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Endobiliary Radiofrequency Ablation in Malignant Biliary Strictures: Nonrandomized Prospective Cohort Study

Malign Biliyer Darlıklarda Endobiliyer Radyofrekans Ablasyon: Nonrandomize Prospektif Kohort Çalışması

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ABSTRACT Objective: Self-expandable metallic stents are superior to establish and preserve biliary drainage in malignant biliary obstructions. Endobiliary radiofrequency ablation (EB-RFA) is an important adjunct to increase the efficacy and length of the stent patency. This study is on the efficacy and safety of transhepatic EB-RFA and discusses its procedural steps and technical tips for successful implementation. **Material and Methods:** Clinical and imaging data of eight patients were retrospectively analyzed. The intervention included EB-RFA, stenting, balloon dilatation and temporary internal biliary catheterization of previously untreated cases. The technical efficacy was determined as the percentage of successfully catheterized patients. The short-term clinical efficacy was determined as the comparison of pre- and post-procedural total and direct bilirubin levels. **Results:** The mean pre-ablation luminal diameter was 2.4±0.7 mm and the mean post-ablation luminal diameter 7.8±2.0 mm. No intraprocedural and 30-day mortality was encountered. Multiple hepatic abscesses developed in a patient who had re-ablation and two others experienced cholangitis. The most common minor complication was abdominal pain. The preprocedural total bilirubin level was 8.39±3.45 and the direct bilirubin level was 6.82±3.11. The postprocedural total bilirubin level at 7th day was 4.10±2.85 and direct bilirubin level was 2.96±2.16. Patients were followed up to 6.5 months after the procedure. The mean patency time was 56 days and the mean survival was 122 days. **Conclusion:** This study supports previous reports on EB-RFA and shows the safety and the efficacy of the technique and its implementation. Keeping all procedural steps and possible complications in mind, it has a relatively short learning curve.

Keywords: Endobiliary radiofrequency ablation; malign biliary obstruction; stent; impedance

ÖZET Amaç: Malign safra yolu darlıklarında, kendi kendine genişleyen metalik stentler biliyer drenajın sağlanmasında ve korunmasında kullanılmaktadır. Endobiliyer radyofrekans ablasyon (EB-RFA) stent açıklığının sağlanmasında ve patens süresinin uzatılmasında önemli bir yardımcıdır. Çalışmanın amacı, transhepatik EB-RFA'nın etkinliği ve güvenliğini göstermek, başarılı uygulama için prosedür adımlarını ve teknik ipuçlarını paylaşmaktır. **Gereç ve Yöntemler:** Maligniteye bağlı biliyer darlığı bulunan 8 hasta retrospektif olarak incelendi. İşlem basamakları; EB-RFA, stentleme, balon dilatasyon ve daha önce tedavi edilmemiş olguların geçici internal safra kateterizasyonunu içermektedir. Teknik etkinlik, başarılı bir şekilde kateterize edilmiş hastaların yüzdesi olarak belirlendi. Kısa süreli klinik etkinlik ise işlem öncesi ve sonrası total ve direkt bilurubin değerlerinin karşılaştırılmasıyla değerlendirildi. **Bulgular:** Ablasyon öncesi ortalama lümen çapı 2,4±0,7 mm ve ablasyon sonrası ortalama lümen çapı 7,8±2,0 mm idi. Prosedür sırasında ve sonrasındaki 30 günde mortalite izlenmedi. İki hastada işleme bağlı kolanjit gelişti ve birinde 2. ablasyon sonrası çok sayıda hepatik apse izlendi. İşlem öncesi total bilurubin düzeyi 8,39±3,45 ve direkt bilurubin düzeyi 6,82±3,11 idi. İşlem sonrası 7. günde ise sırasıyla 4,10±2,85 ve 2,96±2,16 olarak ölçüldü. Hastalar işlemden sonra 6,5 aya kadar takip edildi. Ortalama stent patensi 56 gün ve ortalama sağkalım 122 gündü. **Sonuç:** Bu çalışma, literatürdeki diğer EB-RFA çalışmalarını destekler nitelikte olup, tekniğin ve uygulamasının güvenilir ve etkili olduğunu göstermektedir. Tüm prosedür adımlarını ve olası komplikasyonları göz önünde bulundurarak nispeten kısa bir öğrenme eğrisine sahiptir.

Anahtar Kelimeler: Endobiliyer radyofrekans ablasyon; malign biliyer darlık; stent; empedans

Malignant biliary obstructions, caused by tumoral pathologies at an advanced stage, cannot be treated with curative surgical treatment in most cases.[1] Biliary stents may be used to establish and preserve biliary drainage in these cases.[2,3] However, they eventually become occluded due to several factors.[4] Such an occlusion can traditionally be treated with balloon dilatation with varying degrees

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of success.[5] In that context, endobiliary radiofrequency ablation (EB-RFA), a novel technique, can be used before the stent placement to provide longer patency or to increase the success of balloon dilatation in restoring the patency of occluded stents.[6]

EB-RFA is usually employed via an endoscopic approach.[7,8] However, it may also be used as a part of percutaneous transhepatic radiological interventions. The latter approach, however, is relatively novel, and the number of the published cases is still insufficient to determine the full value of the EB-RFA regarding patency rates. This study reports the efficacy, and safety of EB-RFA procedure in the malignant biliary stenosis on a single-center cohort, and its procedural steps, and technical tips for successful implementation to address that issue.

MATERIAL AND METHODS

PATIENTS

We retrospectively reviewed the clinical and imaging data of 8 patients who underwent palliative therapy for malignant biliary obstruction. The intervention included endoluminal radiofrequency (RF) ablation, stenting, balloon dilatation and temporary internal biliary catheterization. Patients who were ablated to recanalize previously installed stents (without EB-RFA) were excluded. These patients were admitted between May 2017 and June 2020 and all procedures were conducted by authors. All patients had clinical, and laboratory findings for biliary obstruction at referral. They were examined with imaging that included ultrasound (USG), computed tomography, and magnetic resonance imaging, as appropriate, and laboratory tests (complete blood count, coagulation parameters, and blood biochemistry). Inclusion criteria were: 1) Histopathologically proven malignancy, 2) Having clinical and laboratory findings for biliary obstruction at referral, 3) Inoperability of the malignancy, 4) Life expectancy more than three months. Exclusion criteria included uncorrectable coagulopathy, clinical instability, presence of any systemic infection, surgical operability potential and patients who were ablated to recanalize previously installed stents (without EB-RFA). The primary endpoints of the procedure were (1) to achieve adequate endobiliary recanalization through RF ablation, stent insertion and balloon dilatation in novel cases, and (2) to achieve stent recanalization through RF ablation and balloon dilatation in stented cases. Secondary endpoints were clinical improvement, regression of cholestatic symptoms, relevant laboratory values and prolonged survival.

PROCEDURAL STEPS

Radiological data were carefully evaluated before the procedure to determine the exact nature and the location of the obstruction. A detailed hepatic USG (Aplio 500 Platinum or Aplio 300, Toshiba Medical, and 6 MHz multiband convex array transducer PVT-375BT, Toshiba Medical, Japan) was also performed by authors. All patients had percutaneous transhepatic cholangiography under fluoroscopy guidance to evaluate the location, the patency and the length of obstructed lumen a week before the ablative procedure. During the same session, a 8 F, 25 cm long internal-external biliary drainage catheter (Flexima™ APDL Catheter, Boston Scientific, USA) was placed for pre-procedural decompression and kept until the actual ablation session.

The ablation procedure was performed under general anesthesia. A first-generation cephalos-porine (Cefazoline, 1000 mg IV) was administered for periprocedural prophylaxis. A specifically designed endobiliary RF catheter (ELRA™; STARmed Co., Goyang, Korea) was used for ablation. This is a single-use, disposable, bipolar, 7 F catheter with a working length of 175 cm. The bipolar electrodes at the terminal portion of the catheter were stainless steel rings (3 mm in width and 18 mm in length) connected to an RF energy generator (VIVA combo RF Generator System, STARmed, Korea). This system operates in continuous mode and in temperature mode. Temperature mode enables continuous maintenance of the chosen electrode temperature (target temperature was set to 80°C), during the RF procedure so that excessive heating was avoided.

The first step of the procedure is positioning a7 F introducer sheath into the biliary duct using over

the wire technique via previously installed drainage catheter. The contrast was injected via the introducer to exhibit visualized the location, extent, and degree of the obstruction after a week-long decompression. The obstruction level was usually crossed by 0,035-inch hydrophilic guidewire (Radiofocus Stiff Type Angled Wire, Terumo, Japan) and 4 to 5 F vertebral catheters (Tempo Aqua®, Cordis, USA). Micro guidewire and microcatheters were used in difficult cases and they then switched with formers. The hydrophilic guidewire was exchanged with 0.035-inch 260 cm super stiff wire (Amplatz Super Stiff PTF, Boston Scientific, Natick, MA). EB-RFA catheter was inserted over stiff guidewire and positioned across the obstructed segment. A 10 W energy was applied for 2 minutes. In cases with longer segments, the catheter is moved backward and the procedure was repeated as much as necessary. The procedure was repeated for each individual obstruction that was thought to be significant for effective hepatic function. Periodic irrigation with distilled water and aspiration was performed during the EB-RFA procedure to reduce impedance and to provide electrodes' contact with the luminal wall to reach optimal ablation. A control cholangiogram was acquired to evaluate the patency. Pre- and post-procedural diameters of the stenotic segment were fluoroscopically measured. Balloon dilatation (Powerflex Balloon Catheter, Cordis, USA) up to the original size of the lumen was applied at 10 atm to remove the intra-luminal necrotic tissue. Following balloon dilatation, uncovered SEMS (Epic Stent, Boston Scientific, Natick, MA) with appropriate size (4-7 cm) and diameter (4-9 mm) was inserted to assure and prolong luminal patency. Following the stent insertion, a control cholangiogram was obtained and post-procedural balloon dilatation was performed to fully expand the stent, if necessary. An 8 F internal biliary drainage safety catheter (Flexima APDL Catheter, Boston Scientific, Natick, MA) was placed over the guide and was left closed. The safety catheter was then removed after a week and upon the presence of adequate patency on the control cholangiogram. If the tumor involved bilateral hepatic biliary ducts, all procedural steps were repeated on each side.

POST-PROCEDURAL FOLLOW-UP

All patients were followed up overnight in the hospital after the procedure. They were re-examined regarding serum residual symptoms, bilirubin levels, USG findings and the presence of short-term complications at the end of the first week. The safety catheter is also removed at the end of the first week following the demonstration of bile flow under fluoroscopy.

Stent patency and patient survival were followed up with regular intervals (first month, third month and three-month interval). Patients who were found to have insufficient patency or stent occlusion due to tumor in-growth during follow-up were further treated with RF ablation, balloon dilatation and/or biliary drainage catheter insertion, as appropriate.

RESEARCH ETHICS STANDARDS APPROVAL

The study was approved by the Institutional Review Board (Approval no: 17073117_050.06_050.06 on 27.10.2020, 20202/11). Informed consent was obtained for the study.

This study was conducted in accordance with the Helsinki Declaration principles.

STATISTICAL ANALYSIS

Statistical evaluation was performed using IBM SPSS Statistics (version 25, IBM, USA). Data were described using descriptive statistical methods. Continuous variables were reported as the mean±standard deviation with range. The technical efficacy was determined as the percentage of successfully catheterized patients. The short-term clinical efficacy was determined as the comparison of pre- and post-procedural total and direct bilirubin levels. No statistical tests were performed to prevent an atypia II error due to number of patients.

RESULTS

The study group consisted of eight patients. These were seven (87.5%) male and one (12.5%) female. Their age range was between 37 and 84 years (63.0±16.7 years). Of them, six (75.0%) had unresectable/recurrent cholangiocarcinoma, one (12.5%)

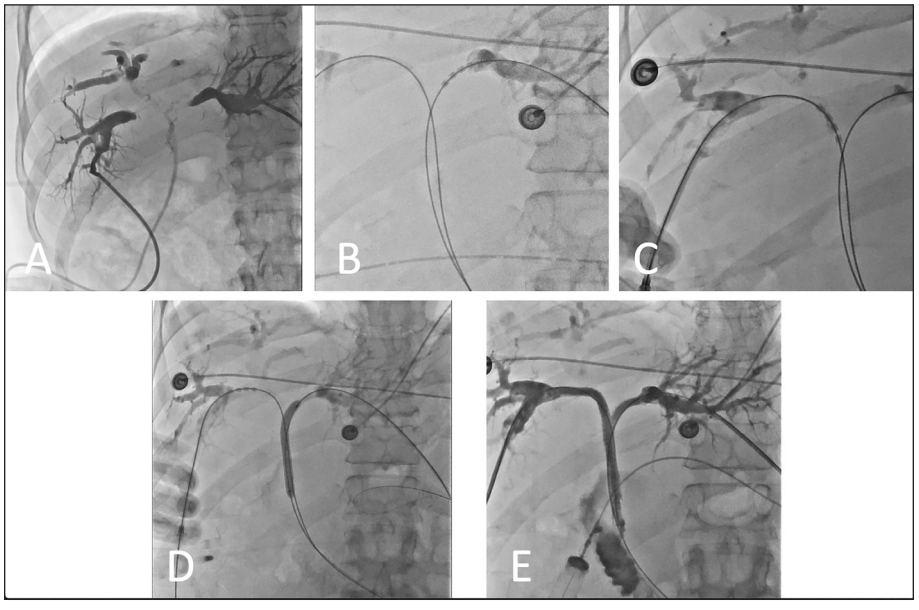

FIGURE 1A-E: Patient with hilar cholangiocarcinoma involving right, left and the main hepatic ducts. A) Percutaneous cholangiogram that was obtained a week before ablation shows total obliteration of all three segments. Insertion of radiofrequency catheter to the left (B) and right (C) hepatic ducts. D) Balloon dilatation of ablated left and main hepatic ducts, (E) simultaneous insertion of two self-expandable stents in the form Y.

had recurrent hepatocellular carcinoma at the transplanted liver and the remaining one (12.5%) had hepatic metastasis due to colon carcinoma. One patient had 3 (Figure 1A) and three patients had 2 obstructed segments to be treated. A total number of initially obstructed and treated segments, therefore, was fourteen (Figure 2, Table 1). All patients were presented with severe jaundice. Two of them had pruritus and three of them had severe pain as additional symptoms.

EB-RFA procedure was technically successful in all cases in terms of optimal positioning and impedance (Figure 1B, Figure 1C). From the morphological standpoint, percutaneous EB-RFA with balloon dilatation (Figure 1D) and stenting (Figure 1E) was performed successfully in all patients and their final patency was found to be adequate during post-procedural fluoroscopic imaging. The mean pre-ablation luminal diameter was 2.4±0.7 (range: 1.0-3.5) mm and mean post-ablation luminal diameter 7.8±2.0 (range: 5.0-11.0) mm. We were able to increase luminal diameter up to 8.8 (5.44±1.99) mm. In one patient, the procedure was repeated to restore right and left hepatic ducts. In that patient, two stents were simultaneously inserted to form a figure Y (Figure 1).

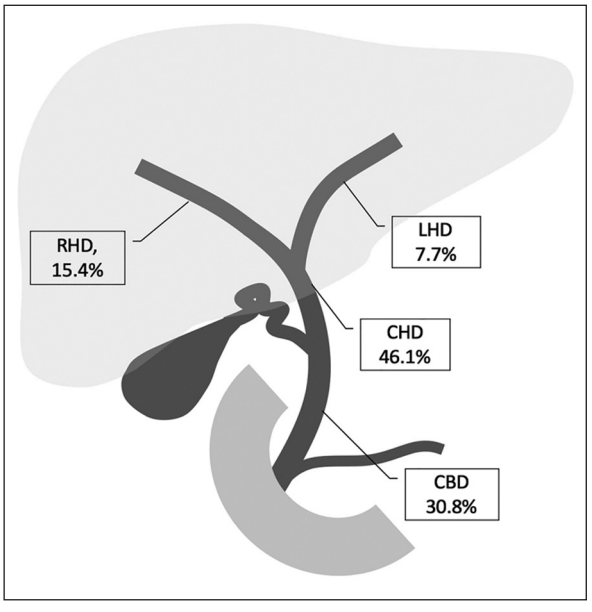

FIGURE 2: Percent share of treated biliary segments.
RHD: Right hepatic duct
LHD: Left hepatic duct
CHD: Common hepatic duct
CBD: Common bile duct.

In all patients, post-procedural balloon dilatation was performed to fully expand self-expanding metallic stents (SEMS).

TABLE 1: Location and number of obstructed segments and pre/post procedural patency parameters.

		Patency parameters			
Location	Frequency (n)	Dpre (mm)	Dpost (mm)	Difference (mm)	Patency (d)
RHD	2	2.4±0.2	11.0±10.3	6.7±3.0	75±0.0
LHD	1	2.5*	8.5*	7.0*	21*
CHD	6	2.2±0.8	7.5±2.2	5.0±2.3	56±36.9
CBD	4	2.5±1.0	6.5±0.5	4.83±0.89	55*
Total	14	2.4±0.7	7.8±2.0	5.44±1.99	55.8±34.8

*Only deceased cases were taken into account; Dpre: Preprocedural luminal diamater; Dpost: Postprocedural luminal diameter; RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; CBD: Common bile duct.

No intraprocedural or 30-day mortality was encountered. Multiple hepatic abscesses developed in a patient who had re-ablation to restore patency in a previously inserted SEMS (Figure 3). The patient was hospitalized and successfully treated with antibiotherapy. Two other patients experienced cholangitis within the first week and were successfully treated with antibiotherapy as an outpatient. The most common minor complication was abdominal pain. It was alleviated with oral analgesics. Clinically, the jaundice was resolved in all cases at the end of the first week following the ablation. The preprocedural total bilirubin level was 8.39±3.45 (5.20-12.92) and direct bilirubin level was 6.82±3.11 (3.97-10.88). The postprocedural total bilirubin level at the 7th day was 4.10±2.85 (1.23-9.55) and the direct bilirubin level was 2.96±2.16 (0.75-7.09). Patients were followed up to 6.5 months after the procedure (mean: 3.4 months, SD: 2.1 months). During follow-up all patients have developed stent occlusion due to tumor in-growth. The mean patency time was 56 days.

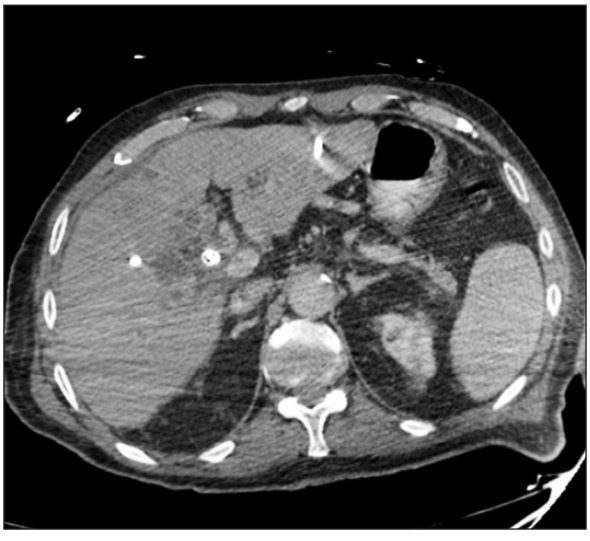

FIGURE 3: Post-procedural hepatic abscess at several segments 6 days after endobiliary radiofrequency ablation to restore patency in a previously inserted self-expandable metallic stent.

These patients were treated with balloon dilatation with EB-RFA (n=1), balloon dilatation without

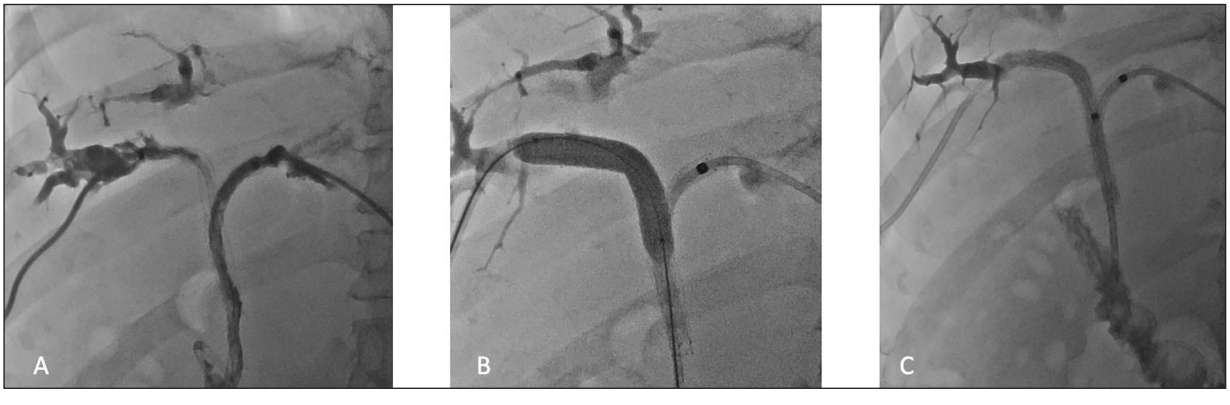

FIGURE 4: A very early stent occlusion at the 21st day. The patient was treated by balloon dilatation and lived for 170 days after the initial ablation.

EB-RFA (n=5) or internal biliary drainage catheter only (n=3) (Figure 4). The re-intervention rate, therefore, was 100%. Six (75%) patients had died 65 to 170 days after the procedure. The mean survival was 122 days. The remaining two patients were still alive and under follow-up during the writing of the manuscript.

DISCUSSION

In patients with malignant biliary obstruction, palliative interventions to establish and preserve adequate biliary drainage are necessary to prolong the survival and to increase the quality of life.[2] In that context, SEMS have become the standard palliative treatment in these patients if their life expectancy is more than three months.[4] SEMS have longer patency than plastic stents and offer adequate palliation and they, therefore, necessitate less re-intervention.[9] However, even SEMS may experience tumoral or non-tumoral re-occlusion such as epithelial hyperplasia and/or sludge formation in more than half of the cases during a period of six months.[4] Although covered SEMS have better patency rates than uncovered SEMS, they tend to migrate distally and may become very problematic.[10] Uncovered stents, on the other hand, are less prone to migration, but they have lower patency rates and are harder to remove if they malfunction.[11] For such cases, EB-RFA may be a less invasive option to establish stent patency.[12] This relatively novel technique is based on the induction of coagulative necrosis in neighboring tissues by its thermal effect. It, therefore, has additional advantages of reducing the tumor load and sensitizing to chemo and immunomodulatory therapies.[13] Several researchers have investigated the use of EB-RFA on laboratory animals and on actual clinical settings. Khorsandi et al. used a pig model and showed that the EB-RFA has caused coagulation necrosis in intraductal tissues without damaging surrounding tissues.[14] Cho et al. also used a pig model on which that investigated long term results of temperature-controlled EB-RFA.[15] In their study, six minipigs were divided into two groups to be exposed to two different settings of EB-RFA: 1) 10 W/33-mm probe, and 2) 7-W/18-mm probe, both operated at 80° C for 120 seconds. Both groups have developed biliary stricture, jaundice, and purulent bile one month after the ablation procedure. A significant difference was present between the two groups regarding the length of the stricture as shown on cholangiograms. Researchers have concluded that EB-RFA's end result was segmental biliary stricture with cholangitis, regardless of the power and the length of the electrode.[16] The results of both studies were favorable for EB-RFA's short-term safety, however, they also pointed out its use not as a stand-alone technique but as an adjunct to SEMS to reach long-term patency and to prevent the above-mentioned side-effects.

Regarding the use of EB-RFA on humans, Steel et al. were the first to report its use in the clinical settings.[7] In their study, EB-RFA catheter was inserted endoscopically in 22 patients. They were able to increase luminal diameter up to 4 mm using RF ablation without experiencing any major complications. In their study, one patient has not responded to dilatation and eventually died within 90 days following the procedure. Stent patency at the 30th day was achieved in the remaining patients. At a 90-day follow-up, one additional patient had died although he had adequate patency, and 3 patients have experienced restenosis. Accordingly, the overall length for stent patency was 119 days. In regard to that study, luminal improvement in our study was slightly better (i.e., 4 mm vs. 5.4 mm). However, our overall length for stent patency was significantly lower (i.e., 119 days vs. 56 days). One possible explanation for this discordance may be the referral of cases much-advanced disease to us. The same explanation may also be given for the similar discordance with the study by Dolak et al.[16] Those researchers have studied the use of endoscopic EB-RFA on 58 patients. According to their findings, the median stent patency time following the ablation was 170 days, and the median survival was 10.6 months.[16] Both studies have implicated the safety and the efficiency of EB-RFA for prolonged stent patency. Percutaneous transhepatic EB-RFA with biliary stenting may be an effective option for endoscopic treatments in malignantß biliary obstruc-

tions.[17] This method much simpler to perform than endoscopic EB-RFA, especially in hiller obstructions and in patients with altered surgical anatomy. Over the last years, several studies have been published on the safety and feasibility of the percutaneous approach.[18] Mizandari et al. were the first to report such approach.[19] In their study, they have decompressed the biliary system using external biliary drainage and they have inserted metallic stents after employing EB-RFA. In that study on thirty-nine patients, there was no 30-day mortality, hemorrhage, bile duct perforation, or pancreatitis. The mean survival time was 89.5 days and the mean stent patency time was 84.5 days, further supporting the safety and feasibility of the technique.[20] As the cited study is on percutaneous radiological intervention, it is more proper to compare with our study than the above-mentioned endoscopic EB-RFA studies. Although limited by a number of patients, the mean survival time in our study is 32 days longer than the survival time that was reported by Mizandari et al.[19] However, our stent patency is 29 days shorter when compared to their patency length.

The effect of the use of EB-RFA on stent patency before its deployment was also the subject of clinical studies. Li et al. investigated the efficacy of combined use of RF ablation and biliary stent.[12] In that study, 12 patients had been treated with RF ablation and biliary stent placement and 14 patients had been treated with biliary stent only. The six-month stent patency rate was higher in the former group, and only two of them have necessitated a repeat ablation in that time period. In the latter group, two patients have died during a similar time period and additionally, 7 of them had required restenting. That study demonstrated the favorable effect of EB-RFA to prolong the stent patency time.[12] Stent patency was evaluated on a larger scale by Sofi in their meta-analysis of 9 studies that include 505 patients.[20] They have found a mean difference of 50.6 days regarding the stent patency time between patients with and without prior EB-RFA, favoring the former. The median survival rate was also significantly better in EB-RFA treated patients.[20] Our study only includes patients where stents were initially inserted after EB-RFA. As stated in our methods and as was also practiced by certain researchers, including Mizanderi et al., we combined EB-RFA and balloon dilatation to move ablated tissue and ensure complete patency in ablated segments.[19] Uncovered SEMS were then inserted to avoid post-ablation stricture due to edema and local inflammation, and not as a primary measure to restore the patency. We, therefore, don't have data to compare the effect of EB-RFA on the mean SEMS patency time and any further comment must be supported by the data from a control group.

There are several procedural options to deal with a tumoral re-occlusion of a SEMS. These include (i) balloon dilatation, (ii) Stent-in-stent preceded and followed by balloon dilatation, (iii) EB-RFA followed by balloon dilatation, (iv) EB-RFA followed by stent-in-stent preceded and followed by balloon dilatation. Safety catheter is left in situ for all cases for a week. According to Betgeri et al. the combination of EB-RFA with balloon dilatation is a safe and useful technique in the restoration of stent patency.[21] In our study only one patient underwent this option, which is a repeat EB-RFA followed by balloon dilatation. Five others were managed with the third option, which is balloon dilatation only. The remaining two had neither of these options and were managed only by the insertion of an 8 F internal biliary drainage catheter. There are few tricks to attain a successful ablation: 1) Obstructed biliary systems should be decompressed at least a week before the ablation, 2) No balloon dilatation should be attempted before ablation as it will prevent electrodes to touch to target tissue, 3) Lumen should be irrigated with distilled water to reach proper impedance level that might otherwise be altered by the mixture of physiological serum and contrast agent, 4) No balloon dilatation should be attempted before the ablation of the obstructed stent as it will prevent electrodes to touch to metallic struts that may alter the impedance, 5) Electrodes, likewise, should not be touching to proximal struts because it may disrupt the impedance, 6) A safety catheter should be left in situ, as long as the patient tolerates, as it will greatly facilitate to re-access to the re-stenotic segment if needed.

There are certain possible complications that one should know how to manage. Of them, infection including cholangitis is the most common complication. This complication may be treated with appropriate antibiotics, percutaneous aspiration, and drainage if needed. Pain, fever, and nausea are among other common complications. Haemobilia, liver failure, perforation, respiratory dysfunction, on the other hand, are among infrequent complications. Of them, haemobilia, also encountered in our study, is usually self-limiting.

CONCLUSION

In conclusion, this study supports previous reports on EB-RFA and shows the safety and the efficacy of the technique and its implementation as described above. Keeping all procedural steps and possible complications in mind, it has a relatively short learning curve and dramatically improves the effectiveness of subsequent balloon dilatations and stenting.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hakkı Muammer Karakaş, Gülşah Yıldırım;* ***Design:*** *Hakkı Muammer Karakaş;* ***Control/Supervision:*** *Gülşah Yıldırım;* ***Data Collection and/or Processing:*** *Gülşah Yıldırım;* ***Analysis and/or Interpretation:*** *Gülşah Yıldırım, Hakkın Muammer Karakaş;* ***Literature Review:*** *Gülşah Yıldırım;* ***Writing the Article:*** *Gülşah Yıldırım;* ***Critical Review:*** *Hakkı Muammer Karakaş;* ***References and Fundings:*** *Hakkı Muammer Karakaş;* ***Materials:*** *Gülşah Yıldırım.*

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