EDITORIAL

Endoscopic radiofrequency ablation to prolong survival for unresectable extrahepatic biliary cancer

For patients with unresectable extrahepatic biliary cancer, the best supportive care to relieve biliary obstruction consists of plastic or metal stent placement. As such, endoscopic drainage is associated with a lower complication rate than is surgical decompression.[1] In this issue of *Gastrointestinal Endoscopy*, Gao et al[2] report a randomized controlled trial on the added value of endoscopic radiofrequency ablation (RFA) in combination with stent placement for malignant extrahepatic obstruction. The authors conclude that additional RFA may improve overall survival and quality of life in patients with inoperable extrahepatic cholangiocarcinoma or ampullary carcinoma.

RFA is widely used to treat both primary and metastatic hepatic tumors. Percutaneous RFA is frequently applied for hepatocellular carcinoma as a palliative and even curative treatment. Endoscopic RFA has been a validated treatment for dysplastic Barrett's esophagus for some time. In 2011, the first report on endobiliary RFA using the Habib EndoHPB bipolar radiofrequency electrode for advanced biliary obstruction was published.[3] In 2016, a systematic review by Zheng et al[4] showed that endoscopic biliary RFA was an effective and relatively safe intervention in the management of unresectable biliary malignancies, with improved patient survival.

The working principle of RFA is the emission of heat energy via a bipolar probe by use of a high-frequency current, which causes localized tissue necrosis resulting in reduction of tumor size and possible regrowth.[5] The amount of thermal damage depends on the tissue temperature achieved and the duration of the heating. If the temperature is too high or too low, the effect is limited. Besides direct ablation, systemic immune mechanisms may also play a role by modulation of circulating immune cells and cytokines.[6] Shortly after the first publication on endobiliary RFA, multiple studies showed promising results in malignant biliary strictures, to prolong both stent patency and overall survival. However, most articles lacked a randomized design.

In 2018, the first randomized controlled trial was published on the efficacy and safety of endoscopic RFA for unresectable extrahepatic cholangiocarcinoma (CCA).[7] Sixty-five patients, excluding those with Bismuth type III and IV hilar CCA, randomly underwent RFA combined with biliary stent placement or stent placement alone. Repeated RFA was performed only in cases of significant tumor growth as estimated by intraductal US. Two patients underwent 1 RFA session, 13 underwent 2, 13 underwent 3, and 4 patients 4. The overall survival time was significantly longer in the RFA group than in the stent-only group (mean, 13.2 ± 0.6 vs 8.3 ± 0.5 months; $P < .001$). Also, stent patency was significantly longer after RFA (mean, 6.8 vs 3.4 months; $P = .02$), whereas adverse events did not differ.

Self-expandable metal stent occlusion is determined by tumor ingrowth; thus, stent patency theoretically may benefit more from RFA. On the other hand, applying RFA in the presence of a metal stent may cause reduced local temperature control.

In the current issue of *Gastrointestinal Endoscopy*, Gao et al[2] describe the second, much larger, randomized controlled trial on this subject. The trial included 174 patients with a diagnosis of extrahepatic CCA or ampullary cancer, with the exclusion of Bismuth IV hilar CCA. The protocol differed slightly from that of the previous RCT because patients routinely underwent a second intervention after 3 months. Similarly to the first trial, the overall survival time was significantly higher in the RFA group (mean, 14.3 vs 9.2 months; hazard ratio, 0.488; 95% confidence interval, 0.351-0.678; $P < .001$), with a significant survival benefit for all tumor subtypes. Also in analogy with the previous trial, they report a higher Karnofsky performance score after RFA, which is an important finding, given the short life expectancy of these patients.

By contrast, this time no difference in cumulative stent patency duration was observed (3.7 vs 4.1 months). As the authors discuss, plastic stents become occluded as a result of sludge and/or biofilm formation, a process that RFA likely has no influence on. Over the past decade, the placement of self-expandable metal stents for unresectable extrahepatic biliary cancer has

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2021.02.018

become the standard of care. Self-expandable metal stent occlusion is determined by tumor ingrowth; thus, stent patency theoretically may benefit more from RFA. On the other hand, applying RFA in the presence of a metal stent may cause reduced local temperature control. This is an important obstacle to overcome in subsequent trials.

The authors encountered more adverse events after RFA (27.6% vs 19.5%, $P = .211$). In particular, they found significantly more cholecystitis in the RFA group (9 vs 0, $P = .003$), for which percutaneous drainage was applied. As the authors discuss, edema formation in the cystic duct may have been responsible. Interestingly, Yang et al[7] did not report any cholecystitis in their RFA group. Perhaps differences in RFA and/or stent placement protocols are responsible for this discrepancy. For instance, multiple plastic stent insertion may be associated with a higher risk of cystic duct blockage. Unfortunately, Gao et al[2] did not report the RFA session after which cholecystitis occurred or how many stents were placed.

In conclusion, we would like to compliment Gao et al[2] for their interesting report. This RCT adds to the limited information on this viable technique. Further studies are needed, for example, to evaluate the use of RFA in combination with metal stent placement. Several studies in Asia are already recruiting patients, and a RCT is in preparation in the Netherlands. In addition, a well-executed cost-effectiveness analysis should be performed to determine the widespread feasibility of this expensive technique. Finally, as with most advanced endoscopy techniques, the actual application will mostly be limited to expert treatment centers.

DISCLOSURE

Both authors disclosed no financial relationships.

David M. de Jong
Djuna L. Cahen, MD, PhD
Department of Gastroenterology and Hepatology
Erasmus University Medical Center
Rotterdam, the Netherlands

Abbreviations: CCA, cholangiocarcinoma; RFA, radiofrequency ablation.

REFERENCES

1. Smith AC, Dowsett JF, Russell RC, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bile duct obstruction. Lancet 1994;344:1655-60.
2. Gao D-J, Yang J-F, Ma S-R, et al. Endoscopic radiofrequency ablation plus plastic stent placement versus stent placement alone for unresectable extrahepatic biliary cancer: a multicenter randomized controlled trial. Gastrointest Endosc 2021;94:91-100.
3. Steel AW, Postgate AJ, Khorsandi S, et al. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. Gastrointest Endosc 2011;73:149-53.
4. Zheng X, Bo ZY, Wan W, et al. Endoscopic radiofrequency ablation may be preferable in the management of malignant biliary obstruction: a systematic review and meta-analysis. J Dig Dis 2016;17:716-24.
5. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur J Ultrasound 2001;13:129-47.
6. Giardino A, Innamorati G, Ugel S, et al. Immunomodulation after radiofrequency ablation of locally advanced pancreatic cancer by monitoring the immune response in 10 patients. Pancreatology 2017;17:962-6.
7. Yang J, Wang J, Zhou H, et al. Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. Endoscopy 2018;50:751-60.