Archives of the Balkan Medical Union
vol. 52, no. 3, pp. 316-322
September 2017

REVIEW

RADIOFREQUENCY ABLATION FOR BILIARY MALIGNANCIES MANAGEMENT: AN EMERGING THERAPEUTIC OPTION – REVIEW

Vasile Sandru[1], Bogdan Silviu Ungureanu[2], Dan Ionut Gheonea[2], Madalina Ilie[1], Irina-Gabriela Diaconu[1], Gabriel Constantinescu[1]

[1] Gastroenterology Department, Clinical Emergency Hospital Bucharest, Romania.
[2] Gastroenterology Department, University of Medicine and Pharmacy of Craiova, Romania

Abstract

The malignancies of the bile duct are often diagnosed in advanced stage, when the biliary obstruction is already present. The palliative treatment for the biliary decompression may improve the patient's survival and his quality of life. Several palliative treatments are possible, such as stent placing and radiofrequency ablation (RFA), both being used by either percutaneous or endoscopic approach. This review focuses on the feasibility, safety and clinical efficacy of endoscopic-guided biliary RFA in the biliary malignancies. Currently, biliary stenting (plastic or metallic biliary stents) is the standard of care for palliative drainage procedures, but there are several studies evaluating the use of RFA in the bilio-pancreatic malignant diseases. There are studies that confirmed that RFA prior to biliary stenting might be more effective than stenting alone. At this moment, available data suggest that endoscopic RFA represents a feasible treatment option, with an acceptable safety profile and with a favorable impact on early survival on patients with malignancies of the bile duct, but prospective randomized controlled trials are needed in order to accurately assess the efficacy in terms of survival and quality of life.

Résumé

Ablation par radiofréquence pour la gestion des malignités biliaires: une option thérapeutique émergente

Les malignités des voies biliaires sont fréquemment diagnostiquées en stades avancés, quand l'obstruction biliaire est déjà présente. Le traitement palliatif pour la décompression biliaire peut améliorer la survie et la qualité de vie des patients. Plusieurs traitements palliatifs sont actuellement possibles, tels que la mise en place des prothèses biliaires ou l'ablation par radiofréquence (ARF), le deux peuvent être utilisées par voie percutanée ou endoscopique. Cette revue est focalisée sur la faisabilité, sécurité et l'efficacité clinique de l'ARF par voie endoscopique des tumeurs des voies biliaires. Actuellement, la pose des prothèses biliaires (en plastique ou métalliques) est le standard dans les soins palliatifs des tumeurs malignes biliaires, mais il y a déjà plusieurs études évaluant l'utilisation de l'ARF dans les cancers bilio-pancréatiques. Une autre étude évalue le dispositif Habib EndoHPB, démontrant sa faisabilité et securité sur 22 patients avec obstruction biliaire d'étiologie maligne. En plus, il y a des études qui confirment que l'ARF utilisée avant la mise en

Corresponding author: Bogdan Silviu Ungureanu
Gastroenterology Department, Emergency Clinical County Hospital of Craiova, University of Medicine and Pharmacy of Craiova, Romania
Address: Tabaci Nr 1 200642; E-mail: bogdan.ungureanu@umfcv.ro

Key words: biliary malignancy, palliative biliary drainage, radiofrequency ablation.

place des prothèses est plus efficace que les prothèses seules. Deux études ont comparé la perméabilité des endoprothèses métalliques auto-expansibles, posées avant et après l'ARF. La perméabilité est semblable, mais on a constaté une amélioration de la survie quand l'ARF a été utilisée avant. En conclusion, en ce moment, les informations disponibles montrent que l'ARF par voie endoscopique semble un traitement faisable, en sécurité, ayant un impact favorable sur la survie, dans les lésions malignes des voies biliaires. Il y a encore besoin des études prospectives randomisées pour mieux estimer l'efficacité concernant la survie et la qualité de vie.

Mots-clés: obstruction des voies biliaires, drainage biliaire palliatif, ablation par radiofréquence.

Introduction

Traditionally, bile duct malignancies have an insidious course and are often diagnosed in advanced stage, when biliary obstruction is already present. With surgery remaining the only curative option and while most of the patients are diagnosed in either local or metastatic stage, palliative techniques have been engaged to overcome this drawback[1]. Consecutively, late diagnosis, poor functional status or the presence of other comorbidities, makes surgical intervention possible in less than 30% of the cases, especially in extrahepatic cholangiocarcinoma (CC)[2,3]. Thus, palliative treatment aimed for biliary decompression represents the primary interventional goal[4] which may improve patient's survival and quality of life.

Several therapies have been suggested so far, in different settings. Stent placement, using either a percutaneous or an endoscopic approach, has become the main focus for palliative drainage procedures[5,6]. When compared to surgical intervention, endoscopic stent insertion has proven to offer a shorter hospitalization period and an overall lower morbidity[7]. Also, the use of self-expanding metal stents (SEMS) provides a better efficacy, compared to plastic stents, for maintaining biliary drainage[8-10]. However, several factors can still lead to SEMS occlusion, including tumor ingrowth and overgrowth, epithelial hyperplasia and biofilm, creating a negative impact on patency period, with a consequent increase in morbidity and mortality.

A better outcome seems to be added with the use of endoscopic therapies such as photodynamic therapy (PDT) or radiofrequency ablation (RFA). PDT proved its superiority compared to simple stenting, with maintenance of biliary drainage and with a significant increase in survival rates[11,12]. Still, high costs, along with the risk of developing photosensitivity or cholangitis, extend the limitations of using PDT[13]. On the other hand RFA became possible along with the relatively recent introduction of the Habib™ EndoHBP probe (EMcision, London, UK). RFA, used via percutaneous or during surgery, is already well-known for its effectiveness as a treatment option for various malignancies in solid organs, such as liver, breast, lung, kidney or even pancreas[14-18]. This technique is based on heat-induced necrosis inside the tumoral tissue, with a curative or, more often, palliative intent. In the case of malignant biliary strictures, the primary objectives of RFA are delaying tumor progression, increasing stent patency period, and as a consequence of the first two, increased survival and an improved quality of life. RFA through a percutaneous transhepatic bile duct was proven feasible, with favorable impact on survival[19]. However, the invasiveness of the percutaneous approach makes it inferior to endoscopic retrograde cholangiopancreatography (ERCP), which is technically more simple to perform, and has a lower risk of procedure-related complications.

This review provides the current status regarding feasibility, safety and clinical efficacy of endoscopic-guided biliary RFA, along with any potential advantages it might possess over other palliative therapies used in the case of biliary malignancies.

General principles in Radiofrequency Ablation

Radiofrequency ablation uses radio waves (400-500 kHz) to increase the local temperature within a tissue, in order to determine cell death by means of coagulative necrosis. One of the main

differentiating factors from other ablative techniques is that the electrode itself does not directly supply heat to the tissue. The RF circuit creates an alternating electrical current, which travels through the body between the electrode positioned in the targeted tissue and the grounding pad (in the case of monopolar probes), or between two electrodes (for bipolar catheters). Ions within the tissue have the tendency to follow the alternating path of the current, causing heat generation determined by frictional forces between moving ions. During RFA procedures, local temperature rises to 50-100°C, which leads to protein denaturation, dehydration and coagulative necrosis. The electrical conductivity of the tissue is one of the main factors which enhance the ablative area. Once the tissue becomes necrotic, the local conductivity decreases, limiting the necrosis extension and making the initial RF current insufficient to cover the entire targeted area[20]. One other factor with limiting capability over the volume of ablated tissue is the heat-sink phenomenon, which is observed in the proximity of large vascular structures. Significant vascular flow near a targeted tumor dissipates enough heat to diminish the effectiveness of the ablative method[21]. Regarding these limiting factors, several strategies have been developed, focused on optimizing the volume of tissue ablation, among which are the use of pulsed RF, internally cooled electrodes, multiple hooked electrodes, or selection of the optimal application time[22].

Besides the obvious effects derived from the direct thermal injury, ablating tumoral tissue through via RFA might enhance the host immune response, stimulating tumor regression through indirect mechanisms. The cellular debris resulted in the ablation area stimulates dendritic cell infiltration, with consequent enhancement of the systemic antitumor T-cell immune responses[23]. Also, another possible mechanism may involve hyperthermia-induced expression of heat shock protein (HSP), which in turn triggers tumor regression through immune mechanisms[24].

Endo-biliary RFA procedure

The Habib™ EndoHPB is an endoscopic bipolar radiofrequency probe with two radiologically marked electrodes at the distal end (6 mm apart). The RF current may be applied during a standard ERCP procedure, without any special patient preparation. Following canulation of the common bile duct, a cholangiography is performed in order to accurately determine the stricture's location and to assess its length and diameter. In some cases, depending on the stricture's diameter, balloon dilation may be necessary before inserting the catheter. Under fluoroscopic guidance, the RF probe is inserted over a guidewire into the bile duct until the stricture is reached. Energy is delivered using a high-frequency generator, set at 7-10 W, typically for 120 s, followed by a period of 1 minute without any movement of the probe, in order to avoid any adherences between the tissue and the electrodes. Based on the stricture size, RFA energy may be delivered repeatedly, during the same session, at different stricture sites, from the proximal margin to the distal one, with minimal overlap. Following RFA, a plastic or metal stent can be placed immediately, according to the routine technique[25,26].

RFA Efficacy

Given the poor prognosis of patients with bile duct malignancies, palliative biliary drainage improves liver function, resolves jaundice and reduces the risk of sepsis. Currently, metal stents are the standard of care for palliative drainage procedures[5,6,27]. Despite the superior patency period of SEMS over plastic stents, the re-occlusion appears in most cases after 6-8 months, due to tumor ingrowth and overgrowth, epithelial hyperplasia or biofilm deposition. As a result, long-term patency of biliary stents remains an on-going challenge. The use of covered stents and PDT have proved to be valid alternatives capable of prolonging biliary stents patency, with a positive impact on survival[11,12,28]. However, there is a proven association between the use of covered SEMS and complications, including pancreatitis and cholecystitis[29]. Also, PDT has been associated with high risk of cholangitis and photosensitivity[13,30].

RFA has shown important outcomes in locally advanced pancreatic cancer, and opened a window for its use in biliary tumors. The safety and feasibility of RFA using the Habib EndoHPB catheter was demonstrated for the first time in a clinical study, which included 22 patients with malignant biliary obstructions[31]. Further on, other studies confirmed that RFA prior to biliary stenting, might be more effective than stenting alone[32-36]. However, most of the available data come from small retrospective series, which, naturally, incur a selection bias for the included patients. On the other hand, there is a heterogeneity regarding the malignancy etiology included in these clinical studies, and also, by the absence of any clear indications regarding the power settings selected, the number of sessions, or the influence of other concomitant palliative therapies. Even so, theoretical efficacy of the technique alongside with the consistency of the acquired results, represent an essential step towards its validation as a feasible treatment option.

Several parameters can be used to determine the success rate of endobiliary RFA procedures. There appears to be a lack of homogeneity regarding the evaluated parameters, leading to possible inconsistencies when trying to standardize the results from the available studies. In some cases, it was observed improvement between pre- and post-RFA luminal diameter: 0 mm vs 4 mm[31], 1.7 mm vs 5.2 mm[37], 1.5 mm vs 5 mm[38], with an overall mean increase of 3.7 mm in the luminal diameter after RFA. *Dolak et al.*[36] performed 84 RFA procedures on 58 patients with biliary obstruction. All procedures were conducted without any technical problems, and the RFA efficacy was extrapolated from the median stent patency time. Both plastic and metal stents showed superior patency time after RFA, compared to solitary stenting[8,9,39], with an overall stent patency of 170 days (95% CI 63–277) after the last performed RFA, with an almost significant difference between plastic and metal stents (115 days vs 218 days, p = 0.051). In this series of patients, the extrapolated median survival is 10.6 months (95% CI 6.9–14.4) from the first RFA procedure, with an overall survival of 17.9 months (95% CI 10.3–25.6) from initial diagnosis, which is significant compared to survival rates documented for best supportive care, of approximately 12 months[40].

Two more recent studies compared stent patency time and survival between patients treated with RFA followed by SEMS placement and patients treated only with biliary stenting. First study included 26 patients in the RFA group and 40 patients in the stent-only group[41]. In these patients, SEMS patency rates between the two groups were similar. Similar results were obtained in the second study, which included 23 patients for the RFA group, and 46 controls[33]. Interestingly, both studies observed improvements

Table 1. Current clinical status on endoscopic radiofrequency ablation for biliary stricture CC – cholangiocarcinoma, PC – pancreatic carcinoma, HCC – hepatocellular carcinoma, IPNM-HGD intraductal papillary mucinous neoplasm with high grade dysplasia, LBBB – left bundle branch block, met – metastasis, GB – gallbladder.

Author	Number of patients	Type of cancer	Power settings	RF sessions	Success rate	Median stent patency	Survival (months)	Complications
Steel et al. [28]	21	16 PC	7-10 W, 120 s	2(1-4)	100%	114 d (0-498)	---	1 biochemical pancreatitis 2 cholecystitis
Monga et al. [29]	1	CC	5 W, 120 s	1	100%	100% at 2-weeks follow-up	---	No complications
Kallis et al. [30]	11	6 PC 3 CC 2 liver met	---	1	100%	146 d	---	No complications
Sharaiha et al. [31]	69	45 CC 19 PC 1 GB carcinoma 1 gastric cancer 3 liver met	8 W, 90 s	1 (1-4)	100%	96 % – 30-days follow-up	11.46 (6.2-25)	1 pancreatitis 2 cholecystitis
Strand et al. [32]	16	13 Klatskin CC 1 intrahepatic CC 2 extrahepatic CC	7 W, 90 s	---	100%	---	9.6	---
Dolak et al. [33]	58	50 CC (45 Klatskin) 4 PC 1 GB carcinoma 1 liver met 1 HCC/CC	10 W, 180 s	1 (1-5)	100%	170 d	10.6	1 partial liver infarction 5 cholangitis 2 cholangiosepsis 3 hemobilia 1 GB empyema 1 hepatic coma 1 LBBB
Figueroa-Barojas et al. [34]	20	11 CC 7 PC 1 IPNM-HGD 1 liver met	7-10 W, 120 s	---	100%	100% – 30-days follow-up	---	5 pain 1 pancreatitis 1 cholecystitis
Alis et al. [35]	10	CC	10 W, 120 s	3 (3-4)	100%	9 months (6-15)	---	2 pancreatitis

in survival rates after RFA, which was found to be an independent predictor of survival at 90 and 180 days (OR = 21.07, 95% CI: 1.45-306.64, p=0.026; OR = 4.48, 95% CI: 1.04-19.30, p=0.044, respectively)[33]. Therefore, it is possible that improvements in survival rates following RFA might not be closely related to better maintenance of biliary drainage.

Observations of any similarities between RFA-based treatment and PDT might be able to further support RFA efficacy. One retrospective study aimed to compare both techniques on a number of 48 patients. The results showed similar survival rates between the RFA group (n = 16) and the patients who underwent PDT, with a median survival of 9.6 vs 7.5 months, respectively (p = 0.799). However, despite similar influences on survival rates, in addition to complications including cholangitis and photosensitivity, PDT remains expensive and time consuming, making RFA a more suitable choice[13].

Currently, with all the available data, it is rather difficult to estimate the real incidence of complications related to RFA for biliary malignancies. Moreover, most studies report procedure-related adverse events, which are known to be associated with ERCP or biliary stenting alone, with only few directly related to the ablation procedure itself. Most frequent adverse events are infectious complications, including cholangitis, cholecystitis, biliary sepsis, and gallbladder empyema[42]. Sepsis and cystic duct encasement prior to ERCP might be able to explain some cases of cholecystitis and gallbladder empyema[31]. Other reported complications include post-procedure abdominal pain, pancreatitis, and hemobilia. A partial liver infarction occurred in a patient with Bismuth IV stage Klatskin tumor, which was probably caused by thermal injury of a segmental liver artery[36]. The patient successfully recovered after conservative treatment and a computer tomography scan performed 3 months later showed normal perfusion of the affected liver areas. This complication emphasizes the need for accurate pre-interventional imaging assessment of the tumor surroundings before applying RFA treatment, especially for proximal strictures. Other serious complications including thermal injury to the duodenum or pancreas, bile duct perforation or bile leak, although theoretically possible, have not been reported.

Future perspectives and conclusions

Given the aggressive nature of bilio-pancreatic cancers, further developments in the palliative field are clearly necessary. RFA has proved to be an important addition to the therapeutic armamentarium in various solid tumors. However, in biliary malignant strictures, the full outcomes of using RFA have yet to be fully understood. Until now, available data suggest that endoscopic RFA represents a feasible treatment option, with an acceptable safety profile and with a favorable impact on early survival of patients with biliary malignancies. Nevertheless, from this point forward, future improvements are clearly necessary. These mandatory developments should be related to the two key limitations extrapolated from the existing data, which are the small, but noteworthy, risk of local adverse events, and, secondly, the design of large cohort patients with specific characteristics. Naturally, these two main limitations have certain interrelated aspects and an integrative future approach should include solutions for both.

Regarding the procedure itself and considering the nature of the local complications observed after biliary RFA, it can be speculated that a more thorough pre-interventional imaging may minimize thermal injury to surrounding vascular or biliary structures. Thus, pre-interventional magnetic resonance imaging, endoscopic ultrasound or intraductal endoscopic ultrasound could reveal essential details needed in order to avoid serious complications, such as liver infarction or hemobilia. Therefore, procedure related aspects, such as probe positioning, energy level and application time, should be adapted to local anatomical particularities, decreasing the risk of local damage to vital structures. These measures could be particularly relevant for hilar lesions and for strictures without an associated mass. Moreover, RF energy levels and application times have been extrapolated mostly from *ex vivo* human studies, without clearly adapting the results to specific in vivo conditions. For that reason, the need of specific parameters represents another necessary improvement, which might be able to positively affect the procedure's success.

Without a doubt, more endoscopic centers performing biliary RFA will translate into a better quality of the procedure and a high rate of efficacy will be obtained. Though current literature suggests a positive effect on survival, conclusions regarding the clinical effectiveness should be reserved until prospective randomized controlled trials will accurately evaluate efficacy in terms of survival and quality of life. Furthermore, an improved study design will benefit the standardisation of the technical parameters in order to reduce the risk of complications. Nevertheless, despite the retrospective nature of the existing studies, they represent a proper foundation upon which large scale prospective trials with a long-term follow-up evaluation period can be designed.

Available data suggest that endoscopic RFA represents a feasible treatment option, with an acceptable

safety profile, and with a important impact on early survival of patients with biliary malignancies. Also, technical aspects for the procedure need to be more clearly established, considering the different stricture locations and other comorbidities that might influence the procedure outcome.

References

1. Skipworth JR, Keane MG, Pereira SP. Update on the management of cholangiocarcinoma. *Dig Dis* 2014;32:570-8.
2. Brandi G, Venturi M, Pantaleo MA, Ercolani G. Cholangiocarcinoma – current opinion on clinical practice diagnostic and therapeutic algorithms: a review of the literature and a long- standing experience of a referral center. *Dig Liver Dis* 2016; 48: 231-241.
3. Jarnagin WR. Cholangiocarcinoma of the extrahepatic bile ducts. *Semin Surg Oncol* 2000; 19: 156-176.
4. Boulay BR, Birg A. Malignant biliary obstruction: From palliation to treatment. World J Gastrointest Oncol. 2016 Jun 15;8(6):498-508
5. Krokidis M, Hatzidakis A. Percutaneous minimally invasive treatment of malignant biliary strictures: current status. *Cardiovasc Intervent Radiol* 2014;37:316-23.
6. Salgado SM, Gaidhane M, Kahaleh M. Endoscopic palliation of malignant biliary strictures. *World J Gastrointest Oncol* 2016;8:240-7.
7. Moss AC, Morris E, Leyden J and MacMathuna P. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. *Cancer Treat Rev* 2007, 33: 213-221.
8. Kaassis M, Boyer J, Dumas R et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. *Gastrointest Endosc* 2003. 57(2):178–182.
9. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. *Gastrointest Endosc* 2006, 63(7):986–995
10. Hong W, Sun X, Zhu Q. Endoscopic stenting for malignant hilar biliary obstruction: should it be metal or plastic and unilateral or bilateral? *Eur J Gastroenterol Hepatol* 2013. Eur J Gastroenterol Hepatol. 2013 Sep;25(9):1105-12.
11. Ortner ME, Caca K, Berr F et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. *Gastroenterology* 2003, 125(5):1355–1363.
12. Zoepf T, Jakobs R, Arnold JC. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. *Am J Gastroenterol* 2005, 100(11):2426–2430.
13. Gao F, Bai Y, Ma SR, Liu F and Li ZS. Systematic review: Photodynamic therapy for unresectable cholangiocarcinoma. *J Hepatobiliary Pancreat Sci* 2010,17: 125-131.
14. Shah DR, Green S, Elliot A, McGahan JP, Khatri VP. Current oncologic applications of radiofrequency ablation therapies. *World J Gastrointest Oncol* 2013; 5: 71-80.
15. Siperstein AE, Berber E, Ballem N and Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. *Ann Surg* 2007, 246: 559-565.
16. Seicean A, Tefas C, Ungureanu B, Săftoiu A. Endoscopic ultrasound guided radiofrequency ablation in pancreas. *Hepatogastroenterology.* 2014;61(134):1717-21.
17. Ungureanu BS, Sandulescu L, Şurlin V, Spârchez Z, Săftoiu A. Surgical hepatic resection vs. ultrasonographic guided radiofrequency ablation in colorectal liver metastases: what should we choose? *Med Ultrason.* 2014;16(2):145-51.
18. Silviu UB, Daniel P, Claudiu M et al. Endoscopic ultrasound-guided radiofrequency ablation of the pancreas: an experimental study with pathological correlation. *Endosc Ultrasound.* 2015;4(4):330-5.
19. Wu TT, Li HC, Li WM, et al. Percutaneous intraluminal radiofrequency ablation for malignant extrahepatic biliary obstruction: a safe and feasible method. *Dig Dis Sci* 2015; 60: 2158-2163.
20. Mirza AN, Fornage BD, Sneige N, et al. Radiofrequency ablation of solid tumors. *Cancer J.* 2011;7:95–102.
21. Patterson EJ, Scudamore CH, Owen DA, Nagy AG, Buczkowski AK. Radiofrequency ablation of porcine liver in vivo: effects of blood flow and treatment time on lesion size. *Ann Surg.* 1998;227:559–565.
22. Goldberg SN, Gazelle GS. Radiofrequency tissue ablation: physical principles and techniques for increasing coagulation necrosis. *Hepatogastroenterology* 2001; 48: 359-367.
23. Dromi SA, Walsh MP, Herby S, et al. Radiofrequency ablation induces antigen-presenting cell infiltration and amplification of weak tumor-induced immunity. *Radiology* 2009; 251: 58-66.
24. Teng LS, Jin KT, Han N, Cao J. Radiofrequency ablation, heat shock protein 70 and potential anti-tumor immunity in hepatic and pancreatic cancers: a minireview. *Hepatobiliary Pancreat Dis Int* 2010; 9: 361-365.
25. Rustagi T, Jamidar PA. Intraductal radiofrequency ablation for management of malignant biliary obstruction. *Dig Dis Sci* 2014; 59: 2635-2641.
26. Mensah ET, Martin J, Topazian M. Radiofrequency ablation for biliary malignancies. *Curr Opin Gastroenterol* 2016; 32: 238-243.
27. Jaganmohan S, Lee JH. Self-expandable metal stents in malignant biliary obstruction. *Expert Rev Gastroenterol Hepatol* 2012; 6: 105–114.
28. Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. *Gastrointest Endosc.* 2011;74:321–327.e1-3.
29. Nam HS, Kang DH. Current status of biliary metal stents. *Clin Endosc* 2016;49:124-30.
30. Yi Lu, Lei Liu, Jia-chuan Wu, Li-ke Bie, Biao Gong, Efficacy and safety of photodynamic therapy for unresectable cholangiocarcinoma: a meta-analysis. *Clinics and Research in Hepatology and Gastroenterology* 2015; 39:718-724.
31. 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;73:149-153.
32. Monga A, Gupta R, Ramchamdani M, Rao GV, Santosh, D Reddy N. Endoscopic radiofrequency ablation of cholangiocarcinoma: a new palliative treatment modality. *Gastrointestinal Endoscopy* 2011;20/10:1-3.
33. Kallis Y, Phillips N, Steel A, et al. Analysis of endoscopic radiofrequency ablation of biliary malignant strictures in pancreatic cancer suggests potential survival benefit. *Digestive Diseases and Sciences* 2015;60(11):3449-55.
34. Sharaiha RZ, Natiov N, Glockenberg KS, Widmer J, Gaidhane M, Kahaleh M. Impact of radiofrequency ablation on malignant biliary strictures: results of a collaborative registry. *Digestive Diseases and Sciences* 2015;60(7):2164-9.

35. Strand DS, Cosgrove ND, Patrie JT, et al. ERCP-directed radiofrequency ablation and photodynamic therapy are associated with comparable survival in the treatment of unresectable cholangiocarcinoma. *Gastrointestinal Endoscopy* 2014;80(5):794-804.
36. Dolak W, Shreiber F, Schwaighofer H, et al. Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. *Surgical Endoscopy* 2014;28(3):854-60.
37. Figueroa-Barojas P, Bakhru MR, Habib NA, et al. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. *J Oncol.* 2013:910897.
38. Alis H, Sengoz C, Gonenc M, Kalayci MU, Kocatas A. Endobiliary radiofrequency ablation for malignant biliary obstruction. *Hepatobiliary Pancreat Dis Int*. 2013;12:423–427.
39. Cheng JL, Bruno MJ, Bergman JJ et al. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic wallstents. *Gastrointest Endosc* 2002, 56(1):33–39.
40. De Groen PC, Gores GJ, LaRusso NF et al. Biliary tract cancers. *N Engl J Med* 1999, 341(18):1368–1378.
41. 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; 59: 3099-3102.
42. Alvarez-Sánchez M-V, Napoléon B. Review of endoscopic radiofrequency in biliopancreatic tumours with emphasis on clinical benefits, controversies and safety. *World Journal of Gastroenterology.* 2016;22(37):8257-8270.