JOHN AMMORI: So I'm going to talk about management of gastrointestinal stromal tumors, or GISTs, I'll call them throughout the talk. So just some basic background, they're the most common GI mesenchymal tumors, and they make about 80% of GI mesenchymal tumors.

They originate from what's called the interstitial tissues of Cajal, or what are the pacemaker cells of the GI tract. They're relatively rare, so about 3,000 - 5,000 cases per year. These, in the past, had been misclassified, essentially, as usually leiomyosarcoma or other tumors. But I'll talk to you a little more about the molecular aspects of the disease, and that's led to basically an uptick in the diagnosis, because we're more able to accurately diagnose these as GI stromal tumors.

Median age is about 60. Males tend to have it a little more than females. But there's no predisposition to males as opposed to females. They can occur anywhere in the GI tract, esophagus to anus, but the most common is the stomach. Next most common is the small bowel, and then a small percentage in the duodenum rectum, very rare in the esophagus.

When you do see someone that has a mass in the abdomen that doesn't seem like a standard adenocarcinoma or mesenchymal-type of tumor, these are the things they should be your differential. So particularly if you have somebody who shows up with a CT scan that shows a gastric mass, for example.

GI stromal tumors should be high on the differential; leiomyosarcoma; leiomyoma, which are benign; lymphomas, which you often be fooled with; neuroendocrine tumors, although these tend to have a pretty characteristic appearance on scan. And adenocarcinoma should always be in the differential, but that usually can be well sorted out from a GI stromal tumor.

So when you think about symptoms that people present with, these are often asymptomatic, get found incidentally for other reasons. When you look at those who present with a symptomatic verses asymptomatic lesion, meaning those found incidentally without symptoms, the asymptomatic ones tend to be small, which makes sense, whereas those that are symptomatic tend to be larger. So many of the patients that we see with GI stromal tumors can have very large tumors doing multi-visceral type resections. And you can also see many patients who had a little bit of stomach upset or something their primary care ordered a CAT scan, and they see a small [INAUDIBLE] that really probably wasn't causing the pain.

Symptoms tend to be relatively nonspecific, nausea, vomiting, early satiety. Before people even bring some of these symptoms to their doctor's attention, because they're so nonspecific, it can be up to six months. People can also have bloody stools just from bleeding into the GI tract. And one thing that's important to know is-- you'll see this on acute care once in while-- somebody will come in with basically a ruptured tumor. And they can rupture and bleed into the tumor. And so they can present with a massive hemorrhage and really terrible pain. They can also rupture intraperitoneally, as well.

So to make a diagnosis, these tumors tend to be submucosal, so as opposed to gastric adenocarcinoma, where when you put an endoscope down, you'll see a mucosal mass, characteristic that you guys have probably all seen. When you go down with a scope, you may see a perfectly normal looking mucosa, but a little bulge, submucosal mass. And that can tip you off that you're dealing with a GIST or with one of these other mesenchymal-type tumors.

It's often inadequate just to do a standard biopsy of the mucosa, because you're not going to get the mass. And so if you're going to do some biopsies, these jumbo biopsies are really the way to go to try to get submucosal, or get the mass.

Another approach is to do an endoscopic ultrasound, visualize the lesion, and then do fine needle aspiration biopsies. Usually, what you get are spindle cells. So the pathologist will tell you spindle cells, and they won't necessarily tell you this is GIST. But the likelihood, if you have a gastric mass and the scenario fits, is that you're dealing with a GIST.

There are some testing you can do, which I'll talk about in a second, the C-kit, which can sometimes be done on the FNA specimens, but you can't do it on such a limited specimen in all cases. OK, now, I'll just back up, actually. So when you do get the spindle cells, it's often usually one of three things. It's either going to be a GIST, a leiomyosarcoma, or a benign leiomyoma. And of those three, leiomyoma is probably the least common, particularly in the stomach.

On cross sectional imaging, either a CAT scan or an MRI, these tend to be well-circumscribed, smooth. Like I said, they're intramural, and they can often be exophytic. So they may be growing in the gastric wall or jejunal wall, or wherever they are. But they're a big exophytic mass. So you don't see a big intra-liminal mass. And on endoscopy, you may see a little bulge, but on CAT scan, you may see an 8 centimeter mass that's exophytic into the peritoneal cavity.

And really, C-kit mutation is what confirms the diagnosis. So that's the characteristic feature of these tumors. And that's easily done on core biopsy or on surgical pathology, not always easily done on FNA. So as far as the molecular basis of this disease, really 95% of these have a KIT mutation, and that's been the defining factor.

And that's why our diagnosis of this tumor has evolved and become better. And when you look at old literature, which you guys probably don't look at the old literature, but these used to often be called leiomyosarcomas. And now, really what was reported was probably really GIST, rather than leiomyosarcoma. You can have a platelet derived growth factor receptor alpha mutation, as well, and that occurs in a small percentage of patients.

So the C-kit encodes a receptor with tyrosine kinase function, participates in cell growth and survival, and mutations cause ligand-independent activation, so uncontrolled growth. So imatinib, which I'll refer to as Gleevec, just because it's easier to say, is a tyrosine kinase inhibitor, and really has revolutionized the treatment of this disease. And what it does is it inhibits C-kit, as well as platelet derived growth factor, and BCR-ABL. And as you guys probably know, it's also in the treatment of CML.

So one of the things we've learned about the C-kit mutation is there are multiple different mutations in the C-kit. And those affect how the tumor can behave and response to treatment. So an Exon 11 mutation is the most common. It occurs in about 70% of cases. And these tend to be the best actors, so to speak. They're pretty responsive to Gleevec at the usual dose. So the usual starting dose of Gleevec is 400 milligrams daily. And this most common mutation tends to respond well to that.

The next most common mutation is an Exon 9 mutation. And these patients tend to be relatively resistant to imatinib treatment, and often will not respond to 400, and require a doubling of the dose. So in patients, we don't typically do this testing on all patients. But the initial, I guess test, so to speak, is if the patient doesn't respond to the standard dose of Gleevec, the next step is to double the dose. And there are several other mutations that are even rarer, and those tend to all be associated with imatinib resistance.

So when we think about staging GIST, these tend to behave more like abdominal sarcomas than adenocarcinomas. And what do I mean by that? Lymphatic spread is rare. So really, less than 5% of GIST will spread to the lymph nodes. Unlike other sarcomas, spread to the thorax is rare. And really, the liver and peritoneum are the primary sites.

So adenocarcinomas, as you know, tend to spread through the lymphatics. Sarcomas, particularly of the extremity, tend to spread to the chest. Abdominal sarcomas can tend to spread to the chest. These tend to spread mostly to the liver and the peritoneum, not to the chest, not to the lymphatics as much.

So the next little bit I'll talk about treatment, and I'll talk about primary disease, as well as metastatic disease. When you think about primary disease, these are really the three things that we should think about. So one is what's the role of surgery in these patients. Two is how do we incorporate our systemic therapies, so how can we incorporate Gleevec into the treatment, both in the adjuvant setting, meaning after you've completely removed the tumor, so when a patient has undergone surgical resection and has no evidence of disease, or before taking the patient to surgery, neoadjuvant.

So for this disease, surgery is really the mainstay of treatment. Goal is for a margin negative resection, and that's a microscopically negative resection. And I'll actually talk about this. So people always ask what's the margin you should get grossly, because we don't have microscopic eyes. So as you're in the operating room planning want do you need to get, and depending on the location, if you can get a centimeter margin on the stomach, easily, that's fine, a centimeter or two, because then you're pretty confident that your margins will be negative.

If you're in a more sensitive area, and you don't have tissue to spare, as long as you can feel it, and you're around the tumor, usually, these tumors tend to not have a more infiltrated pattern, for example, like in gastric adenocarcinoma. They don't tend to spread up the submucosa. And so what you feel, if you can get around it cleanly, you're usually pretty good as far as your margin.

So a lymphadenectomy is unnecessary. So you do not need to do a standard lymphadenectomy when doing an operation for GI stromal tumors. Segmental resections, or wedge resections of the stomach are perfectly fine. You don't need do formal gastrectomy, like the distal gastrectomy or total gastrectomy for these patients. And if you do have a large tumor, en-bloc resections of adjacent organs, pancreas, spleen, et cetera, should be indicated, just as if were treating a large abdominal sarcoma. So again, the key aspect of the treatment is getting a margin negative resection.

So GISTs are a tumor that are practically well-suited to minimally invasive surgery, and probably the first tumor that really was used to treat in the stomach with a laparoscopic approach, because formal gastrectomy is unnecessary. Wedge resections are OK. And a lymphadenectomy is not necessary. So some of the more difficult aspects laparoscopically, as far as treating adenocarcinomas, are unnecessary here.

So depending on the location of the tumor, there's different approaches of dealing with it. If you have something on the greater curve that you can wedge out with a stapler, that's a perfectly good approach. Some of these posteriorly-based tumors can be approaching a couple of different ways. One, this is one way of approaching it, which is going through an anterior gastronomy, basically, bringing the tumor up and then stapling it out of the posterior gastric wall, and then closing the interior gastric wall. Another approach with dealing with something like this would be just to fully mobilize the stomach and kind of flip it, and deal with it, so that now the tumor is looking at you anteriorly.

I'll discuss a couple of cases here. So this is a 55-year-old gentleman. He had an upper endoscopy for dyspepsia, and it showed a submucosal mass. So because of that, he went on to get a CT scan. And that showed an 8 centimeter gastric mass. He had an endoscopic ultrasound, a fine needle aspiration, and that showed what they called a malignant spindle cell neoplasm.

So he came to see me. I don't have his scan, because it was an outside scan. But he saw me, and I recommended surgery with a presumptive diagnosis at this point of GIST, based on all the information that I had. So he had a posteriorly-based tumor at the upper part of his stomach, pretty close to the GE junction. And so he'd seen someone before me, a thoracic surgeon, I believe, who recommended an esophegogastrectomy with a colon interpostion graft.

And so when he saw me, I recommended basically a limited gastric resection. And we did this through a laparoscopic approach. So you can see I'm-- that's the tumor. So I'm making an anterior gastronomy here with the Harmonic device. The GE junction is up here. And actually, you'll see later on, I'll point out an endoscope that we put in there to make sure we didn't cause any problems there.

So here's the tumor on the posterior gastric wall, so placing a stay suture distal to it. There's the GE junction with the scope, so you can see we've got some margin there. Now, I'm putting a stay suture above the tumor. Those are basically used as a handle, so that when you'll see when I put the stapler in, I can grab the sutures and manipulate the tumor.

So here's the stapler. And you can see we've got some good mucosa here. And we're basically getting the posterior gastric wall. So this is a full thickness cut of the posterior gastric wall. And again, you can see I'm checking to make sure we're not causing any problems at the GE junction.

So there's a tumor. There's bagging it. And now to deal with the anterior gastronomy, open obviously, you can just put some stitches in and close it. You could do the same thing, I guess, laparoscopically. But another way of dealing with it is what you'll see here. Put some sutures in, so that you can pull up on that wall, and then just staple that anterior gastronomy closed, and then left to drain.

So this just goes to show you can deal with these tumors without doing a formal gastrectomy. So this was a proximal tumor. If this was an adenocarcinoma, he would have required a total gastrectomy. Like I said, somebody else offered him a really kind of more extensive operation than necessary. And so this is a way of dealing with these tumors. And again, you guys didn't see me taking any lymph nodes out, because these tend not to spread to the lymph nodes.

So here's a second case. This is a 71-year-old woman. She was diagnosed in '09 with a large mass in the upper abdomen. She was taken to the OR by a local surgeon, who explored her, felt that this was unresectable, and that it was too invasive into, I think, the colon and the mesocolon, and down to the mesentery.

So she had a diagnosis at that time of GI stromal tumor. She was put on Gleevec by her oncologist, and really had a pretty nice response. So within the first six months, she went from about 16 cm to about 11 cm. And I'll talk to you a little bit about some of the CT characteristics of a response.

So she showed a good response for quite some time. She actually transferred to a new oncologists. And her most recent scan was essentially similar, maybe a couple millimeters bigger. But regardless, her new oncologists wanted to refer her for another surgical opinion.

So I saw this lady. And you can see here's the stomach, spleen, colon, and here's this tumor. And the suggestion is that it's arising from the stomach. So here it is again. And I'll talk about this a little bit. And here's one of their clips from when they were there before. But I'll show this later on.

But one of the things to note about this CAT scan is this is a very homogeneous tumor. And so this is a classic appearance of a GIST treated with Gleevec. And I'll show you some examples of what one looks like without Gleevec. But they tend to be a little bit more heterogeneous and have some enhancement within them. And then on treatment, they get this nice homogeneous appearance to them. And that lets you know that they're having a response. And so here's just another cut. And you can see the splenic artery here and the pancreas here.

So intraoperatively, this was arising form the posterior gastric wall, and really, was just kind of hanging on a stalk on the gastric wall, and then this large mass that you guys could see. So she had a pretty extensive operation. So like I was telling you before, really, the best treatment is a margin negative resection. And if you can do it without doing anything that's detrimental to the patient's life, then you should go for it.

And so she just got basically a left upper quadrantectomy, partial gastrectomy, partial colectomy of that flexure, pancreatectomy, and splenectomy. And she actually did remarkably well. And she's without recurrence of disease now over a year.

So surgery, again, just to reiterate, surgery is the primary mode of treatment for this disease. But we're going to talk about imatinib in the adjuvant setting. So that means somebody who you've taken to surgery. You've rendered them disease free with an R0 resection. Now, do you give them additional treatment with Gleevec or not?

So the first thing to look at is what are the risks of recurrence? And so we'll start in the upper left here. So size is important. And so the cutoffs really are less than 5 centimeter is better than 5-10, 10 better than greater than 10. So if you have a larger tumor, you have a higher risk of recurrence.

Mitosis is really probably the most important factor when it comes to these tumors. And the cutoff is 5 mitoses per high power field. And this is less than 5, greater than 5. Site is also important. So gastric tumors behave better than esophageal tumors, better than small intestine tumors, better than colon tumors.

And then as I mentioned to you, several of these patients will present with tumor rupture. And it cannot be into the peritoneal cavity. And that puts patients at a much higher risk of having a recurrence, and often a paritoneal recurrence. And so you can see no rupture versus rupture.

So when we take these factors together, and this just shows a table of a study from this pathologist Miettinen, who's from the Air Force Pathology Group, who basically looked at hundreds of specimens, if not thousands, characterized all these things we talked about-- location, mitosis, size, et cetera-- and came up with this risk for recurrent disease or progressive disease, based on these things, so mitotic rate, size, and site.

And the first thing I'll point out is mitotic rate is really the big cut off. And so greater than 5 vs less than 5 is the big cut off. There's size, and then there's the different sites.

And so what we consider high risk of recurrence, I've boxed here. And you can see almost everything in the high mitotic rate is a high risk of recurrence except maybe the very smallest of gastric GISTs. But you can see even a small intestine GIST is quite a high risk of recurrence.

And so taking that altogether, there have now been a few studies done looking at patients who've undergone surgery, have a high risk of recurrence. Should we treat those patients with imatinib or Gleevec to reduce that risk? And so one study was published in *The Lancet* in '09. This looked at patients after surgery and randomized them in a prospective randomized study of one year of Gleevec versus placebo, no treatment. And you can see the had quite a fair number of patients.

So the key finding to the study was the one year recurrence-free survival was quite different, and so 98% versus 83%. This is just after one year. So this is recurrence-free survival. Oops. I don't have the graph here, but when you look at overall survival, the overall survival difference really was not different at that point.

The patients who recurred were put on Gleevec. And also, the follow-up was a very long term. But the key finding here is patients recur.

So the Europeans published this just a year ago. And this now looked at three year versus one year. So we know one year is better for progression-free. We didn't find any difference in overall survival. How about if we give it to them for three years, as long as they're not recurring?

And so here's the, again, the recurrence-free survival. And you can see that patients who got three years of imatinib did better than those who got one year. And the numbers are here, 88%, 62%, so quite a difference.

And this study now actually found a difference in overall survival, as well, so 92% versus 8% five year overall survival. And their p-value was 0.02, so a statistically significant difference in patients who got three years.

So at this point, three years is the standard of care for high-risk GI stromal tumors after surgery. And there's current studies that are looking at five years of adjuvant treatment in patients after resection. And many oncologists with all this data that's accumulating really believe as long as the patient's not recurring, and they're tolerating the medications, probably should continue it for as long as possible.

So that was our talk about adjuvant imatinib. Now, I'll talk about neoadjuvant, which means giving it before planned curative surgery. So this is not necessarily patients that are unresectable. This is the thought of giving it in someone who is resectable.

So really, this is most useful in patients that are difficult anatomically, so meaning if you've got something at the esophagus gastric junction, duodenum or rectum, and you can downsize the tumor in order to make your operation safer for the patient, then you should consider giving Gleevec in the neoadjuvant setting.

It's also useful in that patient that I showed you, somebody who comes in with the 16 centimeter tumor, and you know you're already in for a big operation, but if you can get some downsizing and make the operation a little bit safer, and increase your chances of getting a negative margin, those are patients you should consider this in, as well.

There's really two approaches to neoadjuvant treatment, as far as when you think about treatment planning for the patient and what you're going to tell the patient. One is you just plan surgery for six months. So you meet the patient. You tell them you want to give them neoadjuvant treatment. Plan for surgery six months down the line.

There is a percentage of patients who just won't respond to Gleevec, and so you want to check a CAT scan at three months and make sure that you're actually getting a response. If you're not getting a response, you may want to operate sooner than later, versus changing to a different systemic treatment. Most patients respond and will go on then at six months to get another scan and planned surgery.

The other approach, which some people advocate, is to treat to a maximal effect. So as long as the tumor's responding, treat. And once you've gotten to stable disease-- so check them every three months. If two scans in a row show stable disease without any shrinkage, then that's the time to go operate.

There's no right or wrong approach. This is just kind of two approaches that people tend to use. And knowing that these are things that people use, you can help individualize what you're going to do for the patient, because again, neither one's better than the other.

So even though we're surgeons, and we like to think about surgery, and how we're going to treat the patients, these patients, many them will metastasize. So it's good to know about the overall treatment of metastatic disease. And surgeons do play a role in the treatment of metastatic disease for these patients. So I'll talk first about the role of surgery for patients who are metastatic.

This is a 76-year-old man, who had a large gastric GIST two years prior. On his recent CAT scan, he was found to have this new lesion, which was suspicious for GIST recurrence, basically, presumed GIST recurrence. So we didn't biopsy this because it certainly looked suspicious on MRI. And like I told you, GISTs tend to spread to the liver. So he was offered a laparoscopic resection. And I'll just show you that.

So you can see the tumor right there ultrasounding to make sure there's no other sites, marking out the liver with cautery. And again, as far as margins here, usually try to get 1-2 centimeters, so that you can ensure a good clean margin. And this just shows some parenchymal transaction of the liver using the Harmonic device.

And then in a second, you'll see a stapler coming in. So this was towards the back, or deeper within the liver parenchymal where there's some larger vessels. You can use a stapler to control those, and then hemostasis. And that's just the tissue link device. And here's the topical hemostatic, as well.

So what are the outcomes? Does this make any sense for us to be doing resections of metastatic disease? So there's three studies that have looked at this. This was from Memorial Sloan Kettering, from MD Anderson, and I think from Japan. And when you look at the five year survival rates, they're about 30% in patients who undergo liver metastatectomy. So that's pretty good. And that's better than we would expect in patients who did not undergo surgery.

Median survival, as you can see, can be three to four years. Recurrence is still very high. So the here's the percentage. So you see almost all these patients will recur. And I'm sure if you followed these people out until death, probably 90% of them would recur, I would guess.

And the same is the case, really, for colorectal liver metastases. If you follow these patients long enough, almost all them will recur. But the benefit you give them is you give them a longer overall survival. So you may not be curing them in the sense that we like to say the diseases is never coming back. But you're offering someone an extra few years of life.

So an important thing to consider is who should you operate on, and who shouldn't you operate on. And this is one study from Dana-Farber that looked at patients who are getting Gleevec treatment and then underwent surgery. And what they did is they went back and looked at how these patients were responding to Gleevec before they underwent surgery.

So some patients had stable disease. Some patients had what's called limited disease progression. That means if you have three tumors, one of the tumors is growing. The other two are stable. And that can happen where you get one of the tumors develops a resistant clone to the Gleevec, and only one tumor now is growing, whereas the others are still responding, or people who have what's called generalized progressive disease, so all three tumors are growing.

And what they found is patients who are just not responsive to treatment-- all their tumors are growing-- really do quite poorly with surgery. So you may want to think twice about operating on a patient like this. Because with this type of survival, you may just be putting them through the morbidity of an operation, potential mortality of an operation, without really helping them, whereas those who are stable on Gleevec or have just limited progression at one site tend to do relatively well, from an overall survival standpoint.

And so I think one of the other key points here is this just shows that chemotherapy, as well as surgery, go hand in hand. And so surgery is key for most cancers that we deal with. But outcomes are much better now than they were 20 years ago, not because we're doing better surgery on these people. It's because of chemotherapy is better. And we're able to offer surgery to a lot more people because the chemotherapy is better, and this is just another case of that.

And really, colorectal liver metastases is a similar example. The chemo is better. We're getting more people to surgery. They're living longer because of the combination of the two, not because of one or the other. And I think the fact that you see patients who aren't responding to treatment with the chemo probably have bad biology. And no matter what you do surgically for them, you may not be helping them.

This is just a similar study from Italy, again, those with stable disease versus those with progression. And this is just yet another study that looked at in the pre-imatinib era. So before we could use Gleevec, patients who underwent liver resection, the median survival was 19 months. So obviously this is not comparing apples to apples, because we're taking unselected patients before we had Gleevec and then really patients after Gleevec. We don't have any matching, no randomization, et cetera.

But what it tells us is natural history-wise, we know that patients that were chosen at a good institution, at Memorial Sloan Kettering, to undergo surgery had about a 20 month overall median survival before Gleevec was available. And that's basically doubled since we've had Gleevec. So it suggests that the combination of two is offering more benefits to the patients.

So now, this is going to be a little bit more medical oncology for the next few slides. So like I said, Gleevec really revolutionized the treatment of this disease. And this was a report of one single patient got published in the *New England Journal*. And so this goes to show that if you make a finding that is entirely unexpected, even if it's in one patient, you can get something in the *New England Journal*.

So this was in '01, a 50-year-old lady. This is a PET scan that shows multiple areas of GIST in her abdomen, and basically, disappeared with Gleevec. And prior to Gleevec, patients who had metastatic GIST, there was absolutely no treatment. The chemotherapies were useless. Most patients had basically a year to live.

So there are a few problems with Gleevec, as well. One is that about 5% of people just will not respond from the get-go, and about another 15% of people will become resistant within the first six months. But what that gives us is about partial or stable responses in the majority of patients, 80% of patients.

That response, though, goes away in time. And so the median time of response is about two years, 20-24 months. And like I mentioned, you can have progression of all sites or progression of just limited sites, meaning just one tumor. And many patients will become resistant just in one tumor clone before the rest of them become unresistant.

And I'll mention this now, just because I don't mention it elsewhere in the talk, but there are some oncologists who will refer patients, say, who have six tumors, are clearly unresectable, but have one clone that's growing on Gleevec for, let's just say, in the liver. And we'll refer them for an ablation of that one tumor with the idea being that that one tumor is not responsive to medical therapy anymore. You can treat it. The remaining tumors are still responsive, and you can buy some more time for that patient.

This is just to show you on CAT scan what you will see when patients are treated. And so you can see here, you've got this heterogeneous tumor. It's got this vascular halo. And with some treatment, it becomes totally homogeneous, almost cystic, in a way.

And these tumors didn't change in size. So the radiologist who looks at this will tell you if you're just looking at the size, it may not have changed. So if you have a primary physician, or someone who's just reading the report, or even if they look at this, and they don't know that this is a response, they'll say, oh, this patient's really not responding to Gleevec. But this is what a response looks like to Gleevec. So you don't always see reduction in the size of the tumor.

And this just shows what a secondary resistance looks like. So this is a patient who's responding. There's this big cystic-appearing mass. And then three months later, there are these tumor clones within that tumor that have now developed resistance. And so this is very clear. The radiologists may not tell you that the size has changed when they look at this, but it's clear to the eye something has changed.

So patients with metastatic disease and cancer will often get a prescribed course of chemotherapy and then go on breaks. And so the question with this medication is how long should a patient who's got metastatic disease be treated with Gleevec. And I'll show you if you studies. Pretty much all these studies were done from the French Sarcoma Group.

This shows 58 patients. These are all patients who are stable, responding, and tolerating Gleevec after one year. Randomize them to coming off of Gleevec or continuing the Gleevec. Those who progressed when they came off of Gleevec were restarted on Gleevec.

And so what we see is a big difference in progression-free survival. So if you take these patients off of Gleevec, they progress. However, if you restart the Gleevec, you essentially rescue them. And so these patient did not have a change in overall survival.

So this study was important for two reasons. One is it shows that if you take them off, they will progress. But really, the second important thing was is people were afraid to stop Gleevec. So oncologists, patients were afraid to stop it. And even though it's relatively benign compared to other chemotherapies, there's still some bad side effects people can get.

You can get swelling, periorbital swelling, edema elsewhere in the body, fatigue, nausea. So sometimes, patients need a break. And so this was reassuring for their treating oncologists that it's OK if you give them a break and then start them back on it. You're not losing anything, as far as overall survival.

So a similar study was done at three years, patients who are still responding at three years. This was 50 patients. Half of them stopped the Gleevec. Half of them continued it. And again, they restarted if they progressed.

And this shows essentially the same thing. So most of those patients who come off of it recur. But when you restart it, you get basically a response back. So you kind of rescue them when you start it back up.

And that's the same group in this paper they mention that they have a five year study, and they mention some preliminary reports. And essentially, it looks the same. So the idea is now even in metastatic disease, to continue the Gleevec until the patient starts to progress, as long as they're tolerating it. And again, if they need a break for intolerance, it's OK to give them a break if they can come back on it.

So that's first line treatment. So Gleevec is ingrained as first-line treatment in the management of GIST, metastatic GIST, as well as, like I said, in the adjuvant setting. So this is second-line treatment. This was a study for patients who are either unresectable or metastatic, either didn't tolerate the Gleevec or progressed on Gleevec.

And it randomized patients in a 2 to 1 fashion. So you can see the numbers are skewed. 200 patients got Sunitinib or Sutent, and 100 patients got placebo. And this shows that Sutent provided a benefit in progression-free and overall survival. And so with this study, Sutent is the second-line treatment of GI stromal tumors.

Now, this is a newer medication that's also a kinase inhibitor. It's called Regorafenib. The same group, the Dana-Farber group, studied this again in a 2 to 1 fashion, so you can see the numbers. And these are patients who failed imatinib in the first-line, Sunitinib in the second-line, and then we're randomized to receive Regorafenib in third-line.

And you see the progression-free survival is very good. The overall survival really didn't meet statistical criteria for significance. But you can see the recurrence-free survival was quite significant. And so basically, when you think of first-line, second-line, third-line for this disease, it's imatinib, Sutent, and now it's Regorafenib. This was just published earlier this year.

This is something you guys can probably forget after this slide. This is only approved in Europe and used in Europe. It's being studied here in the United States. It's called Masitinib. It's another kinase inhibitor of both KIT and PDGFRA alpha. So there was actually a phase I study comparing this head-to-head as first line treatment-- actually, I shouldn't say that. There was a phase II study giving this to patients as first line treatment to see if this was safe. And then they looked at the efficacy numbers.

And when you compare their efficacy and safety, it was similar to Gleevec. So this wasn't randomized, but this just showed that these patients did similar to what you would expect if they were receiving Gleevec. They then did a randomized study of 44 patients as second-line. So patients who had failed Gleevec, and now we're randomized either Sutent or Masitinib, and they found that this drug was much better than Sutent.

So at 18 months, nearly 80% versus 20% were alive. And that two years, you can see a big difference. And so there's now phase III studies in Europe looking at this primarily in the second-line setting. But in Europe, they're also looking at this head-to-head with Gleevec as in first-line setting, mainly because they think the side effect profile maybe better than Gleevec. You may hear about this more in the upcoming years.

So just some take-home points, surgery is the primary treatment for localized GI stromal tumor. You give up-front chemotherapy for either large tumors or tumors that are in difficult locations. After surgery, for high-risk GISTs, the standard of care at this point is three years of treatment with Gleevec.

Surgery does play a role in metastatic GI stromal tumors. So I showed you a case of liver, but it can also play a role in perineal disease, where patients who have limited perineal disease and undergo resection can have a benefit, as well. And like I said, in metastatic disease, these are our lines of treatment, currently. That's all. Thanks.

[APPLAUSE]