



The debate on whether to ablate

You'd think that if you ablate a tumor causing a biliary obstruction before placing a stent, it should be better than just placing a stent, right? In fact, we already have studies to support this.^{1,2} Well?... An ancient philosopher, Phaedrus, supposedly said, "Things are not always what they seem; the first appearance deceives many; the intelligence of a few perceives what has been carefully hidden."

In this month's issue of *Gastrointestinal Endoscopy*, Albers et al³ report on their prospective randomized controlled multicenter study of patients with malignant biliary obstruction and nonresectable tumors. The patients were randomly assigned to receive a self-expandable metal stent (SEMS) only, or radiofrequency ablation (RFA) followed by SEMS insertion. The primary outcome measure was stent patency after 3 and 6 months; the secondary outcome measures included patient survival. On the basis of their study results, the authors concluded that RFA as an addition to SEMS implantation had no positive impact on stent patency rate or survival. Whaaaaat? Here we go with the conflicting studies thing again.

Well, it's not like this is the first time. Remember the Harvard study reported by the *New York Times* to show that drinking coffee was associated with an increased risk of pancreatic cancer?⁴ Then there was the meta-analysis published in the *World Journal of Gastroenterology* that reported "there is substantial evidence from both laboratory and animal studies on the favorable influence of coffee on the risk of pancreatic cancer."⁵ So how can different peer-reviewed investigations purportedly testing the same hypothesis produce conflicting results? Is this proof of the multiverse? And should we be using RFA in these patients or not?

After over 30 years of reviewing clinical studies for journals and having a basic science degree, I have had my eyes opened to lots of possible reasons for the conundrum described above. Moreover, working with healthcare providers outside of academia, and also with trainees just starting their academic journey, has also opened my eyes to the many ways that a published peer-reviewed report of a clinical investigation can be interpreted. So, please allow me to give my opinion as to why these "conflicting" results, that appear at first to be so confusing, might be explained and how they can guide our use of RFA in our patients with

malignant biliary strictures. Spoiler alert: Even though I enjoy watching *Stranger Things* on Netflix, I will not be using the multiverse as a reason in my comments below.

Let's first look at the question we are trying to answer. Simple starting point, right? Well?... OK, we just want to know if applying endobiliary RFA in patients with malignant biliary strictures before placing a stent improves stent patency. Is this simple question really that simple? Of course not. We are all aware of the tremendous variability in the ways therapeutic interventions can be applied. The different equipment used by different users using different settings can lead to different effectiveness. We are also aware that malignant biliary strictures can be due to

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different cancers in different stages and different anatomic locations that can respond differently to a therapeutic modality.

More specifically, in our quest to better understand how RFA affects patients with malignant biliary strictures, if we dig deeper into the details, we find that different instruments have been used in different studies and different catheters, providing a variety of RFA effects have been used.⁶ Also, a range of power settings, usually from 7 to 10 watts, has been reported. Furthermore, modifications to RFA equipment have allowed for more precise temperature control of the catheter tip, which brings up another conundrum that we clinical investigation readers must take into account when comparing studies: technology evolution.

The technology used to treat patients can evolve relatively fast. By the time we study it, versions 2.0 and 3.0 are already being used. It's essentially a moving target. So endobiliary RFA equipment will most certainly be different in the future from what has been reported in the past. Another possible moving target is the user's experience with the equipment. Users of this technology also go through learning curves with each version of the equipment. So even with the same user and the same equipment, outcomes may change over time.

So just by taking into account the considerations above, one could theoretically explain how even the same study group could observe results that are different from the results they observed years earlier when they were investigating the same topic. But wait—there's more.

The response to RFA may vary based on tumor type, anatomic location (extrahepatic vs intrahepatic), stricture length, and cancer stage. Different studies of the impact of endobiliary RFA on malignant biliary strictures have included patients with strictures caused by a variety of tumor types, including cholangiocarcinoma, pancreatic cancer, and gallbladder cancer. The location of these strictures may also influence the impact of RFA. In a recent American Society for Gastrointestinal Endoscopy (ASGE) journal scan, Dr. Bret Petersen⁷ reviewed the study done by Albers et al.³ He pointed out that the proportion of patients with intrahepatic lesions in this study was too small to determine whether this subset of patients would benefit from RFA.

Another factor pointed out by Albers et al.³ in their report is the possible effect of different concomitant chemotherapy and other therapies on the outcomes. The patients studied in other investigations may have had different concomitant therapies and proportions of tumor types predisposing to different RFA responses. Likewise, higher proportions of patients with earlier tumor stages could also lead to a more favorable RFA impact in these patients. Moreover, perhaps in patients with a longer life expectancy, longer indwelling stent times would reveal a difference in stent patency response to RFA.

Also, let's not forget to round up the usual suspects. Some other studies of this topic have not been prospective randomized controlled trials. As we all know, retrospective, uncontrolled, nonrandomized, single-center studies are fraught with possible biases and errors leading to the possibility of misleading and/or conflicting results.

So, how should we interpret these “conflicting” study results? Should we still be using endobiliary RFA in patients with malignant biliary strictures? I would suggest that the initial perception and interpretation of these studies having conflicting results is due to our desire to simplify what is, in reality, very complicated. We who review manuscripts for journals will sometimes spend many hours over many days reading and analyzing 1 study. The more time spent focusing and analyzing a study, the more awareness there is of its complexity. When I take off my reviewer cap, like everyone else I tend to read articles more superficially. Sometimes I may just glance at a study title and not get to read the whole thing. As we have seen, sometimes the title of study or even the abstract leaves us with an overly simplified interpretation and perception of something that is in reality very complex.

Clinical studies by their very nature are complex because of all the variables involved. As seen through the lens of a basic scientist, clinical studies are not pure science. Simplifying these complexities and details in an effort to maintain our sanity also prevents “paralysis from

analysis,” meaning that if we were to attend to every possible confounding variable before using a studied technology, we could move so slowly as to withhold real benefits from patients while we figure things out. My point is that we tend to simplify the complex reality of a study for many reasons, but that can sometimes lead us to perceived misconceptions and conflicts because we haven't done a deep dive into the details.

All that being said, what should we surmise from past studies and this report by Albers et al.³ about the impact of endobiliary RFA in patients with malignant biliary strictures?

The study by Albers et al.³ is a well-done prospective randomized controlled study and is the first multicenter study of this type on this topic. It is in accordance with similar findings of a single-center prospective randomized controlled study that used the more recent temperature-controlled RFA equipment mentioned above.⁸ Both of these studies demonstrated that endobiliary RFA as an addition to SEMS implantation had no positive impact on stent patency rate or survival in the patients studied.

This is pretty convincing evidence to support not using endobiliary RFA in every patient who has a malignant biliary stricture. But it is not enough evidence to support stopping its use in all of these patients. I agree with Dr. Bret Petersen⁷ in his recent ASGE journal scan review of this study. His comments were that “The small number of patients with hilar strictures in this study does not allow inference about the benefit, or lack thereof, for these lesions.... Further studies comparing devices in single tissue types and locations are warranted.” There may be subsets of patients with certain tumor types, at certain stages, and in certain locations, that could benefit from endobiliary RFA as an addition to SEMS implantation. However, the numbers of patients in these subsets that have been studied in a prospective randomized controlled multicenter trial are too small to be convincing at this time. Also, at least 1 past study has shown some promise in using endobiliary RFA for treatment after SEMS occlusion occurs in these patients.⁹ And we haven't even addressed what multiple RFA treatments might do.

So, in summary, even though endobiliary RFA may not be the “one and done” “magic bullet” we had hoped for, it still has the potential for helping subsets of patients with malignant biliary strictures. Further studies comparing devices in single tissue types and locations may provide more guidance and uncover—to again quote Phaedrus—“what has been carefully hidden.” It may take years for us to get answers to these apparently simple questions, but as a *Gastrointestinal Endoscopy* reviewer for more than 30 years I've seen Stranger Things. (Sorry, couldn't resist the double entendre and pun.)

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; RFA, radiofrequency ablation; SEMS, self-expandable metal stent.

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