

**MICHAEL LEVY:** Hello. I'm Mike Levy, a gastroenterologist at Mayo Clinic specializing in pancreaticobiliary disease. My areas of clinical expertise include pancreatic disorders, endoscopic ultrasound, endoscopic retrograde cholangiopancreatography, and tumor ablation. Today, I'll be sharing the latest information on EUS-guided pancreatic antitumoral therapy. Well, there are various options available to us for local pancreatic ablation, and they include chemotherapy, alcohol injection, and radiofrequency ablation.

Thus far, the experience has been primarily limited to treatment of pancreatic ductal adenocarcinoma, neuroendocrine tumors, functioning and nonfunctioning, and secondary metastases for non-pancreatic primaries to the pancreas. I'm going to start off by discussing chemotherapy, and this pertains to intratumoral injection of chemotherapy under EUS-guidance. As a little background, you know that there is an estimated 57,000+ patients who will be newly diagnosed with pancreatic ductal adenocarcinoma in the United States this year.

It represents the fourth leading cause of cancer-related mortality, and unfortunately there have been few major advances in therapy or outcomes. At the time of presentation, 50% of patients already have metastatic disease, and only approximately 20% of patients have locally advanced pancreatic carcinoma that's considered resectable, and unfortunately the overall five-year survival is quite poor. It's approximately 5%, although it has increased recently, and is approaching 10%. The question is, can intratumoral therapy-- is it a key to improving outcomes?

Systemic therapy-- more than 90 chemotherapeutic agents have been evaluated thus far, and unfortunately, they provide minimal improvement in terms of resectability rate and survival. This limited efficacy is often the result of the underlying tumor biology, dose restrictions that are necessary to limit the damage to normal tissues, and the fact that drug delivery inside the tumor is limited due to tumor-related desmoplasia and inflammation. The goal, therefore, is to use EUS-guided intratumoral therapy to overcome some of these limitations.

The goal is to increase intratumoral drug concentration to decrease the systemic toxicity. In doing so, we hope to increase the efficacy of systemic chemoradiotherapy, and ultimately increase the success of downstaging, increase and improve the quality of life, increase the survival duration, to decrease the disease recurrence, and to improve the cure rate. I just want to give a little bit of background information on some of the work we've done here. This is one paper in which we evaluated injection of gemcitabine for a locally advanced and metastatic pancreatic carcinoma.

I should state that these patients not only had EUS-guided therapy, they also had standard therapy as well. Our primary aim was to evaluate the toxicity for EUS-guided fine-needle injection with gemcitabine. And secondary endpoints including downstaging that led to RO resection, and overall survival six month, 12 month, and five year. 36 patients were enrolled. 33 patients had unresectable disease. Three patients were resectable, where two were deemed too poor or unoperative candidate to undergo resection, and one patient refused resection even though he was resectable.

For these patients, 92% were Stage Three or Stage Four disease, remembering that Stage Four disease is defined by M1, or distant disease. And as a part of the study, we injected typically 2.5 milliliters of gemcitabine, which equated to a dose of 95 milligrams, and we did so usually with three needle passes. There were no Grade 3 or 4 adverse events and this trial. You can see a video here in which the needle is now located within the tumor, and as gemcitabine is injected, it results in a hyperechoic or bright white cloud that infiltrates the tumor itself.

We also evaluated the extent and pattern of spread. We would regard this as ideal spread because here's the tumor prior to therapy, and after therapy you can see that this hyperechoic bright cloud fills the entire boundary of the pancreas. If you compare that to this patient with suboptimal spread-- here again is the needle. As gemcitabine is injected, you'll see that very little of the gemcitabine actually stays within the tumor. And this was important, because the pattern and extent of spread did correlate with outcomes.

So this is an example of post-therapy, in which there's suboptimal spread of this hyperechoic cloud representing the gemcitabine. In terms of overall survival, the six-month survival was 78%, 12 month was 44%, and five year was 3%. Four patients were able to downstage to R0 resection, and one patient remains alive more than 10 years after therapy. Unfortunately, this gentleman who is disease free at 43 months, died of an alternate cause, which was severe *C. difficile* infection.

So this study, and a few others published elsewhere, suggests the safety and feasibility of EUS-guided antitumoral therapy for pancreatic ductal carcinoma, and it offers promise in terms of tumor downstaging and impact on survival. Nevertheless, it's still regarded as investigational, and is not part of routine clinical care at any center. Ongoing work is underway, and hopefully it will be sometime in the future.

We're now going to turn our attention to the intratumoral injection of alcohol. There are a number of studies, here and elsewhere, that have evaluated alcohol injection for this role, and it appears to be quite efficacious. This was a small study that we published more than 10 years ago. Certainly the experience has grown since then, but I think it does nicely represent our current experience as well. So surgery was not performed in this study, because six patients would have required pancreaticoduodenectomy, and the patient and/or surgeon felt as though that was not in their best interest.

Five patients had comorbidities, one patient had a recent incomplete resection, one patient had multiple prior surgeries and a frozen abdomen, and one patient had intraoperative bleeding during attempted resection. You can see those patients had an array of neurologic and sympathoadrenal manifestations, and the average duration of disease was 6.4 years, and their blood sugar nadir was 26.

CT and endoscopic ultrasound demonstrated that the masses were 12 to 14 millimeters in size, located predominantly in the pancreatic head. Most were enhancing, and if you were calcified. So we treated patients typically with one treatment session, occasionally requiring two, and seldom three separate treatment sessions. Using usually a 22-gauge needle, a mean of 3.2 needle injections per mass per session, and injected 95% to 99% alcohol and a mean volume of less than one milliliter.

The care of this patient nicely highlights our experience. This was a 72-year-old female with a thyroid cancer, COPD, and left atrial myxoma. Although she had hypoglycemic-induced manifestations for approximately 20 years, however, insulinoma was just recently diagnosed, and she was deemed a poor operative candidate. CT here nicely shows the pancreatic mass, which is hyperechoic or enhancing on CT, and magnified views will show the mass again. This was a 17 by 15 millimeter insulinoma located in the pancreatic head. It was enhancing and was calcified.

They CUS video outlines the insulinoma, and in a moment you'll see the needle pass into the mass. And much as our experience with gemcitabine, the alcohol gives a hyperechoic or bright white appearance as it's injected. While surgery is still the standard of care, broad experience here and at other centers indicates the safety and efficacy of EUS-guided antitumoral therapy of ethanol for insulinomas. This is a clinically available alternative, and most of us believe it should be more often considered over major resection, particularly in elderly patients and those with comorbidities.

The use of alcohol is not as fully ablative as we would like for certain tumor types, and that's led to the exploration of other methods and technologies, including radiofrequency ablation. There was an original device that's no longer on the market, but I'd like to talk about it for a moment. RFA devices use electromagnetic energy and involves thermal injury and coagulation necrosis. Again, the care of this patient highlights some of the limitations of the original device.

This was a 69-year-old female who had a resected rectal melanoma in 2012, a lung metastasis that was resected in 2015, and a pancreatic mass was identified on surveillance imaging. Imaging here shows the mass within the pancreas, and EUS demonstrates the mass as well. You'll now see the needle will be advanced into the mass. And this RFA probe involved a 0.035-inch guidewire of sorts that would be advanced through the needle and perform the ablation. The floppiness and the tendency for the needle to become bent in the guidewire often led to some of the poor outcomes.

This nicely shows off fluoroscopy of the needle in the RFA device. And the same here. Here's the needle, and the RFA device being extended through the needle. You can see in this patient, while the mass was originally of this size, there was then this degree of injury because of the RFA probe. It was unclear whether this represented needle track seeding and/or inflammation. Follow-up scanning revealed it was just inflammation, but it highlights some of the problems with this probe, and that it would injure not only the mass itself, but intervening tissues.

That led to the development of the new and current design, which has overcome the limitations thus far. This is a nice probe. It's 19-gauge in caliber. The entire device is the RFA probe. It's not simply a needle with a probe that extends through it. And this part of the needle is the ablation zone. It has an internal cooling mechanism. So what that allows is it limits the injury to the area of interest, and does not allow longitudinal spread through the needle path, which did occur with the prior design. And there are three separate sizes. So we can tailor therapy to the specific tumor.

This patient was a 72-year-old female who had multiple comorbidities. She had an enlarging nonfunctioning neuroendocrine tumor that was starting to impinge the main pancreatic duct. This shows on CT and MRI the enhancing mass, same lesion under endoscopic ultrasound, and it did have tiny cystic components and/or necrosis. Here's the RFA probe on fluoroscopy, and the RFA probe under EUS. This hyperechoic cloud of sorts is the effect after ablation.

This patient responded very nicely. There's no evidence of enhancement on CT, and on contrast-enhanced EUS you can see there's complete loss of blood flow as compared to prior therapy. The clinical efficacy of this device is approximately 85%, based on the broad literature. Ours has approximately 85% to 95%. An adverse of that rate is 5% to 33% in the literature. Most have been minor and Mayo RO rate is approximately 5% to 10%. All have been minor, except one patient did have a severe complication. She had marked ascites and developed an infection afterwards. It's no longer an indication, it's a contraindication of therapy in our center.

So we talk about various options for a local ablation of pancreatic masses-- chemotherapy, alcohol, and radiofrequency ablation. In regard chemotherapy, the experience thus far has shown its safety. It's still investigational due to uncertain efficacy, and the role is still purely investigational. Alcohol is safe. It is clinically used. It is somewhat effective. It depends a little bit on the treatment goals and the type of lesion and pathology that you're treating. And radiofrequency ablation is safe. Rare major complications. It is used clinically, and it appears to be the most effective treatment modality in this setting.

At this point, I would say that pancreatic ductal adenocarcinoma should not be treated clinically. It's purely investigational because we do not impact the overall course and outcomes thus far. But there is a clear role for nonendocrine tumors, functioning, nonfunctioning, and secondary metastases to the pancreas. What are some of the realized or potential advantages of using EUS for guidance? It allows realtime control and monitoring of the ablative dose and settings. There's potential prediction of the ablative zone. It is tolerated by elderly and patients with comorbidities, and has a lower morbidity and mortality, hospitalization rates, and cost relative to surgery.

Some of the disadvantages are the fact that the techniques have not been standardized. They do vary from center to center, which probably impacts the outcomes. And there's an uneven ablative zone. There's a limited ability to treat when the mass is of proximity to large blood vessels and/or ducts, and there's a heatsink effect that occurs when the lesion is vascular, and/or are located proximate to large blood vessels. We continue to refine current and emerging EUS-guided antitumoral therapies to optimize their safety and efficacy, and in doing so, we believe it's important to deliver care in a multidisciplinary manner in order to enhance clinical care and outcomes. Thank you.