^{90}Y Radioembolization for Hepatic Malignancy in Patients with Previous Biliary Intervention: Multicenter Analysis of Hepatobiliary Infections

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Conflicts of interest are listed at the end of this article.

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Purpose: To determine the frequency of hepatobiliary infections after transarterial radioembolization (TARE) with yttrium 90 (^{90}Y) in patients with liver malignancy and a history of biliary intervention.

Materials and Methods: For this retrospective study, records of all consecutive patients with liver malignancy and history of biliary intervention treated with TARE at 14 centers between 2005 and 2015 were reviewed. Data regarding liver function, ^{90}Y dosimetry, antibiotic prophylaxis, and bowel preparation prophylaxis were collected. Primary outcome was development of hepatobiliary infection.

Results: One hundred twenty-six patients (84 men, 42 women; mean age, 68.8 years) with primary (n = 39) or metastatic (n = 87) liver malignancy and history of biliary intervention underwent 180 procedures with glass (92 procedures) or resin (88 procedures) microspheres. Hepatobiliary infections (liver abscesses in nine patients, cholangitis in five patients) developed in 10 of the 126 patients (7.9%) after 11 of the 180 procedures (6.1%; nine of those procedures were performed with glass microspheres). All patients required hospitalization (median stay, 12 days; range, 2–113 days). Ten patients required percutaneous abscess drainage, three patients underwent endoscopic stent placement and stone removal, and one patient needed insertion of percutaneous biliary drains. Infections resolved in five patients, four patients died (two from infection and two from cancer progression while infection was being treated), and one patient continued to receive suppressive antibiotics. Use of glass microspheres (P = .02), previous liver resection or ablation (P = .02), and younger age (P = .003) were independently predictive of higher infection risk.

Conclusion: Infectious complications such as liver abscess and cholangitis are uncommon but serious complications of transarterial radioembolization with ^{90}Y in patients with liver malignancy and a history of biliary intervention.

Online supplemental material is available for this article.

Transarterial chemoembolization (TACE) and yttrium 90 (^{90}Y) transarterial radioembolization (TARE) are commonly used palliative treatments for patients with unresectable hepatic malignancies. Infectious complications are rare after TACE, but their risk has been reported to be much greater in patients with biliary enteric anastomosis or stents and drains spanning across the ampulla of Vater (1,2). Infection risk has been shown to remain elevated despite antibiotic prophylaxis (3). The purported mechanism for infection is ischemic injury of bile ducts colonized with enteric organisms (4).

Unlike TACE, which combines ischemia from embolization with local delivery of chemotherapeutic agents, the end point of TARE is delivery of a prescribed activity of ^{90}Y microspheres without vascular stasis. The risk of hepatobiliary infection after TARE in the setting of an intact ampulla of Vater and no previous biliary intervention has been reported to be approximately 0%–2% (5–7). Data regarding hepatobiliary infection risk after TARE in patients with a compromised ampulla of Vater or previous biliary tract intervention are limited to single-institution reports. These studies have not reported any instances of hepatobiliary infection for patients with a history of biliary tract intervention (8,9). Nevertheless, serious hepatobiliary infections in this patient population are known to occur. The purpose of our study was to determine the frequency of hepatobiliary infections after ^{90}Y radioembolization in patients with liver malignancy and a history of biliary intervention.

Abbreviations

CI = confidence interval, HR = hazard ratio, TACE = transarterial chemoembolization, TARE = transarterial radioembolization

Summary

In patients with a liver malignancy and a history of biliary intervention who undergo transarterial radioembolization with ^{90}Y microspheres, infectious complications and morbidities such as liver abscess and cholangitis occur but are uncommon.

Implications for Patient Care

- In patients with liver malignancy and prior biliary intervention, transarterial radioembolization (TARE) with yttrium 90 (^{90}Y) may be a safer local-regional treatment alternative with respect to hepatobiliary infection risk when compared with transarterial chemoembolization.
- For patients with previous biliary tract interventions, the relative risks and benefits of TARE with ^{90}Y should be carefully weighed, as infections tend to result in substantial clinical sequelae.
- Radioembolization with ^{90}Y resin microspheres may result in a lower risk of hepatobiliary infection compared with ^{90}Y glass microspheres.

Materials and Methods

Our Health Insurance Portability and Accountability Act–compliant retrospective multicenter study was approved by the institutional review boards of all participating institutions. The requirement to obtain informed consent was waived. Our study included all consecutive adult patients with a history of bile duct intervention who were subsequently treated with TARE at one of 14 participating medical centers in the United States and Canada between January 2005 and December 2015. None of the patients were excluded. TARE was performed by attending interventional radiologists (authors N.F., M.C.S., M.S.J., G.E., C.N., K.F., R.P.L., R.C.G., D.B.B., S.W.K., S.C.R., D.M.L., S.B.W., and R.G., with 8, 30, 28, 9, 20, 9, 5, 10, 18, 6, 27, 14, 7, and 8 years of experience, respectively) using glass (Therasphere; BTG, London, England) or resin (SIR-Sphere; Sirtex Medical, New South Wales, Australia) ^{90}Y microspheres. The choice between glass and resin microspheres was made by the individual interventional radiologists. This decision was uniform among individual patients (ie, the same agent was used when patients were treated more than once). Medical internal radiation dose and body surface area methodology were used for calculation of glass and resin microsphere activity, respectively.

A data collection spreadsheet template (Excel, version 14.6.0; Microsoft, Redmond, Wash) was distributed to all authors at each participating center. Demographic data included patient age at the time of the first TARE and sex. Collected clinical data included tumor type; type of previous bile duct intervention; information regarding history of liver resection, ablation, embolization, external beam radiation, concurrent systemic chemotherapy, or biologic agent use; and Eastern Cooperative Oncology Group performance status. Laboratory parameters included preprocedure white blood cell count, platelet count, total serum bilirubin level, aspartate and alanine aminotransferase levels, alkaline phosphatase level, serum creatinine level, and international normalized ratio for prothrombin time. Data regarding technical aspects of TARE included procedure date, type of ^{90}Y carrier (glass or resin microspheres), extent of liver coverage during TARE treatment (whole organ, lobar, other), estimated extent of liver parenchyma replacement by tumor (<25%, 25%–50%, 51%–75%, >75%), volume of treated liver, delivered ^{90}Y activity, and absorbed liver radiation dose. The data instrument also included information on periprocedural antibiotic and antiseptic bowel preparation use, including medications, doses, and duration of periprocedural therapy.

The primary outcome was development of hepatobiliary infection, which was defined as liver abscess or cholangitis. For the subset of patients who developed hepatobiliary infection, collected information included type of infection (including pathogens if any were isolated), date of diagnosis, number and duration of hospitalizations and intensive care unit stays, and concomitant complications including septicemia, vasopressor medication use, renal failure, hemodialysis use, respiratory failure requiring intubation, and liver failure. Collected information regarding treatment of hepatobiliary infection included antibiotics, duration of antibiotic therapy, number and types of invasive procedures (abscess drainage, endoscopic stent placement, percutaneous transhepatic biliary drainage), and days with a percutaneous drain or a biliary stent in situ. Outcome data for all infections categorized as infection resolution, ongoing treatment at the time of data censor date of March 31, 2017, and survival were also tabulated.

Descriptive statistics (eg, medians and percentages) were used to describe the patient characteristics and technical details. Univariable analysis of the primary dichotomous outcome, presence of hepatobiliary infection, was performed by using generalized estimating equations with logit link function to account for patients who experienced multiple procedures (up to four procedures) clustered within one of 14 participating centers. The univariable predictors with $P < .20$ were then assessed in a bivariate generalized estimating equation model with two variables that included ^{90}Y agent. Six bivariate models were assessed for *(a)* age and ^{90}Y agent, *(b)* neuroendocrine tumor and ^{90}Y agent, *(c)* previous resection and ^{90}Y agent, *(d)* international normalized ratio for prothrombin time and ^{90}Y agent, *(e)* delivered activity and ^{90}Y agent, and *(f)* greater than 25% liver replacement with tumor and ^{90}Y agent. Variables were included in the final multivariable generalized estimating equation analysis if their P values were less than .05 in the bivariate model. The final multivariable model included age (in years), previous liver resection or ablation, and ^{90}Y agent. ^{90}Y agent was planned a priori to be included in the final model regardless of statistical significance at $P < .05$ in the bivariate analysis. The multivariable model included 11 infection events. We relaxed the rule of 10 events per variable (10) by including three variables in the final model (ie, age, previous resection, and glass microspheres). We compared this multivariable model to the other models, bivariable and univariable models, to assess whether the magnitude of the results, confidence intervals (CIs), and/or P values changed. We found the results

Table 1: Patient Characteristics

Variable	Value
Median age (y)*	64 (30–89)
Sex	
M	84 (67)
F	42 (33)
Primary liver tumor	
Hepatocellular carcinoma	18 (14)
Cholangiocarcinoma	21 (17)
Metastatic disease	87 (69)
Adenocarcinoma	42 (33)
Neuroendocrine tumors	40 (32)
Sarcoma	3 (2.4)
Squamous cell carcinoma	1 (0.8)
Pseudopapillary tumor of pancreas	1 (0.8)
Liver parenchyma replacement	
<25%	68 (38)
25%–50%	64 (36)
51%–75%	14 (7.8)
>75%	5 (2.8)
Not specified	29 (16)
Biliary intervention	
Biliary-enteric anastomosis	64 (51)
Indwelling biliary stent	
Metal	19 (15)
Plastic	19 (15)
Sphincterotomy (no stent)	16 (13)
Internal-external biliary drain	5 (4.0)
Not specified	3 (2.4)
Concurrent systemic chemotherapy	
Yes	25 (14)
No	134 (74)
Not specified	21 (12)
Prior liver radiation therapy	
Yes	8 (6.3)
No	118 (94)
Prior liver resection or ablation	
Yes	41 (33)
No	85 (67)
Prior chemoembolization or bland embolization	
Yes	21 (17)
No	105 (83)
ECOG performance status	
0	97 (54)
1	52 (29)
2	3 (1.7)
3	2 (1.1)
Not specified	26 (14)
Median baseline laboratory values*	
White blood cell count (10^3/mL)	6.1 (2.2–15.2)
Total bilirubin level (mg/dL)	0.87 (0.2–8.0)
Alkaline phosphatase level (U/L)	169 (55–2127)
Aspartate aminotransferase level (U/L)	37 (11–148)
Alanine aminotransferase level (U/L)	32 (10–147)
International normalized ratio for prothrombin time	1.1 (0.8–2.4)
Platelet count (10^3/mL)	206 (33–484)
Creatinine level (mg/dL)	0.94 (0.4–6.4)

Table 1 *(continues)*

Table 1 *(continued)*: Patient Characteristics

Note.—Except where indicated, data are numbers of patients or procedures, with percentages in parentheses. ECOG = Eastern Cooperative Oncology Group.

* Numbers in parentheses are the range.

were similar and remained statistically significant regardless of the results reported by the model (ie, univariable, bivariable, or multivariable). The magnitude of the association between the outcome and each variable was reported as the hazard ratio (HR) with associated 95% CIs. Two-sided *P* values were reported, and $P < .05$ was considered indicative of a statistically significant difference in the final model. Owing to the low number of events, interaction terms between ^{90}Y agent and each of the variables were not considered and a forward stepwise approach to analysis was undertaken. Statistical analyses were performed by author A.A.L. by using software (SAS, v. 9.4; SAS, Cary, NC).

Results

Patient Characteristics

A total of 126 patients (mean age, 68.8 years; age range, 30–89 years; 84 men) who underwent 180 TARE procedures after biliary tract intervention were included in our study. Baseline demographic, clinical, and laboratory parameters are summarized in Table 1. TARE procedures were performed for the treatment of a primary liver malignancy in 39 patients (18 patients with hepatocellular carcinoma and 21 with cholangiocarcinoma), whereas 87 of the 126 patients (69%) were treated for metastatic disease to the liver. The extent of liver parenchyma replacement by tumor was less than 25% or 25%–50% before most TARE procedures (38% and 36%, respectively). None of the patients had a history of liver transplantation or neutropenia or were known to be immunocompromised. The mean duration of follow-up was 10.9 months (range, 0.3–52.5 months).

Infectious Complications

Eleven of the 180 procedures (6.1%) resulted in hepatobiliary infections in 10 of the 126 patients (7.9%). Six patients had liver abscesses (Figs 1, 2), three with liver abscess and cholangitis and two with cholangitis. The median time between TARE and diagnosis of infection was 46 days (range, 3–132 days). Nine of the procedures used ^{90}Y glass microspheres.

Antibiotic prophylaxis was used before nine of the 11 TARE procedures that resulted in infection (82%). Ten of the 11 hepatobiliary infections (91%) necessitated treatment in the inpatient setting. One patient with cholangiocarcinoma who had an indwelling endoscopic biliary stent was successfully treated for cholangitis as an outpatient 18 days after TARE to two

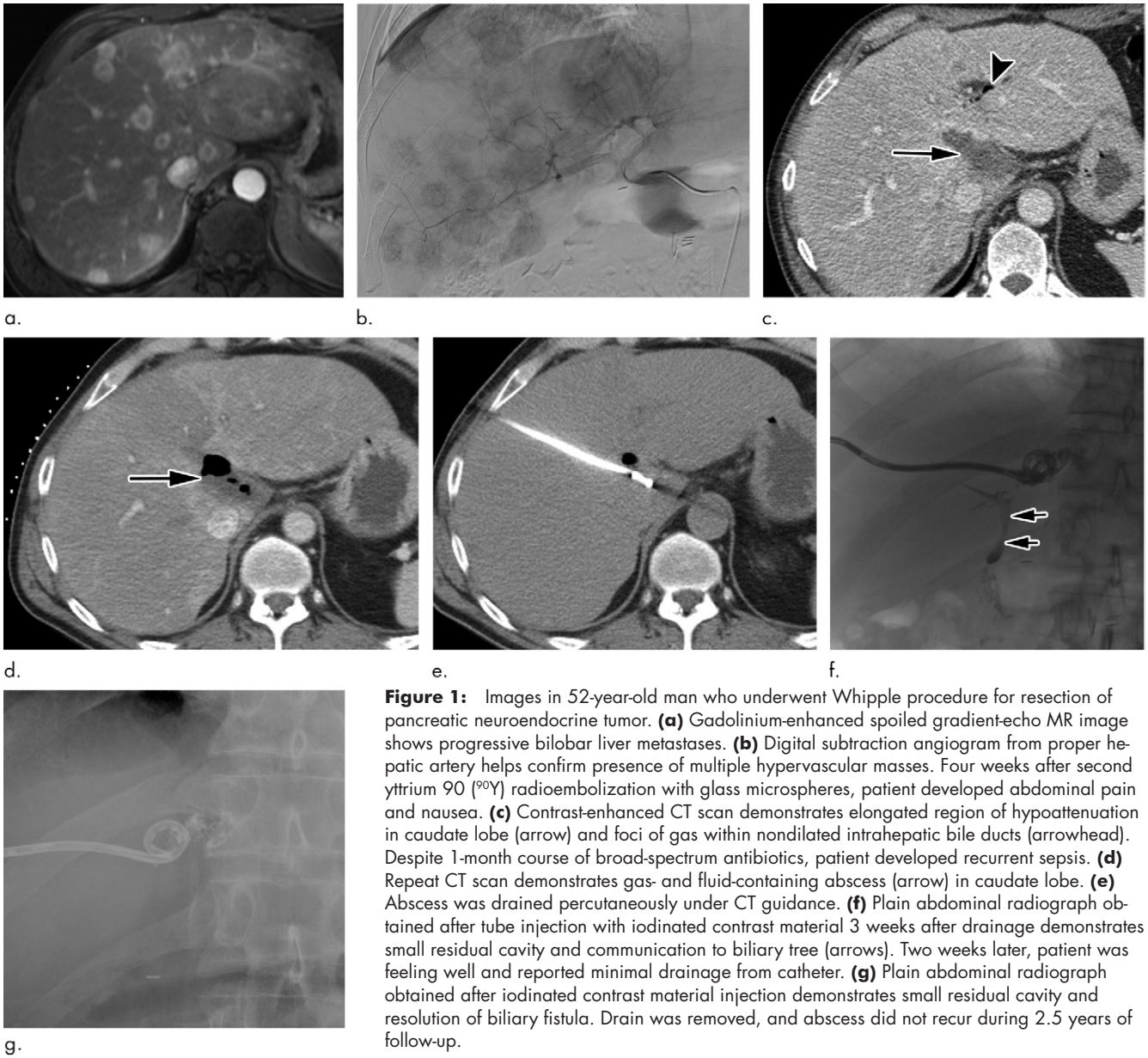


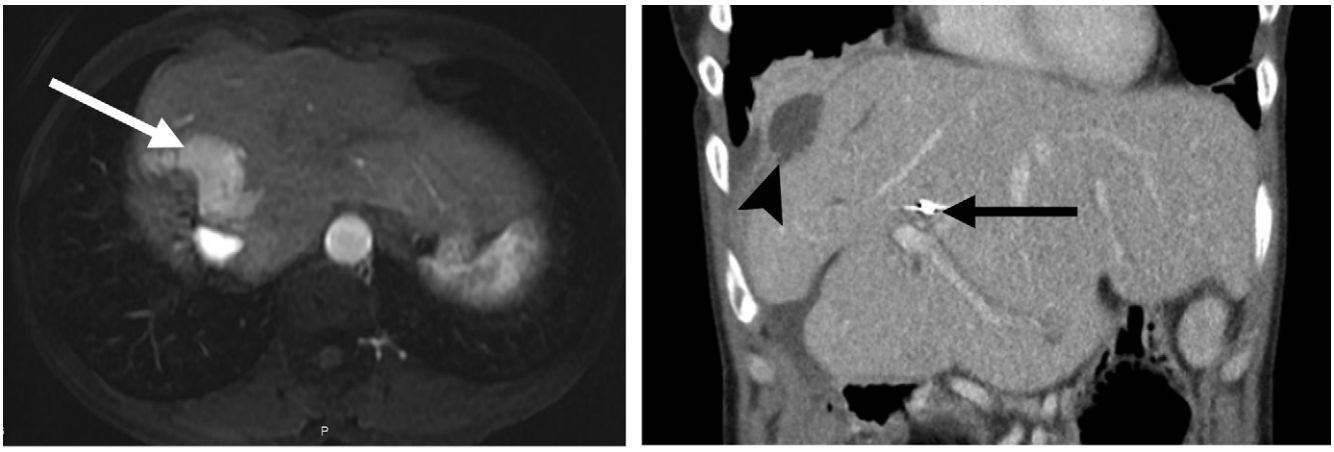
Figure 1: Images in 52-year-old man who underwent Whipple procedure for resection of pancreatic neuroendocrine tumor. **(a)** Gadolinium-enhanced spoiled gradient-echo MR image shows progressive bilobar liver metastases. **(b)** Digital subtraction angiogram from proper hepatic artery helps confirm presence of multiple hypervascular masses. Four weeks after second yttrium 90 (^{90}Y) radioembolization with glass microspheres, patient developed abdominal pain and nausea. **(c)** Contrast-enhanced CT scan demonstrates elongated region of hypoattenuation in caudate lobe (arrow) and foci of gas within nondilated intrahepatic bile ducts (arrowhead). Despite 1-month course of broad-spectrum antibiotics, patient developed recurrent sepsis. **(d)** Repeat CT scan demonstrates gas- and fluid-containing abscess (arrow) in caudate lobe. **(e)** Abscess was drained percutaneously under CT guidance. **(f)** Plain abdominal radiograph obtained after tube injection with iodinated contrast material 3 weeks after drainage demonstrates small residual cavity and communication to biliary tree (arrows). Two weeks later, patient was feeling well and reported minimal drainage from catheter. **(g)** Plain abdominal radiograph obtained after iodinated contrast material injection demonstrates small residual cavity and resolution of biliary fistula. Drain was removed, and abscess did not recur during 2.5 years of follow-up.

liver segments with ^{90}Y glass microspheres. The same patient developed cholangitis and liver abscess 33 days after the second TARE procedure performed with glass microspheres and targeting one liver segment.

The clinical course and outcomes of patients with infectious complications are outlined in Table 2. Infections resolved in five patients. Two patients died of cancer progression while receiving antibiotics and with drainage catheters in place. One patient continued to receive rotating suppressive antibiotic treatment (amoxicillin and clavulinate and trimethoprim-sulfamethoxasole) 27 months after the diagnosis of a liver abscess (based on data censor date of March 31, 2017). Hepatobiliary infections resulted in two deaths. One patient with pancreatic neuroendocrine tumor and history of biliary-enteric anastomosis developed a liver abscess 30 days after TARE with resin microspheres. One day after presenting with infectious symptoms, the patient died of sepsis, before abscess drainage could be performed. The second patient with hepatocellular carcinoma and previously placed endoscopic biliary stent developed liver abscess and cholangitis 74 days after TARE with glass microspheres. The patient was hospitalized for 12 days, underwent exchange of the endoscopic biliary stent, and completed a 14-day course of intravenous vancomycin and ceftazidime. However, 9 days after completing the course of antibiotics, the patient died of sepsis attributed to a hepatobiliary source. The two deaths occurred in patients who did not receive antibiotic prophylaxis or bowel preparation before TARE.

Technical Details of TARE

Glass ^{90}Y microspheres were used in 92 of the 180 TARE procedures (51.1%) performed in 61 of the 126 patients (48.4%), whereas resin ^{90}Y microspheres were used in 88 procedures (48.9%) performed in 65 patients (51.6%). None of the patients were treated with both agents. Seventy-nine patients



a. b.

Figure 2: Images in 48-year-old woman who underwent right hepatectomy for multifocal well-differentiated metastatic pancreatic neuroendocrine tumor to liver. The clinical course was complicated by common hepatic duct stricture, which was treated with sphincterotomy and endoscopic stent placement. **(a)** Contrast-enhanced MR image shows that patient subsequently developed multiple metastases in left liver lobe remnant (arrow). Left liver lobe yttrium 90 radioembolization with resin microspheres was performed. **(b)** CT scan obtained for work-up of fever and abdominal pain 105 days after radioembolization reveals a fluid collection (arrowhead) in hepatic segment 4A. An endoscopic stent was in place (arrow). Abscess was treated with US-guided aspiration and a prolonged course of antibiotics, which included imipenem and linezolid for extended spectrum beta-lactamase–producing *Escherichia coli* and vancomycin-resistant *Enterococcus faecium* species.

were treated once (40 with glass microspheres, 39 with resin microspheres), 41 patients were treated twice (19 with glass microspheres, 22 with resin microspheres), five patients were treated three times (two with glass microspheres, three with resin microspheres), and one patient was treated four times with resin microspheres. For patients who underwent more than one radioembolization procedure, the average time between the procedures was 2.5 months (range, 0.7–12.3 months). For five procedures, the previously treated vascular territory was targeted. For the remaining 49 procedures, a different territory was treated. Median delivered activity was 2.36 GBq for glass microspheres and 1.04 GBq for resin microspheres (Table 3). The corresponding median absorbed liver doses were 116 Gy and 73 Gy for glass and resin microspheres, respectively. ^{90}Y microsphere administrations were to the entire liver for 21 of the 180 procedures (11.7%), were to the right or left lobe for 125 (69.4%), and targeted one to three segments for 30 (16.1%) (Table 3). The median targeted liver parenchyma volumes for whole liver, right lobe, and left lobe treatments were 1565 mL, 1115 mL, and 620 mL, respectively (Table 3).

Antibiotic Regimens

Selection of the preprocedure antibiotic prophylaxis and postprocedure therapy was at the discretion of the physicians at each of the participating clinical sites. Antibiotics were used for 151 of the 180 TARE procedures (85.8%) involving 106 patients. Antibiotics were started at least 1 day before TARE for 135 of the 180 procedures (75%) (Table E1 [online]). The median duration of preprocedure antibiotic therapy was 2 days (range, 1–14 days). Most patients (62%) were treated for 2–5 days before radioembolization. The most commonly used antibiotics were a combination of levofloxacin and metronidazole (62 procedures, 46%), single-agent moxifloxacin (35 procedures, 26%), and a combination of ciprofloxacin and metronidazole (nine procedures, 6.7%).

Postprocedure antibiotics were administered after 143 of the 180 TARE procedures (79%) (Table E2 [online]). The median duration of postprocedure antibiotic therapy was 14 days (range, 3–30 days). Most patients (58%) were treated for 8–14 days. The most commonly used antibiotic regimens in the postprocedure period were levofloxacin with metronidazole (61 procedures, 43%), single-agent moxifloxacin (36 procedures, 25%), single-agent ciprofloxacin (16 procedures, 11%), ciprofloxacin with metronidazole (nine procedures, 6.3%), single-agent levofloxacin (six procedures, 4.2%), and amoxicillin clavulinate (four procedures, 2.8%).

Antiseptic Bowel Preparation

Selection of bowel preparation regimens was at the discretion of the physicians at each of the participating clinical sites. A bowel preparation regimen was used before 48 of the 180 TARE procedures (27%) (Table E3 [online]). The most common regimens were neomycin with erythromycin (33 procedures, 69%) and polyethylene glycol with bisacodyl (nine procedures, 19%).

Predictors Associated with Risk of Infection

Univariable generalized estimating equation analysis demonstrated that younger age at the time of TARE, lower international normalized ratio for prothrombin time, higher delivered ^{90}Y activity, use of glass microspheres, and history of liver resection or ablation were associated with the development of hepatobiliary infection after TARE (Table 4). Risk of infection was independent of the number of TARE procedures performed for a given patient. Bivariate analyses of infection showed an association ($P < .05$) of ^{90}Y glass microsphere agent with previous liver resection or ablation (HR = 7.28; 95% CI = 1.79, 29.56; P = .006) and with younger age at the time of TARE (HR = 0.92;

95% CI = 0.87, 0.97; P = .003). Multivariable analysis showed that use of glass microspheres (HR = 6.90; 95% CI = 1.40, 35.10; P = .02), previous liver resection or ablation (HR = 6.10; 95% CI = 1.30, 27.60; P = .02), and younger age per year (HR= 0.92; 95% CI = 0.88,0.97; P = .003) were associated with greater risk of developing hepatobiliary infection after TARE.

Discussion

Our study demonstrated a 7.9% frequency of liver abscess and/or cholangitis after TARE in patients with a history of biliary intervention. The rate of infection in our cohort was greater than the hepatobiliary infection rates of 0%–2% reported in patients with an intact ampulla of Vater who had undergone TARE (5–7). For example, the largest published series of biliary sequelae after TARE in 327 patients with no prior biliary intervention demonstrated three suspected infections (1.0% complication rate from infection) (5).

Overall, the frequency of hepatobiliary infection in our study was much lower than that reported for patients with a history of biliary intervention treated with TACE. For example, Woo et al (11) reported that 12 of 25 patients (48%) with biliary enteric anastomosis developed a liver abscess after TACE. Kim et al (2) reported that six of seven patients (86%) with a history of Whipple procedure developed liver abscesses after TACE. High rates of infection after TACE in patients with biliary enteric anastomosis have also been noted despite aggressive antibiotic prophylaxis. Cholapranee et al (8) reported that three of 13 patients (23%) developed liver abscesses after TACE despite 2 weeks of levofloxacin and metronidazole beginning 2 days before the procedure. Patel et al (3) reported that two of seven patients (28.6%) developed liver abscesses after chemoembolization despite a similar regimen of levofloxacin and metronidazole. Khan et al (12), however, found no infections among 10 patients undergoing 25 TACE procedures who were treated with moxifloxacin starting 3 days before their procedure and continuing for 17 days thereafter.

Two single-institution studies have investigated the rates of hepatobiliary infection after TARE in patients with a history of biliary intervention after TARE. Cholapranee et al (8) reported no infectious complications in a cohort of 16 patients undergoing 24 ^{90}Y resin microsphere TARE procedures. This subset of patients was included in our study. All patients in that study received a prophylactic regimen consisting of oral levofloxacin and metronidazole 2 days before the procedure and continuing for 14 days after, oral neomycin-erythromycin bowel preparation the day before, and intravenous levofloxacin-metronidazole

Table 2: Treatment Summary for Patients with Infectious Complications

Parameter	Value
Primary tumor site	
Pancreatic neuroendocrine tumor	6
Cholangiocarcinoma	2
Hepatocellular carcinoma	1
Leiomyosarcoma	1
Hospitalizations	
Median hospital admissions per patient	1 (1–7)
Median cumulative days in the hospital	12 (2–113)
ICU stays	
No. of patients admitted to ICU	4
Median ICU admissions per patient	1 (1–3)
Median cumulative days in the ICU	3 (2–31)
Complication specifics	
Septicemia	8
Vasopressor requirement	3
Acute kidney injury	3
Hemodialysis	1
Mechanical ventilation	0
Liver failure	2
Microbiology	
Actinobacter	1
Bacteroides fragilis	1
Candida species	3
Clostridium species	2
Enterobacter species	1
Enterococcus species	5
Escherichia coli	3
Klebsiella species	2
Pseudomonas aeruginosa	2
Raoultella ornithinolytica	1
Streptococus species	3
Invasive procedures	
No. of patients needing an invasive procedure	9
Median no. of invasive procedures per patient	1 (1–8)
No. of patients needing imaging-guided abscess aspiration	4
Median no. of imaging-guided abscess aspirations per patient	1 (1–3)
No. of patients needing imaging-guided abscess drain insertion	5
Median no. of imaging-guided abscess drain insertions per patient	2 (1–3)
No. of patients needing PTBD	1
No. of PTBD procedures per patient	2
No. of patients needing ERCP with stent exchange	3
No. of ERCP procedures per patient	1

Note.—Except where indicated, data are numbers of patients. Numbers in parentheses are the range. ERCP = endoscopic retrograde cholangiopancreatography, ICU = intensive care unit, PTBD = percutaneous transhepatic biliary drain.

Table 3: Microsphere Composition, Delivered Activity, and Treated Liver Volume

Variable	No. of Procedures*	Median Target Volume (mL)†	Median Activity (GBq)†	Median Absorbed Liver Dose (Gy)†
^{90}Y microspheres				
Glass	92 (51.1)	977 (30–3127)	2.36 (0.13–6.01)	116 (57–203)
Resin	88 (48.9)	662 (256–1430)	1.04 (0.34–2.02)	73 (19–207)
^{90}Y distribution				
Whole liver	21 (11.7)	1565 (1094–3127)	2.76 (1.30–5.85)	65 (59–71)
Right lobe	80 (44.4)	1115 (300–2600)	1.83 (0.60–4.67)	110 (49–157)
Left lobe	45 (25.0)	620 (120–1982)	0.95 (0.34–2.73)	103 (19–170)
One segment	10 (5.6)	177 (30–880)	0.76 (0.13–1.51)	131 (51–196)
Two segments	17 (9.4)	488 (132–1735)	1.35 (0.40–4.50)	135 (106–203)
Three segments	2 (1.1)	256, 2200	1.10, 6.01	207, 124

Note.—^{90}Y = yttrium 90.

* Numbers in parentheses are percentages.

† Numbers in parentheses are the range.

on the day of treatment. Giesel et al (9) also demonstrated no infectious complications in their cohort of nine patients. These patients were also treated with resin microspheres but did not undergo preprocedural bowel preparation or antibiotic prophylaxis.

The clinical course of the patients who developed cholangitis and/or liver abscess was complex. All patients required at least one hospitalization, four patients needed intensive care unit level of care, and two patients died as a result of the infections. Furthermore, preprocedural bowel preparation or administration of antibiotic prophylaxis were not found to be associated with a lower risk of infection, unlike reductions seen in similar groups of patients who were treated with TACE (3,8,12). Despite this, the two deaths in our cohort occurred in patients who did not receive bowel preparation or antibiotic prophylaxis.

Table 4: Results of the Univariable Analyses

Variable	HR	*P* Value
Demographic characteristics		
Age	0.93 (0.88, 0.97)	.001
Female sex	1.75 (0.47, 6.52)	.40
Clinical parameters		
Biliary-enteric anastomosis	2.00 (0.48, 8.37)	.34
Neuroendocrine tumor	2.66 (0.69, 10.17)	.15
ECOG performance status >0	0.60 (0.15, 2.39)	.47
>25% liver replaced with tumor	0.40 (0.10, 1.59)	.20
Concurrent chemotherapy	0.59 (0.078, 4.43)	.60
Prior resection	6.90 (1.69, 28.13)	.007
Laboratory parameters		
Total bilirubin level	0.69 (0.15, 3.18)	.63
Aspartate aminotransferase level	1.00 (0.95, 1.04)	.86
Alanine aminotransferase level	1.00 (0.96, 1.03)	.87
Alkaline phosphatase level	1.00 (0.99, 1.00)	.24
White blood cell count	1.06 (0.87, 1.28)	.55
Platelet count	1.00 (0.99, 1.00)	.49
International normalized ratio for prothrombin time	0.0006 (0.0001, 0.46)	.03
Creatinine level	0.98 (0.96, 1.01)	.26
Technical parameters		
Glass microspheres	5.73 (1.17, 28.13)	.03
Delivered activity	1.37 (1.04, 1.80)	.02
Absorbed dose	0.99 (0.98, 1.01)	.64
Whole liver treatment	0.70 (0.092, 5.86)	.77
Antibiotic prophylaxis	1.50 (0.28, 8.02)	.63
Bowel preparation	0.704 (0.088, 6.34)	.79

Note.—Numbers in parentheses are 95% confidence intervals. ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio.

In our study, the use of ^{90}Y glass microspheres was associated with a 6.9 times higher odds of hepatobiliary infection compared with the use of ^{90}Y resin microspheres. This difference may be related to the typically higher radiation doses delivered during TARE with glass microspheres (due to difference in radiation dosimetry models used for resin and glass microspheres) as well as due to higher activity carried by the individual ^{90}Y glass microsphere particles. At the time of calibration, the average individual activity of ^{90}Y glass microspheres is 2500 Bq, 50-fold higher than the average individual activity of ^{90}Y resin microspheres (50 Bq) (13). Furthermore, glass microspheres are smaller in diameter compared with resin microspheres, which may result in more distal deposition of glass microspheres and, therefore, in a greater ischemic potential. Deposition of microspheres with higher activity and smaller

size in the vicinity of bile ducts may make biliary epithelium more susceptible to necrosis, thus predisposing patients to translocation of bacteria from the colonized biliary tract into the liver parenchyma and into the bloodstream.

Our study has several limitations. First, this was a retrospective study, and the reported data were limited to the information contained in the medical records obtained as a part of routine medical care. Second, due to the multisite nature of our study, the clinical approaches to TARE with respect to volume of target liver tissue, choice of radioembolization agent, and dosimetry were specific to the investigator. Third, the antibiotic prophylaxis and bowel preparation regimens varied widely between the individual institutions. Fourth, despite the large sample size, the low rate of infectious complications and heterogeneity of antibiotic prophylaxis and bowel preparation regimens may have limited statistical assessment of the protective role of antibiotic prophylaxis and bowel preparation before TARE.

In patients with a liver malignancy and a history of biliary intervention who undergo TARE with ^{90}Y microspheres, infectious complications and morbidities such as liver abscess and cholangitis occur but are uncommon. Therefore, the relative risks and benefits of TARE for patients with previous biliary tract interventions should be carefully weighed before proceeding with TARE treatment. Further multicenter prospective evaluation with a larger cohort is required to make recommendations regarding an optimal periprocedure antibiotic regimen and the potential role of preprocedure bowel preparation.

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