come into much use in the end. But there were some promising studies a while back suggesting that the seizure-free outcomes of gamma knife for temporal lobe epilepsy might be as good as patients who have standard resections, like 60% seizure free rate, a couple of years out. The problem is that gamma knife has a couple of disadvantages.

First of all, the seizure improvement happens in a delayed way. One year out was the median time for the onset of seizure freedom for patients in this small trial here. And then there's this delayed edema and change on imaging. And sometimes, this can cause different problems-- headaches, sometimes even focal neurological problems. And it's difficult to control, other than treating with steroids, once that happens.

There was a NIH-funded trial, comparing this technique to standard temporal resection. That trial was halted because of poor enrollment, earlier this year. But it'll be interesting to see what the results show. This was the first, I think, major attempt to try seeing if a less-invasive technique might be possible, than actually resecting a part of the brain. But I have a feeling this is not going to come into standard use.

So then, just to summarize the key points of this talk, the first thing I hope I convinced you of is that refractory epilepsy or drug-resistant epilepsy has a huge impact on patient quality of life and mortality. Now, the primary goal of epilepsy treatment is seizure freedom. And for many patients, epilepsy surgery may be by far their best chance of attaining seizure freedom.

So any patient who has failed to become seizure free after two trials of maximally tolerated drugs should be referred to an epilepsy center to consider surgical evaluation. And we have numerous different epilepsy surgery techniques. So the choice of the technique for a given patient is based on the results of this detailed presurgical evaluation. And then that's it. Any questions?

[APPLAUSE]