Risk factors of intrahepatic biloma and secondary infection after thermal ablation for malignant hepatic tumors

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ABSTRACT

Objective: This study aimed to evaluate the risk factors of biloma formation and secondary infection after thermal ablation for malignant hepatic tumors.

Patients and methods: A total of 58 patients with 68 bilomas after thermal ablation were recruited as the complication group, and 61 patients with 72 lesions without major complications were selected randomly as the control group. The potential risk factors for biloma formation were analyzed with the chi-square test and multivariate logistic regression analysis. To determine the optimum management method for biloma, patients with secondary infection were included for the subgroup analysis of risk factors.

Results: A history of transcatheter arterial chemoembolization (TACE) treatment (odds ratio [OR]: 3.606, 95% confidence interval [CI]: 1.165–11.156, \( p = .026 \)) and tumor location (OR: 37.734, 95% CI: 13.058–109.034, \( p = .000 \)) were independent predictors of biloma formation. Among the 58 patients with biloma, 49 (84.5%) showed no symptoms (i.e., the asymptomatic group), while the remaining 9 (15.5%) developed symptoms related to secondary infections (i.e., the symptomatic group). There were significant differences in the history of biliary manipulation (\( p = .031 \)) between the symptomatic and asymptomatic groups.

Conclusion: A history of TACE treatment and the distance from the biliary tract were independent predictors of biloma formation after thermal ablation. Therefore, protecting the bile duct (i.e., cooling of the bile duct and combing thermal ablation with chemical ablation) should be considered for high-risk patients. Moreover, active monitoring and management should be performed for patients with bilomas who underwent biliary surgery before.

Introduction

As thermal ablation has the benefit of better liver function preservation and usually results only in minor trauma, it has largely replaced conventional treatment approaches (e.g., surgery and transplantation) for patients with malignant hepatic tumors, especially for patients who are not eligible for surgical resection [1]. Even though thermal ablation is considered a safe procedure, it still results in many complications in clinical practice. Bile duct injury is among the main complications that may result in poorer prognosis, with an incidence ranging from 0.1% to 12% [2,3].

Thermal damage and mechanical injury to the biliary epithelial cells are the main causes of bile duct injury during thermal ablation. Generally, mild injury to the bile duct is characterized by localized dilatation. However, when the lesions are large enough for the leakage of bile into the liver parenchyma, a cystic cholestasis, i.e., a biloma, may be detected. In most cases, a biloma may present with limited clinical symptoms with no need for treatment. However, when a biloma occurs along with an infection, the bile duct injury may not only increase the length of post-operative stay and the associated cost of treatment, but may also result in severe complications, such as septic shock or liver failure, or even death. Furthermore, on long-term follow-up, biloma was significantly associated with death and recurrence [4]. Therefore, it is important to identify the risk factors for bile duct injury and the related infections. Only a few studies have evaluated the risk factors for bile duct injury after thermal ablation [3]. Therefore, this study aimed to analyze the risk factors associated with the formation of biloma and secondary infection after thermal ablation for malignant hepatic tumors.

Patients and methods

The study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (Guangzhou, People’s Republic of China). Because the study...
was retrospective, the need for informed consent for using the patient's data was waived. However, written informed consent was obtained from each patient before thermal ablation.

**Patient selection**

Between January 2010 and December 2018, a total of 2772 ultrasound-guided thermal ablations were performed for patients with liver tumors in the Third Affiliated Hospital of Sun Yat-Sen University (Guangzhou, People's Republic of China). The inclusion criteria used to select patients were as follow: (1) clinically or pathologically diagnosed with malignant hepatic tumors; (2) receiving radical radiofrequency ablation (RFA) or microwave ablation (MWA) treatment; and (3) undergone follow-up for >6 months. The exclusion criteria were as follows: (1) follow-up period of <6 months and (2) bile duct injury induced by other treatment before thermal ablation, such as transcatheter arterial chemoembolization (TACE). The criteria used for diagnosing bile duct injury were the observation of upstream bile duct dilatation, because of bile duct stenosis after thermal ablation, and the formation of a biloma. In addition, the time interval between the most recent RFA and TACE should have been more than 3 months [5].

Bilomas were confirmed by using contrast-enhanced ultrasonography (CEUS), contrast-enhanced computed tomography (CECT), or contrast-enhanced magnetic resonance imaging (CEMRI) to detect the presence of focal effusion in or around the necrotic tissue of the ablation zone, with or without intrahepatic bile duct dilatation; or via US-guided aspiration or drainage. A total of 58 patients with 68 bilomas were recruited and assigned to the complication group. From among the remaining patients who had no major complications, including any bile duct injury, 61 patients with 72 lesions were selected randomly as the control group.

**Equipment**

Thermal ablation was performed using a cool-tip RFA instrument (Valleylab, Mansfield, MA, USA) with a maximal output power of 200 W and single-pole, internally cooled radiofrequency electrodes with 3-cm tips, or by using a KY-2000 water-cooled MWA treatment system (Kangyou Co, Nanjing, China) with the output power of 10–180 W, and a water-cycle internally cooled microwave probe. The My Lab Twice and My Lab ClassC ultrasound machine (Esoate, Genoa, Italy) with CnTI contrast-specific imaging was used for the ablation procedure. Convex probes CA541 and CA431 were used for US scanning and guidance.

**Ablation procedure**

All ablations were performed by interventional doctors with at last 5 years of experience in liver tumor ablation. The choice between RFA and MWA was made upon the operator experience, with predilection of RFA for lesions located closed to the biliary tract at preoperative imaging. Before ablation, the tumor and an additional 5 mm of the safety margin were first outlined by using the fusion imaging navigation system. The microwave probe or radiofrequency electrode was punctured percutaneously or directly into the center of each tumor. According to the size of the tumor, multiple overlapping ablations were performed as needed. The artificial ascites technique was used when tumors were located near the diaphragmatic muscle, gallbladder, heart, or other organs. The electrode path was cauterized while retracting the electrode to minimize the risk of post-ablation bleeding and tumor seeding. After the ablation procedure, the technical success was assessed by combining navigation and intraoperative CEUS. The endpoint for a technically successful procedure was a no-perfusion zone that included the tumor and the 5-mm margin around the tumor. However, the safety margin may be difficult to achieve in cases where it was difficult to create a puncture, cases of perivascular lesions, and those with severe liver function damage.

**Follow-up and data analysis**

The follow-up duration after complete ablation for all recorded patients was at least 6 months. Tumor biomarker and liver function measurements were recorded, and CEUS, CECT, or CEMRI was performed. The baseline clinical data of all patients were recorded, including tumor characteristics (type, size, and location), patient characteristics (gender, age, diabetes history, liver function measurements, ultrasonography findings, and clinical manifestations), relevant treatment history for hepatobiliary surgery and TACE, and ablation parameters (mode, ablation time, and ablation energy). Preoperative intrahepatic bile duct dilatation was defined as general or local bile duct dilatation that was not due to TACE. The tumor location was determined considering the shortest distance between the edge of the target tumor and the right/left main duct or segmental bile duct as measured on CEUS, CECT, or CEMRI images before ablation. According to the tumor location, patients were subgrouped into group A (<5 mm), group B (5–10 mm), and group C (>10 mm).

**Statistical analysis**

The data were presented as the mean ± standard deviation, or median ± range if the data were not normally distributed. The chi-squared test and an independent sample t-test were used to compare the data of biloma formation and secondary infection between the complication group and the control group. Variables were significant when p values were <.05, and these data were analyzed via multiple logistic regression analysis. Data analysis was performed using SPSS software (version 22.0 SPSS) for Microsoft Windows.
Results

Univariate analysis of factors predicting biloma formation

Among the 2772 thermal ablation procedures, 68 bilomas were identified in 58 patients (51 men and 7 women, mean age, 53.9 ± 11.7 years) who were assigned to the complication group, and 6 of them showed both biloma formation and upstream intrahepatic bile duct dilatation as well as slight increase in the bilirubin levels. In the control group, there were 48 men and 13 women (mean age, 53.6 ± 10.4 years). The characteristics of the included patients are listed in Table 1.

Univariate analysis showed that most of the characteristics were not different between the two groups. However, a history of hepatectomy (p = .029), a history of TACE treatment (p = .001), preoperative intrahepatic bile duct dilatation (p = .031), ablation mode (p = .008) and tumor location (p < .001) were significantly different between the complication group and the control group.

Further analysis of tumor location revealed that the risk of intrahepatic biloma was significantly different between group A and group C (p = .000) and between group B and group C (p = .000). However, there was no significant difference between group A and group B (p = .718).

Multivariate analysis of factors predicting biloma formation

As to tumor location, a distance of ≤10 mm from the bile duct was identified group A (<5 mm) and group B (5–10 mm). A distance of >10 mm was identified group C. Multivariate analysis showed that the variables of a history of TACE treatment and tumor location (whether the tumor was located ≤10 mm away from the bile duct) were independent predictors of biloma formation (p < .05, with an odds ratio [95% confidence interval] of 3.606 [1.165–11.156] and 37.734 [13.058–109.034]), respectively. The results of multiple logistic regression analysis are shown in Table 2.

Discussion

In the present study, a short distance (<10 mm) between the bile duct and tumor and a history of pre-operative TACE were two independent predictors for biloma formation after thermal ablation for malignant hepatic tumors.

The tumor location is a well-known independent predictor of bile duct injury [6]. A 5–10 mm area of liver parenchyma around the tumor should be ablated to achieve safety margins [7]. Therefore, in some cases, it is inevitable that there would be damage to the bile duct, leading to stenosis, bile leakage, and biloma formation, as observed in animal studies [8]. Partial necrosis and full thickness bile duct necrosis

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Table 1. Univariate analysis of factors predicting biloma formation.

| Complication group (58 patients, 68 lesions) | Control group (61 patients, 72 lesions) | t/2 | p |
|---------------------------------------------|----------------------------------------|-----|---|
| Age (years)                                 | 53.9 ± 11.7                           | 53.6 ± 10.4 | −0.013 | .990 |
| Gender (M/F)                                | 51/7                                  | 48/13       | 1.816 | .178 |
| Liver cirrhosis (Y/N)                       | 72.1% (49/19)                         | 79.2% (57/15) | 0.961 | .327 |
| Diabetes (Y/N)                              | 13.2% (9/9)                           | 5.6% (4/68)  | 2.449 | .118 |
| Hepatocellular histology (Y/N)              | 39.7% (27/69)                         | 22.2% (16/72) | 4.793 | .029* |
| TACE history (Y/N)                          | 41.2% (28/68)                         | 16.7% (12/70) | 10.294 | .001* |
| Intrahepatic bile duct dilatation before ablation (Y/N) | 11.8% (8/68) | 5.6% (4/68) | 4.661 | .031* |
| Ascites history (Y/N)                       | 2.9% (2/66)                           | 11.1% (8/64)  | 2.395 | .122 |
| Child-Pugh class (A/B)                      | 66/2                                  | 72/0        | 2.148 | .143 |
| ALT (<35/35–150 U/L)                        | 41/27                                 | 49/23       | 0.918 | .338 |
| AST (<40/40–100 U/L)                        | 50/18                                 | 48/24       | 0.784 | .376 |
| Tumor (PLC/SLC)                             | 65/3                                  | 72/0        | 1.483 | .072 |
| Tumor size (cm)                             | 21 ± 9.2                              | 18.7 ± 6.3  | −1.182 | .237 |
| Tumor location (<5/5–10/10 mm)             | 50/9/9                                | 13/1/58     | 63.904 | .000* |
| Ablation (RFA/MWA)                          | 49/19                                 | 36/36       | 7.134 | .008* |
| Ablation energy (kJ)                        | 117.5 ± 115.1                         | 99.9 ± 77.1 | −1.301 | .193 |
| Ablation time (min)                         | 23.6 ± 13.1                           | 21.4 ± 12.9 | −1.086 | .278 |

M: male; F: female; Y: yes; N: no; PLC: primary liver cancer; SLC: secondary liver cancer; TACE: transcatheter arterial chemoembolization; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RFA: radiofrequency ablation; MWA: microwave ablation; KJ: kilojoule. *Significant difference.

Clinical manifestation of biloma and the possible risk factors for secondary infection of biloma

Of the 58 patients with biloma, 49 showed no symptoms during the follow-up period (i.e., the asymptomatic group), while the remaining 9 developed symptoms (i.e., the symptomatic group) including fever, stomachache, or jaundice, which were associated with secondary infection. The symptoms and infection disappeared after percutaneous drainage and antibiotics therapy in the symptomatic group.

The results of the possible risk factors for secondary infection due to biloma are shown in Table 3. Among all the potential factors, only a history of biliary tract surgery (bilioenteric anastomosis or endoscopic duodenal sphincterotomy) was significantly different between the symptomatic group and the asymptomatic group (p = .031).

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Table 2. Multivariate analysis of factors predicting biloma formation.

| Odds ratio | 95% confidence interval | p |
|------------|-------------------------|---|
| Hepatocellular histology (Y/N) | –           | –                      | .279 |
| TACE history (Y/N)              | 3.606       | 1.165–11.156           | .026* |
| Intrahepatic bile duct dilatation before ablation (Y/N) | 0           | 0                      | .999 |
| Tumor location (<5/5–10/10 mm) | 37.734      | 13.058–109.034         | < .001* |
| Ablation (RFA/MWA)              | –           | –                      | .264 |

TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation; Y: yes; N: no. *Significant difference.
(including cytolyis, fibrosis, and loss of bile duct structure) due to thermal ablation were detected in dogs when the distance between the RFA electrode tip and bile ducts was <5 mm [9]. In particular, when the tumor was located close to the hilum, more heat is often required to overcome the ‘heat-sinking effect’ of the large blood vessels, which may increase the risk of peripheral bile duct damage [10]. Hence, determining the safe distance between the intrahepatic major bile duct and the tumor is very important for high-risk tumor ablation. In the current study, although we chose 5 mm as the safety margin, a significant difference in biloma formation was observed between group B and group C, but not between group A and group B, comparable to the findings of a previous study [3]. Thus, we can conclude that the minimum safe distance was 10 mm for ablating lesions located near the main bile ducts.

In a study by van Tilborg et al. [11], MWA resulted in higher biliary complication rates compared to RFA for peribiliary tumors, because of shaft heating, large diameter probes, less predictable ablation zone, and higher peak temperatures. The operators in our center agree with the above-mentioned reasons, and hence, RFA was preferred for lesions located <5 mm from the right/left main duct or segmental biliary tract in general. Univariate analysis showed that the ablation mode (p = .008) was significantly different between the complication group and the control group, because the proportion of lesions in group A was much higher in complication group than in control group. However, we found that WMA was not an independent predictor of biloma formation in the current study; selection bias and the relatively small number of cases might explain this finding.

It is important to improve the safety of thermal ablation for preventing the formation of biloma, especially in patients with high-risk tumors adjacent to the bile duct and in patients with a history of TACE treatment. Better margin control is an effective measure. Hence, the microwave probe or radiofrequency electrode should be inserted parallel to the wall of the bile ducts to avoid accidental penetration of the bile duct due to prongs; the outcome of this strategy is acceptable [12]. Moreover, multiple methods have been used in clinical practice for high-risk tumors, including cooling of the bile duct [13,14]. In an animal study, cooling of the bile ducts with a cold 5% glucose isotonic solution significantly protected the intrahepatic bile ducts from damage caused by the heat generated during RFA [8]. Intraductal chilled saline perfusion decreased the incidence of biliary injury from 46% to 2.5% compared to the control group (p < .0001) [14]. However, the possibility of bile duct stenosis remains to be explored [15]. In addition, combing thermal ablation with chemical ablation (e.g., using ethanol or lyso-thermosensitive liposomal doxorubicin) could be another treatment option [16,17].

TACE treatment is performed via intubation of the tumor-feeding artery by injecting embolic particles or chemotherapy drugs to cause tumor necrosis [18]. In the present study, a history of TACE treatment was a risk factor for biloma formation. This may be associated with the decrease in the heat-sink effect owing to adjacent vessels. Unlike the supply to the normal liver tissue, hepatic carcinoma and bile ducts are mainly supplied by the hepatic artery. After occlusion of the arteries occurs due to TACE, blood flow around the tumor might be reduced, thereby leading to the decrease in the heat-sink effect and the consequent increase in the risk of thermal damage to the bile tract wall [19,20]. In addition, the reduction in the blood supply to the bile duct might result in susceptibility to thermal damage after TACE. However, other studies have found negative results, possibly because of differences in the TACE mode and the long time interval between the most recent ablation and TACE [3,12]. Therefore, more strictly controlled trials are needed to identify the mechanism.

The management of biloma is another critical issue. Traditionally, observation only without active treatment was considered sufficient for biloma, except for cases with symptoms or infections [2,21,22]. The results of the current study support this claim: among all the 68 bilomas, only 12 developed infective lesions and needed drainage and antibiotics. The incidence rate was 17.6%, similar to that reported by Su (16.7%) [23]. Generally after ablation, patients may experience a transient fever, but if the fever persists for >2 weeks,
the possibility of secondary infection should be considered [24]. Although the current mechanism of secondary infection of biloma is not fully understood, bacteria are suspected to ascend via the biliary tract [22]. The incidence rate of biloma formation was much higher than the incidence rate of liver abscess after ablation (0.3–3%) [23], indicating that biloma formation may be a risk factor for secondary liver abscesses. Therefore, subgroup analysis was performed to identify the risk factors for secondary infection due to biloma.

In the present study, surgery for the biliary tract, such as bilioenteric anastomosis and endoscopic duodenal sphincterotomy, was performed for 2 patients with secondary infection. Biliary tract surgery can destroy the integrity of the duodenal papilla and bile duct epithelium, making it easier for intestinal bacteria to ascend and invade the intrahepatic lesion and cause infection. Elias [25] reported that the incidence of liver abscess after thermal ablation was 44% in 11 patients with a history of biliary anastomosis or biliary stenting. De Baere [26] reported that hepatic abscess occurred in all the 3 patients who underwent cholangioenterostomy. In addition, biliary tract diseases such as biliary malformations, bile duct stones, and cholangitis were also risk factors for secondary infection [23,27].

The prophylactic use of antibiotics for patients with biloma remains controversial [24]. In the study by Su [23], patients with a history of bile duct surgery and ablation treatment had a 3% probability of developing liver abscesses after prophylactic antibiotic use, compared to 17.3% of patients treated without antibiotics, indicating the need for prophylactic antibiotics for patients at high risk. Similar results were found in other studies [4,27]. However, limited studies have analyzed the effect of antibiotic use in patients with biloma. In the present study, patients with bilomas had a 16.3% (8/49) probability of developing liver abscesses after prophylactic antibiotic use, compared to 21.1% (4/19) in patients treated without antibiotics. However, the values were not significantly different. Hence, further research is needed to determine the role of prophylactic antibiotics, especially progressive antibiotics, in patients with biloma.

The present study has several limitations, including those owing to its retrospective nature. Moreover, because of the continuous improvement in the technology of ablation, the process is constantly regulated, which may result in deviations in information, measurement, and classification. While selecting ablation procedures, the choice between RFA and MWA was based on tumor location which may have resulted in a high selection bias. Furthermore, although we randomly selected patients for the non-biliary injury control group, there may still be sampling errors.

**Conclusion**

A history of TACE and tumor location (whether the tumor was located <10 mm away from the bile duct) were independent predictors of the formation of biloma in patients with hepatic carcinoma after thermal ablation. The treatment of lesion located within 10 mm from main bile ducts was associated with biloma formation regardless of the technique used.

Protection of the bile duct should be performed for high-risk tumors. The majority of patients with biloma showed no symptoms and did not need any additional treatment. However, if a patient had a history of biliary surgery, active monitoring and management are needed.

**Disclosure statement**

The authors declare no conflicts of interest.

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