Douglas G. Adler MD, FACG, AGAF, FASGE, Series Editor

Radiofrequency Ablation for Biliary Disease

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INTRODUCTION

Biliary obstruction remains a common clinical compliant, and strategies to treat this such as ERCP have been widely employed. The majority of patients with biliary obstruction harbor an underlying malignancy, most commonly pancreatic adenocarcinoma and cholangiocarcinoma. Hepatocellular carcinoma, metastatic masses or adenopathy, gallbladder carcinoma, and ampullary carcinoma are also seen frequently.[1] Surgical resection is the treatment of choice, and if possible leads to better long term outcomes.[2,3] However, because of the insidious and progressive nature of these malignancies, the presentation and diagnosis often occurs late in the disease and most cases are surgically unresectable. Therefore, the palliative relief of biliary obstruction has become the standard of care, and has been shown to improve quality of life.[3,4]

The development of self-expanding metal stents (SEMS) has been shown to give symptomatic relief and offers improved quality of life. However, tumor ingrowth, overgrowth, and stent occlusion from sludge or stones can cause stent failure, often at a median time of 6-8 months.[5,6,7] While most stent occlusions are treated by placement of a new stent within the old stent, interest in other approaches has resulted in the development of endoscopic strategies to relieve stent occlusion, including photodynamic therapy (PDT) and radiofrequency ablation (RFA).

In PDT, a photosensitizer is administrated 48 hours prior to the procedure and is taken up by tumor tissue. An ERCP-directed laser fiber is passed across the malignant stricture, and apoptosis is induced via specific light wavelengths. PDT has demonstrably improved both quality of life, and outcomes in malignant biliary obstruction. The photosensitizer is believed to possibly be preferentially absorbed by malignant cells, and so it may have the advantage of causing relatively little damage to nearby non-malignant cells. [8,9,10,11]

Radiofrequency Ablation

Radiofrequency ablation utilizes an electric current to induce thermal coagulative necrosis of localized tissue. The circuit is composed of either a monopolar probe coupled with a dispersive electrode placed

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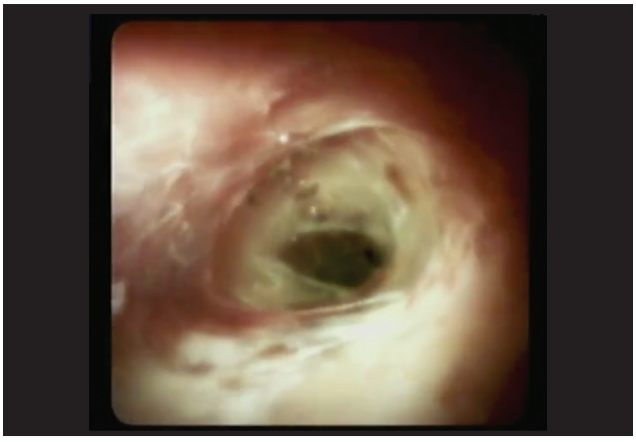

Figure 1a. Cholangioscopic image of a malignant biliary stricture before application of RFA. *(Image courtesy Amy Tyberg MD)*

Figure 1b. Same location following RFA. Note superficial mucosal ablation. *(Image courtesy Amy Tyberg MD)*

on the skin of the patient, or a local bipolar probe. The current alternates between probes at the frequency of radio waves, typically 400-600 hertz (Hz). Tissue is a poor electrical conductor, and so as the current flows it causes the target tissue to heat up to 50-100 degrees Celsius.[12] Heat causes protein denaturation, followed by cell dehydration and coagulative necrosis. The heat generated is directly proportional to the current generated, and so tissue nearest the probe experiences the greatest rise in temperature. Necrosis causes eventual dehydration and charring with loss of the conducting ions within the cells. This leads to a rise in impedance, reducing the depth to which RFA can penetrate.[12,13,14] One strategy to reduce this impedance is by using pulsed RFA, which allows the tissue to cool and rehydrate between pulses, allowing the current to travel deeper into the tissue. Another strategy is to use internally cooled RFA probes. In this case, the goal is to reduce the heat gradient between the probe and the tissue while maintaining current, thereby reducing charring, and allowing deeper penetrance of adequate heat to induce coagulative necrosis.[14]

RFA has also been proposed to stimulate systemic antitumor immunity. Theoretically, by exposing tumor antigen with modalities such as RFA, antigen presenting cells can direct the immune system against targets that would otherwise be hidden.[15,16] Further research into the field of synergistic immunomodulation with RFA is ongoing.

Percutaneous or intraoperative RFA has been historically quite successful in the management of solid tumors including liver, breast, lung, and kidney. More recently RFA has been used in the management of various gastrointestinal disorders as well including Barrett's esophagus, gastric antral vascular ectasia, and metastatic hepatocellular carcinoma.[13] First described in 2011, Habib et al. developed a bipolar catheter that could be directed via ERCP to enter the biliary tree. Since its development, several groups have investigated the safety and efficacy of RFA in biliary obstruction. Its use has been described mostly in the management of malignant biliary obstruction, both before SEMS placement, and after SEMS occlusion. Newer uses are being investigated as experience with RFA grows.

ENDOBILIARY RADIOFREQUENCY ABLATION PROCEDURE

The Habib EndoHPB catheter (Habib EndoHPB, EMcision Ltd, London, UK) is an 8Fr catheter with two 8 mm stainless electrodes separated by 6 mm. The proximal end is connected to an electrosurgical generator, where the power and duration can be adjusted. The biliary tree is accessed via standard ERCP. Opacification of the biliary tree is used to demarcate the stricture location and size, and the guidewire is directed across the stricture. The RFA catheter is then threaded over a guidewire. Energy is supplied by the generator at desired specifications (typically 5-10 watts for 90-120 seconds with a 60 second cooling period). After RFA, the biliary tree is then swept via balloon to remove debris.

Depending on the size and location of the stricture, multiple RFA applications may be required, and these may be to some extent overlapping. This is usually followed by the application of SEMS. If RFA is applied to an already obstructed stent, several applications may be required.[13,14]

RFA FOR MALIGNANT BILIARY STRICTURES

In the vast majority of patients, RFA is used in the setting of a malignant obstruction, either prior to SEMS placement or in an occluded SEMS that has developed tumor ingrowth or overgrowth. (Figure 1)

RFA Prior to Stent Placement

The first group to look at the use of RFA prior to SEMS placement in humans was Steel et al. in 2011. In this study, a total of 21 patients underwent RFA for malignant biliary stricture by either cholangiocarcinoma or pancreatic adenocarcinoma. At 30 days, there were no mortalities, and at 90 days 16 of the initial 21 patients were alive with patent stents. This paper introduced RFA as a relatively safe modality to reduce obstruction prior to SEMS placement.[17]

Four additional small studies from 2013 to 2015 also investigated the safety and feasibility of RFA in malignant biliary obstruction. In a retrospective study, Alis et al. investigated obstruction secondary to cholangiocarcinoma in 17 patients. Of this group, 7 did not have successful ERCP or endobiliary RFA, although the group did not describe the technical difficulties. Of the 10 remaining patients, 30-day mortality was 0%. Two patients developed ERCP-pancreatitis. The authors concluded that RFA was a safe modality for malignant obstruction, although there was a high rate of technical failure.[18] A pilot study by Figueroa-Barojas et al. looked at 20 total patients (11 with pancreatic adenocarcinoma, 7 with cholangiocarcinoma, 1 intraductal papillary mucinous neoplasm and 1 metastatic gastric cancer). All 20 patients underwent successful RFA, and complication rates were similar to rates that had been published for ERCP with stent alone. With a 0% immediate and 30-day mortality, the group concluded that RFA was a safe, and technically feasible technique for malignant obstruction.[19] In a 2014 study of 12 patients, Tal et al. investigated the safety of RFA in hilar tumors (mostly Klatskin Bismuth IV), followed by placement of plastic stents. RFA was technically successful in all cases, but there was a higher frequency of complications. Hemobilia occurred in three patients between 4 and 6 weeks: one of which was spontaneous, and two, which occurred during removal of the plastic stent. Two of these cases were fatal, and one was successfully treated with a SEMS. 30 and 90-day mortality were 8.3% and 50% respectively. Given their higher mortality and complication rate than prior studies, the group reported RFA as a technically feasible technique, but one that required further investigation with large controlled trials to avoid fatal complications.[20] In a 12 patient case series, Laquiere et al. investigated the safety of RFA in a relatively homogenous group of patients with extrahepatic cholangiocarcinoma. Endobiliary RFA was technically successful in all cases. Within 30 days, there was one patient with sepsis thought to be secondary to bacterial translocation, and one patient with acute cholangitis secondary to stent migration. 30-day mortality was 0%. Patients were followed to 9 months and of the 12 patents, 6 received a second RFA session, 3 of which were due to acute stent obstruction with or without acute cholangitis, 3 of which were planned to prevent re-obstruction. This study demonstrated again that RFA was a safe technique for treatment patients with malignant obstruction, and suggested that scheduled repeat session may also be effective at preventing biliary re-obstruction.[21]

In 2014, Dolak et al. published a retrospective, multicenter study of 58 patients undergoing a total of 84 total RFA procedures to look at safety and feasibility.[22] 78 procedures were performed via ERCP and 6 were performed via a percutaneous approach. The patient population had varying malignancies (51 with biliary tract cancer, 4 with pancreatic cancer, and 3 with hepatocellular cancer), and over 50% had received other treatment modalities prior to RFA. The majority had SEMS placed (35 of 58 pts), and 19 received plastic stents. 30-day mortality was 1.7%, and 90 day mortality was 19%. Within 30 days, there 5 cases of cholangitis, three cases of hemobilia, two cases of cholangiosepsis, and one case each of gallbladder empyema, hepatic coma, and newly diagnosed left bundle branch block. The patient with hepatic coma had a fatal oucome. One patient

had a severe complication of liver infarct, which was thought to be secondary to thermal damage to a segmental branch of the hepatic artery. The patient with hepatic coma Median survival rates were extrapolated to 10.6 months post RFA procedure, and 17.9 months from initial diagnosis. Median stent patency was found to be 115 days in plastic stents and 218 days in metal stents. This was the largest retrospective analysis of RFA to date, and while it again demonstrated RFA as a relatively safe option, the size of the cohort allowed the authors to suggest RFA as a way to improve survival and extend stent patency in malignant biliary obstruction.

While the above studies provide data regarding the safety and feasibility of RFA for malignant obstruction, several groups have investigated whether this procedure could impact stent patency and patient survival. To this end, Sharaiha et al. compared patients receiving RFA prior to SEMS placement to patients who received SEMS alone.[23] Of 66 total patients, 26 underwent RFA prior to SEMS placement, and they were matched with 40 patients treated with SEMS alone. RFA was technically successful in all attempts. There were five adverse events in both groups including 3 with abdominal pain, one with pancreatitis, and one with cholecytitis. There was no difference in adverse events between the two groups. There was no significant difference in survival rates between the two groups. However, Multivariate Cox proportional analysis showed that RFA was an independent predictor of survival, with a hazard ratio of 0.29 (95% confidence interval 0.11-0.76). The following year, the same group retrospectively studied 69 patients: 45 with cholangiocarcinoma, 19 with pancreatic cancer, 2 with gallbladder cancer, 1 with gastric cancer, and 3 with liver metastases.[24] These patients all underwent RFA in addition to stent placement for malignant biliary stricture, and were compared to Surveillance, Epidemiology, and End Results (SEER) database patients. In the study group, 78% had received prior or concurrent chemotherapy, and there was a mixture of plastic stents and SEMS. In the study group, the authors described survival rates of 14.6 and 17.7 months for pancreatic and cholangiocarcinoa respectively. These were significantly improved over SEER database survival rates: 5.9 months for pancreatic cancer and 6.2 months for cholangiocarcinoma. The authors concluded that their study suggested that RFA prior to stenting can improve survival rates. However, their study was limited in its retrospective nature, and use of historical data, necessitating larger and prospective trials.

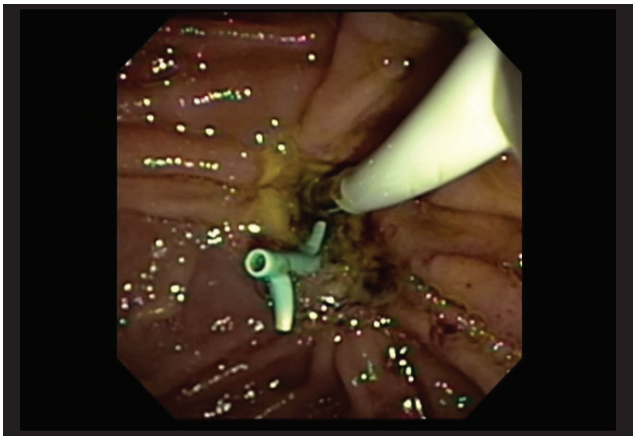

Figure 2a. Use of RFA to treat adenomatous tissue extending into the distal common bile duct in a patient undergoing ampullectomy. Note that the ampullary mass has already been removed and the area treated with argon plasma coagulation. A pancreatic duct stent is in place and the RFA catheter is introduced into the distal common bile duct.

Kallis et al. (2015) performed a similar study to assess the efficacy of RFA in biliary obstruction secondary to pancreatic adenocarcinoma.[25] In this study, 23 patients receiving RFA prior to SEMS were matched with 46 controls receiving SEMS alone. 30 day mortality was 0%, and adverse events were limited to one case each of hyperamylasemia and antibiotic-responsve cholangitis. Of note, the two groups were stringently matched based on demographic characteristics and chemotherapeutic regimens. The group found that there was a statistically significant difference in survival: median survival 226 days with the RFA group vs. 123.5 days in the SEMS only group. Multivariate analysis revealed that RFA afforded an early survival benefit, but this was lost after the 180 day mark. They also found that stent patency was not significantly improved with RFA, and that a majority of patients died from carcinomatosis rather than complications arising from biliary obstruction. The authors concluded that while there was a survival benefit associated with RFA, they could not necessarily connect it to improved stent

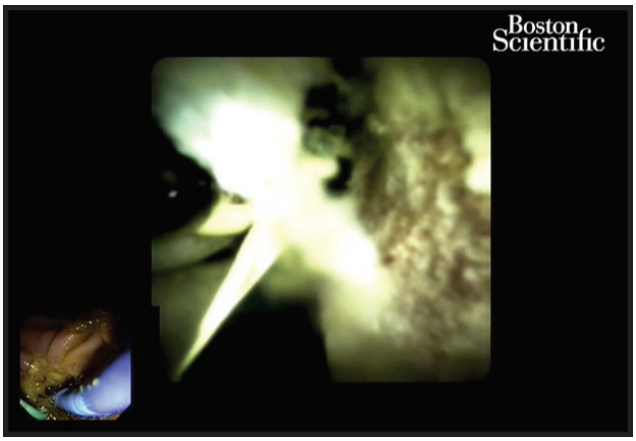

Figure 2b. Cholangioscopic image of the distal common bile duct after RFA application.

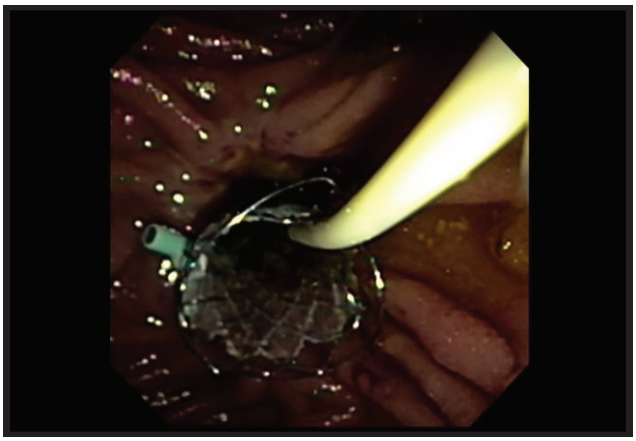

Figure 2c. Placement of a fully covered metal stent across the distal CBD to reduce the risk of stricture formation.

patency. While their data could not adequately demonstrate improved stent patency, just 9 of 23 patients in the RFA group, and 14 of 46 patients in the control group reached the end point of stent occlusion due to mortality. The high mortality rate of these malignancies makes correlation between patency and survival inherently difficult.

Dutta et al. published a study that also looked at RFA vs stenting alone.[26] This was a smaller study, with 15 patients in the RFA arm, and 16 receiving stent alone, and compared various malignancies causing biliary obstruction. RFA median survival was 220 days vs 106.5 days in those receiving SEMS alone. Multivariate analysis was able to demonstrate a survival advantage with RFA independent of age, malignancy type, or obstruction site. Although many of the above studies were able to demonstrate statistically significant efficacy, they were limited in their retrospective nature, and small sample size.

In an attempt to combine the data from several of these smaller studies, Sofi et al. performed a meta-analysis to evaluate survival and stent patency benefits, as well as complication rates in RFA for malignant biliary strictures.[27] Their study population included 505 patients from nine studies, and had patients receiving both percutaneous and endoscopic RFA. The authors found that stent patency was significantly improved by a mean of 50.6 days in the RFA group. Survival rates were significantly better as well with a median 285 days in the RFA group versus 248 days in the controls. When evaluating for adverse events, the RFA group was found to have significantly more episodes of abdominal pain, but all other common adverse events (cholangitis, acute cholecystitis, acute pancreatitis, and hemobilia) were not significantly different between the two groups. Sofi et al. concluded that while their pooled data was promising, they acknowledge the need for larger prospective trials to fully elucidate the efficacy of RFA and the correlation between stent patency and survival.

In a randomized, controlled, single-center prospective study, Yang et al. investigated the use of RFA in 65 patients with unresectable extrahepatic cholangiocarcinoma.[28] The patients were randomized to RFA combined with plastic stenting, or stenting-only. Of note, patients receiving chemotherapy, and those with Bismuth types III and IV lesions were excluded from the study. All patients received endoscopic ultrasound prior to intervention to fully characterize the lesions, and had repeat RFA at a mean of 6 months after initial RFA. Adverse event rates were not significantly different between the two groups, and included 3 cases of acute cholangitis, and one each of acute pancreatitis and hemorrhage. The authors found that stent patency was significantly improved with RFA (6.8 months vs 3.4 months). Survival rates were also significantly improved in the RFA group with a mean survival of 13.2 months vs 8.3 months in the stent-only group. The authors concluded that RFA prior to stenting can significantly improve both survival and stent patency in extrahepatic cholangiocarcinoma.

RFA vs PDT Prior to Stent Placement

In the only study to date to directly compare PDT to RFA prior to stent placement, Strand et al. performed a retrospective analysis of 48 patients with unresectable cholangiocarcinoma. [29]Of these patients, 16 received RFA, and 32 underwent PDT, followed by either plastic stent or SEMS. The PDT group received primarily plastic stents (90.6%) whereas the RFA group received primarily uncovered SEMS (68.7%). Tumor type, and percentage of patients receiving chemotherapy were not significantly different between the two groups. Median survival rates were 9.6 months in the RFA arm, and 7.5 months in the PDT arm, which were not significantly different. In general, adverse event rates were comparable in the two arms, although stent occlusion and cholangitis were significantly increased in the RFA arm. The authors concluded that while their study was limited in its retrospective nature and small sample size, it suggested that RFA and PDT were comparable methods for the palliative treatment of unresectable cholangiocarcinoma. They also discussed the relative advantages and disadvantages between the two methods. While PDT does potentially preferentially select malignant cells, it requires a pre-treatment with photosensitizer and subsequent avoidance of sun exposure for at least 48 hours. The continued comparison between these two methods requires further, large, prospective trials.

RFA for Occluded SEMS

Pozsar et al. were the first to report the use of RFA for occluded biliary SEMS in 2011.[30] In this small trial, 5 patients with occluded SEMS secondary to cholangiocarcinoma were treated with RFA. In all patients, biliary obstruction was successfully relieved without complication. The median stent patency after RFA treatment was 62 days, and the authors concluded that RFA was a relatively safe method for treating occluded SEMS. In a larger trial, Kadayifci et al. investigated the use of the RFA in 50 patients with occluded SEMS.[31] In their study, patients with occluded SEMS were split into two groups. The first group had a new, plastic stent placed within the occluded stent. The second group had RFA to the occluding tissue, without subsequent stent placement. In the RFA group, only 56% had successful ablation, defined as >80% obstruction removed. In the remaining 44%, RFA was considered to have failed, and plastic stents were placed. Analysis of RFA failure found that pancreatic cancer and distal obstruction were predictive of RFA success. Survival rates were not significantly different between the two groups. However, stent patency was found to be significantly improved in the successful ablated group when compared to those with stent alone. The authors concluded that while RFA success was dependent on tumor type and location, when >80% ablation was achieved, there was a demonstrable improvement in stent patency compared to re-stenting alone.

Percutaneous Intraductal RFA

While not the focus of this review, it should be noted that percutaneous intraductal RFA has been described in the literature as a viable tool. Several studies have looked at the use of percutaneous intraductal RFA in malignant biliary strictures. In general, these groups have shown this technique to be safe and feasible. [32,33,34,35] Larger trials, such as those by Wu et al. and Cui et al., have demonstrated a significant improvement in both stent patency and survival.[36,37] Their outcomes were comparable to those found in endoscopic RFA trials discussed above.

OTHER USES FOR ENDOBILIARY RFA

Ampullary Adenoma with Intraductal Extension

Ampullary adenomas are typically treated successfully with endoscopic or surgical resection. However, when the adenoma extends into the biliary tree itself, it often presents a therapeutic challenge for clinicians. (Figure 2) Suarez et al. investigated the use of RFA for the treatment of ampullary adenomas with intraductal extension in a 4 patient case series.[38] Three of the patients had benign ampullary adenomas, and the fourth had an ampullary adenoma with a foci of adenocarcinoma. All cases were technically feasible, and aside from a delayed biliary stricture in one patient, there were no immediate adverse events. Those with benign adenomas had no recurrence of ampullary lesions, but the patient with adenocarcinoma developed overt invasive ampullary cancer and passed away from their disease, demonstrating the limitations

of this technology. Rustagi et al. investigated the use of RFA in ampullary neoplasms in a slightly larger trial of 14 patients.[39] The group had mixed pathology, including two adenocarcinomas, and a mix of tubulovillous and tubular adenomas. There were also varied treatment strategies, with half receiving RFA-only, and half receiving a mix of RFA in combination with argon plasma coagulation, PDT, or electrocoagulation. Despite the heterogenous nature of the cohort, the authors reported 92% of patients with successful eradication of disease after a 16 month median follow up period. Adverse event rates were high at 43%, the majority of which were benign common bile duct strictures. These studies demonstrate that RFA has potentially beneficial applications in the management of ampullary lesions, but will require more robust, standardized trials to further elucidate its clinical utility.

Benign Biliary Strictures

As several groups reported the safety and efficacy of RFA in malignant biliary strictures, this technique was proposed by some as a means to manage benign strictures as well. Benign strictures are fairly heterogenous in nature, resulting from multiple etiologies including liver transplant, pancreaticobiliary surgery, and any condition causing chronic inflammation. The majority results in stiff fibrinous tissue, histologically far different than malignant strictures. Typically managed by dilatation and multiple stenting procedures, up to 40% of strictures are refractory to current endoscopic techniques. Hu et al. investigated the use of RFA in 9 patients with benign biliary strictures.[40] All patients had successful RFA followed by balloon dilatation. No serious adverse events occurred, and all patients achieved immediate improvement or resolution of their benign strictures. There were variable follow up times, but at a median of 12.6 months, 4 patients had achieved full stricture resolution without need for further stenting. The authors concluded that RFA was a feasible and safe method for benign biliary strictures, but refrained from making conclusions on efficacy given the relatively small and heterogenous study design. Swine models are currently being developed, and further studies are needed to investigate the use of RFA in benign biliary strictures.

CONCLUSION

Biliary RFA has emerged as a viable method for the ablation and palliation of biliary strictures. Data thus far has been largely limited to retrospective analyses, but the results from these studies suggest that endobiliary RFA is a safe, and feasible technique. In unresectable malignancy, RFA may confer both survival and stent patency benefits, but further investigation is required before definitive statements can be made. Clinicians should be aware of the adverse events common to endobiliary RFA, including abdominal pain, cholangitis, acute cholecystitis, stricture formation or worsening, and hemobilia. As experience with endobiliary RFA grows, further questions remain; including the effect of chemotherapy on survival and how plastic vs metal stents may alter stent patency duration. Continued investigation with large, randomized, controlled, prospective trials is required to answer these questions and further elucidate the efficacy of endobiliary RFA in the management of biliary strictures. ■

References

1. Shah JN, Muthusamy VR. Endoscopic palliation of pancreaticobiliary malignancies. Gastrointest Endosc Clin N Am. 2005 Jul;15(3):513-31, ix. Review.PubMed PMID: 15990055. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology. 2013 Dec;145(6):1215-29. doi:10.1053/j.gastro.2013.10.013. Epub 2013 Oct 15. Review. PubMed PMID: 24140396;PubMed Central PMCID: PMC3862291.
2. Bismuth H, Nakache R, Diamond T. Management strategies in resection for hilar cholangiocarcinoma. Ann Surg. 1992 Jan;215(1):31-8. PubMed PMID: 1309988; PubMed Central PMCID: PMC1242367.
3. Ballinger AB, McHugh M, Catnach SM, Alstead EM, Clark ML. Symptom relief and quality of life after stenting for malignant bile duct obstruction. Gut. 1994 Apr;35(4):467-70. PubMed PMID: 7513672; PubMed Central PMCID: PMC1374793.
4. O'Brien S, Hatfield AR, Craig PI, Williams SP. A three year follow up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction. Gut. 1995 Apr;36(4):618-21. PubMed PMID: 7537708; PubMed Central PMCID: PMC1382508.
5. Loew BJ, Howell DA, Sanders MK, Desilets DJ, Kortan PP, May GR, Shah RJ, Chen YK, Parsons WG, Hawes RH, Cotton PB, Slivka AA, Ahmad J, Lehman GA, Sherman S, Neuhaus H, Schumacher BM. Comparative performance of uncoated, self-expanding metal biliary stents of different designs in 2 diameters: final results of an international multicenter, randomized, controlled trial. Gastrointest Endosc. 2009 Sep;70(3):445-53. doi: 10.1016/j.gie.2008.11.018. Epub 2009 May 30. PubMed PMID: 19482279.

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6. Kullman E, Frozanpor F, Söderlund C, Linder S, Sandström P, Lindhoff-Larsson A, Toth E, Lindell G, Jonas E, Freedman J, Ljungman M, Rudberg C, Ohlin B, Zacharias R, Leijonmarck CE, Teder K, Ringman A, Persson G, Gözen M, Eriksson O. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc. 2010 Nov;72(5):915-23. doi:10.1016/j.gie.2010.07.036. PubMed PMID: 21034892.
7. Ortner ME, Caca K, Berr F, Liebetruth J, Mansmann U, Huster D, Voderholzer W, Schachschal G, Mössner J, Lochs H. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study.Gastroenterology. 2003 Nov;125(5):1355-63. PubMed PMID: 14598251.
8. Gao F, Bai Y, Ma SR, Liu F, Li ZS. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. J Hepatobiliary Pancreat Sci. 2010 Mar;17(2):125-31. doi: 10.1007/s00534-009-0109-3. Epub 2009 May 20. Review. PubMed PMID: 19455276.
9. Zoepf T, Jakobs R, Arnold JC, Apel D, Riemann JF. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol. 2005 Nov;100(11):2426-30. PubMed PMID: 16279895.
10. Strand DS, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, Mann JA, Sauer BG, Shami VM, Wang AY. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. Gastrointest Endosc. 2014 Nov;80(5):794-804. doi:10.1016/j.gie.2014.02.1030. Epub 2014 May 15. PubMed PMID: 24836747.
11. Goldberg SN. Radiofrequency tumor ablation: principles and techniques. Eur J Ultrasound. 2001 Jun;13(2):129-47. Review. PubMed PMID: 11369525.
12. Shah DR, Green S, Elliot A, McGahan JP, Khatri VP. Current oncologic applications of radiofrequency ablation therapies. World J Gastrointest Oncol.2013 Apr 15;5(4):71-80. doi: 10.4251/wjgo.v5.i4.71. PubMed PMID: 23671734; PubMed Central PMCID: PMC3648666.
13. Alvarez-Sánchez MV, Napoléon B. Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety. World J Gastroenterol. 2016 Oct 7;22(37):8257-8270. Review. PubMed PMID: 27729733; PubMed Central PMCID: PMC5055857.
14. den Brok MH, Sutmuller RP, van der Voort R, Bennink EJ, Figdor CG, Ruers TJ, Adema GJ. In situ tumor ablation creates an antigen source for the generation of antitumor immunity. Cancer Res. 2004 Jun 1;64(11):4024-9. PubMed PMID: 15173017.
15. Slovak R, Ludwig JM, Gettinger SN, Herbst RS, Kim HS. Immuno-thermal ablations – boosting the anticancer immune response. Journal for Immunotherapy of Cancer. 2017;5:78. doi:10.1186/s40425-017-0284-8.
16. Steel AW, Postgate AJ, Khorsandi S, Nicholls J, Jiao L, Vlavianos P, Habib N, Westaby D. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. Gastrointest Endosc. 2011 Jan;73(1):149-53. doi: 10.1016/j.gie.2010.09.031. PubMed PMID: 21184881.
17. Alis H, Sengoz C, Gonenc M, Kalayci MU, Kocatas A. Endobiliary radiofrequency ablation for malignant biliary obstruction. Hepatobiliary Pancreat Dis Int. 2013 Aug;12(4):423-7. PubMed PMID: 23924501.
18. Figueroa-Barojas P, Bakhru MR, Habib NA, Ellen K, Millman J, Jamal-Kabani A, Gaidhane M, Kahaleh M. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. J Oncol. 2013;2013:910897. doi: 10.1155/2013/910897. Epub 2013 Apr 8. PubMed PMID: 23690775; PubMed Central PMCID: PMC3649248.
19. Tal AO, Vermehren J, Friedrich-Rust M, Bojunga J, Sarrazin C, Zeuzem S, Trojan J, Albert JG. Intraductal endoscopic radiofrequency ablation for the treatment of hilar non-resectable malignant bile duct obstruction. World J Gastrointest Endosc. 2014 Jan 16;6(1):13-9. doi: 10.4253/wjge.v6.i1.13. PubMed PMID: 24527176; PubMed Central PMCID: PMC3921441.
20. Laquière A, Boustière C, Leblanc S, Penaranda G, Désilets E, Prat F. Safety and feasibility of endoscopic biliary radiofrequency ablation treatment of extrahepatic cholangiocarcinoma. Surg Endosc. 2016 Mar;30(3):1242-8. doi:10.1007/s00464-015-4322-7. Epub 2015 Jul 11. PubMed PMID: 26162420.
21. Dolak W, Schreiber F, Schwaighofer H, Gschwantler M, Plieschnegger W, Ziachehabi A, Mayer A, Kramer L, Kopecky A, Schrutka-Kölbl C, Wolkersdörfer G, Madl C, Berr F, Trauner M, Püspök A; Austrian Biliary RFA Study Group. Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. Surg Endosc. 2014 Mar;28(3):854-60. doi: 10.1007/s00464-013-3232-9. Epub 2013 Oct 3. PubMed PMID:24196547.
22. Sharaiha RZ, Natov N, Glockenberg KS, Widmer J, Gaidhane M, Kahaleh M. Comparison of metal stenting with radiofrequency ablation versus stenting alone for treating malignant biliary strictures: is there an added benefit? Dig Dis Sci. 2014 Dec;59(12):3099-102. doi: 10.1007/s10620-014-3264-6. Epub 2014 Jul 18. PubMed PMID: 25033929
23. Sharaiha RZ, Sethi A, Weaver KR, Gonda TA, Shah RJ, Fukami N, Kedia P, Kumta NA, Clavo CM, Saunders MD, Cerecedo-Rodriguez J, Barojas PF, Widmer JL, Gaidhane M, Brugge WR, Kahaleh M. Impact of Radiofrequency Ablation on Malignant Biliary Strictures: Results of a Collaborative Registry. Dig Dis Sci. 2015 Jul;60(7):2164-9. doi: 10.1007/s10620-015-3558-3. Epub 2015 Feb 21. PubMed PMID: 25701319.
24. Kallis Y, Phillips N, Steel A, Kaltsidis H, Vlavianos P, Habib N, Westaby D. Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit. Dig Dis Sci. 2015 Nov;60(11):3449-55. doi: 10.1007/s10620-015-3731-8. Epub 2015 Jun 3. PubMed PMID:26038094.
25. Dutta AK, Basavaraju U, Sales L, Leeds JS. Radiofrequency ablation for management of malignant biliary obstruction: a single-center experience and review of the literature. Expert Rev Gastroenterol Hepatol. 2017 Aug;11(8):779-784. doi: 10.1080/17474124.2017.1314784. Epub 2017 Apr 7. PubMed PMID: 28362129.
26. Sofi AA, Khan MA, Das A, Sachdev M, Khuder S, Nawras A, Lee W. Radiofrequency ablation combined with biliary stent placement versus stent placement alone for malignant biliary strictures: a systematic review and meta-analysis. Gastrointest Endosc. 2017 Nov 3. pii: S0016-5107(17)32426-4. doi: 10.1016/j.gie.2017.10.029.[Epub ahead of print] Review. PubMed PMID: 29108980.
27. Yang J, Wang J, Zhou H, Zhou Y, Wang Y, Jin H, Lou Q, Zhang X. Efficacy and safety of endoscopic radiofrequency ablation for unresectable extrahepatic cholangiocarcinoma: a randomized trial. Endoscopy. 2018 Jan 17. doi:10.1055/s-0043-124870. [Epub ahead of print] PubMed PMID: 29342492.
28. Strand DS, Cosgrove ND, Patrie JT, Cox DG, Bauer TW, Adams RB, Mann JA, Sauer BG, Shami VM, Wang AY. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. Gastrointest Endosc. 2014 Nov;80(5):794-804.

doi: 10.1016/j.gie.2014.02.1030. Epub 2014 May 15. PubMed PMID: 24836747.

29. Pozsár J, Tarpay A, Burai J, Pap A. Intraductal radiofrequency ablation can restore patency of occluded biliary self-expanding metal stents. Z Gastroenterol. 2011;49:A70.
30. Kadayifci A, Atar M, Forcione DG, Casey BW, Kelsey PB, Brugge WR. Radiofrequency ablation for the management of occluded biliary metal stents. Endoscopy. 2016 Dec;48(12):1096-1101. Epub 2016 Oct 7. PubMed PMID: 27716861
31. Pai M, Valek V, Tomas A, Doros A, Quaretti P, Golfieri R, Mosconi C, Habib N. Percutaneous intraductal radiofrequency ablation for clearance of occluded metal stent in malignant biliary obstruction: feasibility and early results. Cardiovasc Intervent Radiol. 2014 Feb;37(1):235-40. doi: 10.1007/s00270-013-0688-x. Epub 2013 Jul 11. PubMed PMID: 23842684.
32. Li TF, Huang GH, Li Z, Hao CF, Ren JZ, Duan XH, Zhang K, Chen C, Han XW, Jiao DC, Zhang MF, Wang YL. Percutaneous transhepatic cholangiography and intraductal radiofrequency ablation combined with biliary stent placement for malignant biliary obstruction. J Vasc Interv Radiol. 2015 May;26(5):715-21. doi:10.1016/j.jvir.2015.01.037. Epub 2015 Mar 24. PubMed PMID: 25817458.
33. Betgeri S, Rajesh S, Arora A, Panda D, Bhadoria AS, Mukund A. Percutaneous endobiliary RFA combined with balloon-sweep for re-opening occluded metallic biliary stents. Minim Invasive Ther Allied Technol. 2017 Apr;26(2):124-127. doi: 10.1080/13645706.2016.1235052. Epub 2016 Sep 27. PubMed PMID: 27611763.
34. Wang Y, Cui W, Fan W, Zhang Y, Yao W, Huang K, Li J. Percutaneous intraductal radiofrequency ablation in the management of unresectable Bismuth types III and IV hilar cholangiocarcinoma. Oncotarget. 2016 Aug 16;7(33):53911-53920. doi:10.18632/oncotarget.10116. PubMed PMID: 27322076; PubMed Central PMCID: PMC5288231.
35. Wu TT, Li WM, Li HC, Ao GK, Zheng F, Lin H. Percutaneous Intraductal Radiofrequency Ablation for Extrahepatic Distal Cholangiocarcinoma: A Method for Prolonging Stent Patency and Achieving Better Functional Status and Quality of Life. Cardiovasc Intervent Radiol. 2017 Feb;40(2):260-269. doi:10.1007/s00270-016-1483-2. Epub 2016 Oct 14. PubMed PMID: 27743089.
36. Cui W, Fan W, Lu M, Zhang Y, Yao W, Li J, Wang Y. The safety and efficacy of percutaneous intraductal radiofrequency ablation in unresectable malignant biliary obstruction: A single-institution experience. BMC Cancer. 2017 Apr 24;17(1):288. doi: 10.1186/s12885-017-3278-5. PubMed PMID: 28438130; PubMed Central PMCID: PMC5404294.
37. Suarez AL, Coté GA, Elmunzer BJ. Adjunctive radiofrequency ablation for the endoscopic treatment of ampullary lesions with intraductal extension (with video). Endosc Int Open. 2016 Jul;4(7):E748-51. doi: 10.1055/s-0042-107665. Epub 2016 Jun 29. PubMed PMID: 27556089; PubMed Central PMCID: PMC4993901.
38. Rustagi T, Irani S, Reddy DN, Abu Dayyeh BK, Baron TH, Gostout CJ, Levy MJ, Martin J, Petersen BT, Ross A, Topazian MD. Radiofrequency ablation for intraductal extension of ampullary neoplasms. Gastrointest Endosc. 2017Jul;86(1):170-176. doi: 10.1016/j.gie.2016.11.002. Epub 2016 Nov 17. PubMed PMID:27866907.
39. Hu B, Gao DJ, Wu J, Wang TT, Yang XM, Ye X. Intraductal radiofrequency ablation for refractory benign biliary stricture: pilot feasibility study. Dig Endosc. 2014 Jul;26(4):581-5. doi: 10.1111/den.12225. Epub 2014 Jan 9. PubMed PMID: 24405166.

Answers to this month's crossword puzzle:

1 R	E	2 F	R	3 A	C	4 T	O	5 R	Y		6 D	7 A	M	8 P
E		L		H		R		U		9 P		L		U
10 I	S	O	M	E	R	A	S	E		11 C	O	L	O	N
N		R		I		C				T		E		G
12 F	L	A	13 B		14 S	T	O	15 O	L		16 A	L	O	E
E			I		U			P		17 L		E		N
18 C	Y	19 S	T	20 O	M	A		21 S	O	Y			22 F	T
T		E		C			23 S			M		24 M	E	
25 I	N	D	U	C	E		L		26 S	P	R	U	E	
O		E		L		27 L	I	P		H		T		28 P
29 N	O	N		30 U	R	I	C		31 F	O	32 L	A	33 T	E
		T		S		34 G	E	35 T		36 C	A	T	E	R
37 C	L	A	R	I	T	H	R	O	M	Y	C	I	N	
E		R		V		T		R		T		O		38 A
39 O	X	Y	G	E	N		40 I	N	T	E	R	N	A	L