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Assessment of safety and adverse events in endoscopic radiofrequency ablation for malignant biliary obstruction

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Abstract

Background: Endoscopic radiofrequency ablation (RFA) is used for the treatment of unresectable malignant biliary obstruction (MBO). The postoperative adverse events associated with RFA treatment have gained importance.

Objective: To investigate the early adverse events and their risk factors associated with RFA for the treatment of MBO.

Design: Observational retrospective study.

Methods: We collected data from patients diagnosed with MBO and treated with endoscopic RFA at our hospital between January 2010 and June 2022. Based on the collected data, the patients were divided into two groups: the adverse event group and the nonadverse event group. Early postoperative adverse events were recorded, and risk factors were assessed.

Results: One hundred and twenty patients with MBO underwent endoscopic RFA, with 20 developing adverse events (16.6%; 20/120). Among these, 13 patients (10.8%) developed biliary infection after RFA treatment, while 7 (5.8%) developed acute pancreatitis, and no bleeding or perforation occurred. Type 2 diabetes mellitus, bile duct stricture length >2.5 cm, segmental RFA, and the proportion of patients receiving single stent drainage were all significantly greater in the adverse event group compared to the nonadverse event group ($p<0.05$). The results of the logistic regression analysis showed that type 2 diabetes, segmental RFA, and single stent drainage were the three independent risk factors for getting a biliary infection after RFA therapy.

Conclusion: Unresectable MBO combined with type 2 diabetes mellitus, segmental RFA, and postoperative single stent drainage can be the risk factors for adverse events after RFA. More attention should be paid to patients with multiple risk factors and preventive measures should be taken.

Plain language summary

Assessment of safety and adverse events in endoscopic radiofrequency ablation for malignant biliary obstruction

The number of cases of malignant biliary obstruction (MBO) has been increasing recently, and nonsurgical treatment of MBO is a major problem. Radiofrequency ablation (RFA) has shown promising effects as palliative therapy. However, adverse events after the RFA treatment are a point of concern. In this retrospective study, we analyzed data from 120 patients who received RFA treatment.

Keywords: adverse events, malignant biliary obstruction, radiofrequency ablation, risk factors

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Introduction

Biliary obstruction is induced by various malignant tumors. The most prevalent types of malignant tumors that cause this condition include extrahepatic cholangiocarcinoma, gallbladder carcinoma, and pancreatic carcinoma.[1] Surgical resection is currently the only possible cure. However, due to the difficulty of early diagnosis, the vast majority of patients with malignant biliary obstruction (MBO) have lost the opportunity for radical surgery. The 5-year survival rate for patients with cholangiocarcinoma is 30%, while the 5-year survival rate for patients with pancreatic cancer is only 20%.[2–4] Surgical treatment is typically intolerable for older patients with poor general health or several comorbidities. The placement of a biliary stent, which allows bile to drain and improves liver function, is currently the primary treatment for obstructive jaundice caused by MBO. However, stents alone cannot significantly prolong the survival time of patients because there is no treatment for these tumors.[5,6]

With the development of endoscopic technology, many studies have shown that endoscopic radiofrequency ablation (RFA) can extend the survival time and improve patients' quality of life with unresectable MBO.[7–10] The use of endoscopic RFA for the treatment of MBO is rising year by year due to the development of clinical applications, and the postoperative adverse events associated with this treatment have also gained attention. There are, however, very few studies on adverse events and risk factors following RFA.

For better clinical treatment and prevention of adverse events in the future, we performed this retrospective analysis of the endoscopic RFA treatment for patients with MBO at our hospital. This included an evaluation of postoperative adverse events and their risk factors.

Materials and methods

Patients

Patients with MBO were enrolled at the First People's Hospital of Hangzhou (Hangzhou, China) between January 2010 and June 2022. All patients were diagnosed with MBO after having an upper abdominal CT, magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) examination. MBO was confirmed with pathology by an endoscopic retrograde cholangiopancreatography (ERCP) cell brush or biopsy, a cholangioscopy-guided biopsy, or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). They were treated with endoscopic RFA after multidisciplinary discussion without any indication for radical surgery.

Patients with MBO treated with endoscopic RFA were divided into an adverse events group and a nonadverse events group. An electronic medical record system and an endoscopic image system were used to collect the demographic and clinical data of the patients. The data collected included the patients' sex, age, comorbidities, preoperative and postoperative biochemistry, tumor staging based on imaging data, bile duct obstruction site, and stenosis length shown by ERCP, endoscopic RFA operation, postoperative drainage, and other information.

RFA procedure

After inserting a 100-mg indomethacin drug into the anus 30 min before ERCP, the patient received intravenous injections of 5–10 mg of midazolam, 40 mg of norepinephrine, and 50–100 mg of pethidine hydrochloride for analgesia and sedation. After cannulation was successful, cholangiography and intrabiliary ultrasonography were performed to determine the precise location, length, and wall thickness of the common bile duct stenosis. Under X-ray fluoroscopy, the RFA probe (Habib EndoHPB; Emcision, London, UK) was inserted into the bile duct along the guide wire. To accomplish the RFA, 7–10 W of power was applied for 90 s. If the stenosis was more extensive than 2.5 cm in diameter, RFA was performed in stages from the hilar to distal bile duct, with fluoroscopic monitoring to determine whether the ablated coagulation area covered the entire target area. In cases of hilar Bismuth type III–IV obstructions, RFA was conducted independently on the left and right hepatic ducts. A balloon was used to further clear the bile duct of any ablated necrotic tissue or debris. For patients with hilar Bismuth I–II type obstructions or a distal bile duct, the type (metal or plastic) and number (single or multiple) of biliary stents to be placed was determined by the operating physician. For hilar Bismuth type III–IV obstructions, multiple stents were placed in both the left and right hepatic ducts, and nasobiliary drainage was also performed. In our study all the procedures were primary RFA procedures (Figure 1).

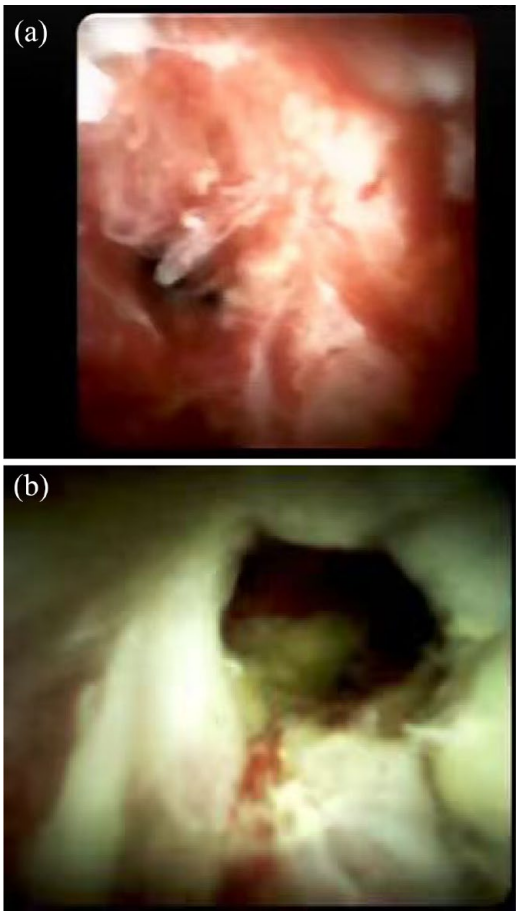

Figure 1. (a) Direct inspection of the bile duct mass under cholangioscopy visualization. (b) After receiving radiofrequency ablation treatment.

Postoperative treatment

Antibiotics, fluid replacement, and symptomatic care were administered postoperatively, and blood amylase levels were assessed 6 and 24 h following RFA treatment. Postoperative abdominal pain, abdominal distension, fever, vomiting, and abdominal symptoms were monitored, and abdominal CT scans were conducted if abdominal pain was present.

Outcome and definition

Infection of the bile duct, acute pancreatitis, bleeding, and perforation were among the postoperative adverse events that were recorded. The diagnostic criteria were as follows: (1) Biliary tract infection: The body temperature was increased more than 38°C and the white blood cells were $>10\times10^9$/L within 48 h after RFA treatment, and infection in other parts were excluded; (2) Acute pancreatitis: continuous abdominal pain occurred within 48 h after the RFA treatment, and the increase in blood amylase was more than three times the normal level; Mild: no organ dysfunction or local complications; Moderate to severe: one of the local or systemic complications without persistent organ failure or transient organ failure (recovery at 48 h); Severe: persistent (over 48 h) organ failure; (3) Postoperative hemorrhage: new hematemesis or melena occurred within 1 week after the RFA treatment and/or active bleeding in the biliary tract confirmed by endoscopy; and (4) Perforation: intraabdominal or retroperitoneal gas was found during the RFA treatment and/or indicated by the postoperative imaging examination.

Statistical methods

Statistics were performed using SPSS 26.0 (Armonk, NY). When the measurement data were at a normal distribution, they were expressed as the mean and standard deviation (SD) or mean (m) SD(s), but when they were skewed, they were described as the median and interquartile range (M (P25, P75)). The Chi-square test was used to compare enumeration data by group. To investigate the risk variables influencing the occurrence of complications, the screened differential factors were integrated into a binary logistic regression analysis. If $p<0.05$, the difference is significant at the test level.

Results

Clinical features of patients

One hundred twenty patients were involved in the study, including 67 males and 53 females. The patients' ages ranged from 44 to 91 years old, with a mean of 74 ± 12 years. There were 28 patients with hypertension, 58 with diabetes (insulin resistance), and 13 with coronary heart disease. The malignant obstructions were caused by extrahepatic cholangiocarcinoma (80 cases), gallbladder carcinoma (10 cases), pancreatic carcinoma (18 cases), or duodenal papilloma carcinoma (12 cases). The hilar part of the bile duct was obstructed in 27 cases, while the distal bile duct was blocked in 93 cases (Table 1). Both groups showed a cannulation success rate of more than 95%, and no patients received chemotherapy as an additional treatment. Both groups received perioperative antibiotic prophylaxis (cephalosporin-class, i.e., indomethacin).

Table 1. Analysis of related risk factors of postoperative adverse events.

Variables	Adverse event group ($n=20$)	Non-adverse event group ($n=100$)	p-Value
Age (years)	72 ± 8.4	74 ± 11.5	0.43
Gender (%)			0.93
Male	11 (16.4%)	56 (83.6%)	
Female	9 (16.9%)	44 (83%)	
History of hypertension			0.87
Yes	4 (14%)	24 (84.7%)	
No	16 (17.4%)	76 (82.6%)	
History of type 2 diabetes			0.002
Yes	16 (27.5%)	42 (72.4%)	
No	4 (6.4%)	58 (93.5%)	
History of coronary heart disease			0.69
Yes	1 (7.7%)	12 (92.3%)	
No	19 (17.7%)	88 (82.2%)	
Serum albumin (g/L)			0.2
⩽30	6 (23%)	20 (76.9%)	
>30	14 (14.8%)	80 (85.1%)	
Obstruction site (%)			0.48
Hilar bile duct	2 (7.4%)	25 (92.6%)	
Distal bile duct	18 (19.3%)	75 (80.6%)	
Stenosis length (%)			0.049
⩽2.5 cm	7 (10.7%)	58 (89.2%)	
>2.5 cm	13 (23.6%)	42 (76.4%)	
EST performed preoperatively			1.000
Yes	17 (16.6%)	85 (83.3%)	
No	3 (16.7%)	15 (83.3%)	
Combined choledochoscope			0.29
Yes	4 (10.8%)	33 (89.2%)	
No	16 (19.3%)	67 (80.7%)	
Segmental RFA			0.039
Single segment	5 (8.9%)	51 (91%)	
Multisegments	15 (23.4%)	49 (76.6%)	

(Continued)

Table 1. (Continued)

Variables	Adverse event group ($n = 20$)	Non-adverse event group ($n = 100$)	p-Value
Drainage mode			0.25
Simple biliary stent	9 (21.4%)	33 (78.5%)	
Nasobiliary drainage tube + biliary stent	11 (14.1%)	67 (85.9%)	
Stent type			0.67
Metal stents	3 (18.7%)	13 (81.3%)	
Plastic stents	17 (16.3%)	87 (83.7%)	
Number of supportive drainage			0.0000
Single drainage	15 (53.6%)	13 (46.4%)	
Multiple drainage	5 (5.4%)	87 (94.6%)	

EST, endoscopic sphincterotomy; RFA, radiofrequency ablation.

Incidence of postoperative adverse events

One hundred twenty patients with malignant biliary stenosis underwent RFA, with a 100% technical success rate. There were 20 cases of postoperative adverse events, and the incidence rate was 16.6% (20/120). Biliary tract infection was the most common adverse event in 13 cases (10.8%), 9 (7.5%) cases of acute cholangitis, and 4 (3.3%) cases of acute cholecystitis.

Six of the nine patients with acute cholangitis underwent a secondary ERCP for placement of nasobiliary drainage. Two of the four patients with acute cholecystitis had ultrasound-guided endoscopic gallbladder drainage (EUS-guided GBD), and two had percutaneous transhepatic GBD. Every patient was treated with anti-inflammatory medication. Seven cases (5.8%) of acute pancreatitis were classified as moderate, and all seven of these patients were cured with conservative treatment. Other adverse events, such as intrabiliary bleeding, perforation, or death, did not occur (Table 2).

Table 2. Number of adverse event cases after RFA treatment.

Adverse event	Number of cases
Overall adverse event	20 (16.6%)
Biliary tract infection	13 (10.8%)
Acute cholangitis	9 (7.5%)
Acute cholecystitis	4 (3.3%)
Acute pancreatitis	7 (5.8)

RFA, radiofrequency ablation.

Single-factor analysis of adverse events after RFA

The nonadverse event group included 100 patients, while the adverse event group included 20 patients. Patients in the adverse event group had a higher proportion of type 2 diabetes mellitus, stenosis length >2.5 cm, segmental RFA, and single-stent drainage than patients in the nonadverse event group ($p < 0.05$). There was no difference between the groups concerning age, sex, hypertension, coronary heart disease, hypoproteinemia, obstruction site, preoperative EST, intraoperative use of a cholangioscopy, postoperative drainage method, or stent type (plastic or metal) ($p > 0.05$).

Multifactor analysis of adverse events after RFA

The logistic regression model was constructed with the occurrence of postoperative adverse events as the dependent variable and the statistically significant variable in the results of

Table 3. Multivariate analysis of adverse events after RFA.

Factor	Evaluation	*B*	SE	Wald	*p*-Value	Exp(*B*)	95% CI lower limit	95% CI upper limit
Type 2 diabetes mellitus								
No	0							
Yes	1	1.95	0.88	4.9	0.025	6.8	1.26	38.7
Segmental RFA								
No	0							
Yes	1	2.12	0.85	6.01	0.015	8.30	1.63	45.2
Stent drainage								
Single stent	0							
Multiple stents	1	-3.4	0.810	17.990	0.000	0.04	0.009	0.17

$p < 0.05$ statistically significant.
CI, confidence interval; RFA, radiofrequency ablation; SE, standard error.

single-factor analysis as the independent variable. The multivariate analysis showed that combined type 2 diabetes mellitus and segmental RFA were independent risk factors for postoperative biliary tract infection, with odds ratios (ORs) of 6.8 (95% confidence interval (CI) 1.26–38.7) and 8.3 (95% CI 1.6–45.2), respectively, and multiple stent drainage was a protective factor for postoperative adverse events, with an OR of 0.04 (95% CI 0.009–0.17) (Table 3).

Discussion

This study involved 120 patients to assess the incidence of adverse events following RFA for MBO. An incidence rate of 16.6% was found among patients, indicating the occurrence of adverse events that include acute cholangitis, acute cholecystitis, and pancreatitis. The majority (65%) of the recorded adverse incidents were related to bile duct infections. There was an increased risk of adverse events following RFA in patients with type 2 diabetes mellitus, segmental RFA, and a single drainage stent.

Numerous clinical studies in recent years have investigated the effectiveness of endoscopic RFA in the treatment of MBO. Prospective randomized trials have indicated that, compared with a stent alone, endoscopic RFA performed in combination with a stent improves the stent's patency and the patient's survival time.[11,12] Endoscopic RFA has been effective in treating MBO, and its clinical application is increasing. The rise in cases has gradually brought to light the occurrence of short-term adverse events. According to the research, the incidence of adverse events following RFA ranges from approximately 5.6% to 27.1%. These adverse events include acute cholangitis, cholecystitis, acute pancreatitis, bleeding, postoperative abdominal pain, and many others.[13–16] After medical treatment, the vast majority of adverse events are improved or cured. Jarosova et al.[17] have also stated that biliary RFA has been found to have positive effects on survival and stent patency, and it is considered to have an acceptable level of safety.

Mohan et al. discovered that RFA treatment improved stent patency and survival, and the most common adverse event was cholangitis. A total of 9.5% of RFA patients developed cholangitis, 4.3% developed hemobilia, and 2.5% developed liver abscesses.[18] Khizar et al. performed a meta-analysis of 15 trials and found that RFA improved survival and stent patency time. However, adverse events such as bleeding, cholangitis, abdominal pain, and pancreatitis were similar in the RFA and stent-alone groups.[19] Kong et al.[20] found that RFA combined with stent treatment improved MBO patients' quality of life and survival time compared to stent-alone treatment, with no significant difference in adverse events. A multicenter randomized trial revealed that patients in

the RFA with stent group had a longer overall survival time than those in the stent alone group and that 24 RFA patients (27.6%) had adverse events compared to 17 control patients (19.5%).[11] In our study, the most common adverse events were biliary tract infection (10.8%) and severe pancreatitis (5.8%). Intrabiliary hemorrhage and perforation did not occur, which was consistent with previous reports.[21]

Biliary tract infection is one of the most frequent adverse events of ERCP due to inadequate biliary drainage.[22] Intestinal bacteria may enter the biliary system during ERCP. Inadequate biliary drainage causes infection from intestinal pathogens in the bile duct. In severe cases, high bile duct pressure enables pathogens to penetrate the biliary-blood barrier and enter the blood, causing sepsis. Segmental RFA and single stent drainage were risk factors for RFA adverse events. Because tumor necrosis and shedding can block stents, the biliary tract does not drain properly after RFA. To prevent biliary tract infection, routine preoperative antibiotics and removing necrotic tissue and debris using balloon cleaning following RFA are recommended. Patients with long stenosis, especially hilar obstruction, are susceptible to infection because it is difficult to obtain adequate drainage.[21,23] In our study, cholangitis was less common in hilar obstruction than in distal biliary obstruction. This could be because of multiple stents or combined nasobiliary drainage for hilar obstruction, which results in adequate drainage after RFA.

Postoperative pancreatitis is another frequent adverse event of RFA. When RFA is performed on the region of the duodenal papilla close to the pancreatic duct orifice, the pancreatic duct area may be damaged. According to a meta-analysis, the incidence of pancreatitis following ERCP was 0.5% (1.6%–15.4%).[23] The frequency of acute pancreatitis after RFA in this study was not significantly different from that after conventional ERCP, suggesting that pancreatitis after RFA was due primarily to the ERCP technique itself or to the use of indomethacin rectally for all patients before the treatment procedure. The pathogenesis of cholecystitis complicated by RFA may be caused by edema of the mucosa of the bile duct wall after RFA or by tumor necrotic tissue blocking the opening of the cystic duct after ablation, resulting in poor bile drainage.

In this study, intrabiliary bleeding was less frequent with RFA, and there were no adverse events related to bleeding. The mechanism of RFA is high temperature-induced coagulation necrosis, which serves the role of electrocoagulation hemostasis. Therefore, RFA will not increase the postoperative hemorrhage rate compared to traditional ERCP. In contrast, a retrospective analysis revealed that three patients suffered hemobilia a few weeks following RFA treatment, all of whom experienced hemobilia during stent extraction. The authors hypothesized that it could be related to the damage of blood vessels in normal tissues when the stent was withdrawn or when there was formation of new blood vessel branches in the treated tissues due to the rise in angiogenesis in tumors caused by the severe necrotic impact induced by RFA.[24] Our study demonstrated that the number of diabetic patients in the group with adverse events was more significant than that in the group without adverse events and that diabetes was an independent risk factor for postoperative adverse events. Hyperglycemia reduces the intestinal mucosal barrier function and heightens vulnerability to diseases of intestinal origin. Inadequate long-term glucose control results in an abnormal immune system, as evidenced by neutrophil and macrophage immune insufficiency, altered complement function, and a dysfunctional lymphocyte response. The glucose levels before surgery should be monitored in patients with diabetes.[25]

This study has certain limitations. This study is a retrospective study conducted at a single center. A future investigation is necessary due to the presence of confounding factors, bias, and limitations in the research design, calculation, and selection of available case data. Our investigation focused on only the short-term adverse events associated with RFA. Long-term adverse events, such as stent obstruction and stent migration, were not included in our study. Absence of competitor group without RFA is also a limitation that should be addressed in future studies. Patients should undergo long-term follow-up to assess the incidence of adverse events.

Conclusion

This study identified that type 2 diabetes, segmental RFA, and single stent drainage can be the independent risk factors for adverse events following RFA. Clinicians should focus on high-risk

patients and take preventative steps to control adverse events.

Declarations

Ethics approval and consent to participate

The Hangzhou First People's Hospital's Institutional Review Board approved this study (Approval Number: 2020-008-017). All the patients provided their informed written consent for the treatment. All authors have approved to this submission to your esteemed journal. Its publication is also approved tacitly by the responsible authorities where the work was carried out.

Consent for publication

Not applicable.

Author contributions

Hayat Khizar: Conceptualization; Data curation; Formal analysis; Software; Writing – original draft.

Yufei Hu: Conceptualization; Data curation; Software; Writing – original draft.

Weigang Gu: Data curation; Methodology; Resources; Supervision; Validation.

Jin Yang: Conceptualization; Formal analysis; Investigation; Resources; Validation.

Hangbin Jin: Formal analysis; Investigation; Methodology; Resources; Visualization.

Xiayin He: Methodology; Software; Supervision; Validation; Visualization.

Xiaofeng Zhang: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Writing – review & editing.

Jianfeng Yang: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All the data related to manuscript is published. More information can be found from corresponding author (J.F.Y.) on reasonable request.

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