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CLINICAL INVESTIGATION

Root Cause Analysis of Gastroduodenal Ulceration After Yttrium-90 Radioembolization

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Abstract
Introduction A root cause analysis was performed on the occurrence of gastroduodenal ulceration after hepatic radioembolization (RE). We aimed to identify the risk factors in the treated population and to determine the specific mechanism of nontarget RE in individual cases.
Methods The records of 247 consecutive patients treated with yttrium-90 RE for primary ($n = 90$) or metastatic ($n = 157$) liver cancer using either resin ($n = 181$) or glass ($n = 66$) microspheres were reviewed. All patients who developed a biopsy-proven microsphere-induced gastroduodenal ulcer were identified. Univariate and multivariate analyses were performed on baseline parameters and procedural data to determine possible risk factors in the total population. Individual cases were analyzed to ascertain the specific cause, including identification of the culprit vessel(s) leading to extrahepatic deposition of the microspheres.
Results Eight patients (3.2 %) developed a gastroduodenal ulcer. Stasis during injection was the strongest independent risk factor ($p = 0.004$), followed by distal origin of the gastroduodenal artery ($p = 0.004$), young age ($p = 0.040$), and proximal injection of the microspheres ($p = 0.043$). Prolonged administrations, pain during administration, whole liver treatment, and use of resin microspheres also showed interrelated trends in multivariate analysis. Retrospective review of intraprocedural and postprocedural imaging showed a probable or possible culprit vessel, each a tiny complex collateral vessel, in seven patients.
Conclusion Proximal administrations and those resulting in stasis of flow presented increased risk for gastroduodenal ulceration. Patients who had undergone bevacizumab therapy were at high risk for developing stasis.

Keywords Radioembolization/Radioembolisation · Liver/Hepatic · Interventional Oncology · ulcer

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Introduction

Radiation-induced gastroduodenal ulceration is perhaps the most common serious complication of yttrium-90 (^{90}Y) hepatic radioembolization (RE). It is generally caused by nontarget microsphere distribution, which is attributable to unrecognized hepaticoenteric or collateral splanchnic arterial circulation. The pathogenesis of ulceration is predominantly direct radiation injury from the pure beta radiation and has a component of ischaemia after mechanical occlusion of arterioles by the 30-μm microspheres [1–4]. Symptoms, including pain, nausea,

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vomiting, anorexia, and hemorrhage, usually start hours to days after RE but may appear as late as 9 months later. Definitive diagnosis requires identification of microspheres in endoscopic ulcer biopsy specimens. Ulcers may be refractory to acid suppression, and symptoms may persist for months or years and/or require surgical excision [5]. The reported incidence is approximately 8 % in large studies [6], but a large variation in reported incidences exists across the published literature (0 to >20 %) due to variations in techniques, methodology, imaging, follow-up, and reporting [2]. Multidisciplinary consensus has been published on the recommended techniques, imaging protocols and interpretation, and reporting standards for complications [7–11].

To avoid gastrointestinal complications, all hepaticoenteric anastomotic vessels, including the gastroduodenal artery (GDA) and the right gastric artery (RGA), may be coil embolized [9]. This is especially advocated for resin microspheres (SIR-Spheres; Sirtex Medical Limited, Lane Cove, Australia), which are more embolic than glass microspheres (TheraSphere; Nordion, Ottawa, Canada). During pretreatment preparatory angiography, the hepatic artery may be "skeletonised" by elimination of all branches leading to extrahepatic viscera. The anticipated distribution of microspheres is characterized by contrast-enhanced imaging (digital subtraction angiography [DSA] and cone beam C-arm computed tomography [CACT]) and also by scintigraphy after intra-arterial administration of technetium-99m–macroaggregated albumin (^{99m}Tc-MAA). In addition, during infusion of the more embolic resin microspheres, iterative angiography is performed to monitor for any changes in flow dynamics, such as stasis or reflux. In severe cases of stasis, complete administration of the prescribed dose may be impossible.

Despite these precautionary efforts, radiation-induced gastroduodenal ulceration still occurs due to a variety of factors, including incomplete delineation of vascular anatomy, unpredictable vascular physiology, imperfect technique, and/or lack of compliance with existing recommendations [2]. Consensus recommendations also continue to evolve and are likely still imperfect. Previous studies of radiation-induced gastroduodenal ulceration have prompted anecdotal observations and recommendations for prevention, which are in need of validation [4, 5]. Rigorous studies that may identify risk factors leading to radiation-induced gastroduodenal ulceration are therefore imperative to protect patients from this chronic, difficult-to-treat complication, and should ultimately improve our daily practice.

The aim of the present study was to use a large, prospectively maintained database to perform a risk assessment for the occurrence of radiation-induced gastroduodenal ulceration by evaluating baseline and procedural characteristics and to perform a root cause analysis of each individual case of gastroduodenal ulceration.

Materials and Methods

Patient Selection

Between June 2004 and September 2011, 247 consecutive patients (143 men, 104 women; median age 62 years [range 20 to 92]) underwent RE at our institution. Baseline characteristics are listed in Table 1. Baseline, procedural, and follow-up data were collected on all 247 patients as standard of care. This study was a retrospective analysis of all prospectively collected data. Data were processed and analyzed in accordance with the Health Insurance Portability and Accountability Act, and the study was approved by our Institutional Review Board.

Imaging

During initial vascular mapping, DSA images were obtained with a 5F catheter placed in the common (CHA) or proper hepatic artery (PHA) to administer power injection of contrast medium (Omnipaque 300 or Visipaque 320; GE Health Care, Princeton, NJ) at a rate sufficient to result in reflux. Subselective DSA images were obtained using microcatheters in all vessels potentially perfusing extrahepatic tissue and in need of prophylactic embolization. The gastroduodenal and right gastric arteries were coil embolized in all patients. Additional coiling of common or proper hepatic side branches, such as supraduodenal (SDA), retroduodenal, or falciform arteries, was performed when necessary. Since 2006, CACT was used as an adjunct to DSA when end-organ tissue perfusion or vascular anatomy was unclear. In addition, CACT was performed to delineate the vascular territory served by the planned catheter placement and, therefore, to predict distribution of the microspheres [12]. After CACT, the patients underwent ^{99m}Tc-MAA intra-arterial administration, followed by whole-body planar images and upper abdominal single photon emission computed tomography (SPECT) to estimate the hepatopulmonary shunt, to demonstrate intrahepatic perfusion of the tumors, and to evaluate for any extrahepatic deposition of the radiopharmaceutical suggestive of collateral flow.

At the subsequent administration session, all patients underwent confirmatory DSA and CACT studies to evaluate for any interim changes in perfusion before administration of the microspheres. If any extrahepatic perfusion was detected on planar or SPECT images or on confirmatory DSA or CACT, additional coil embolization or catheter repositioning was performed until imaging showed no evidence of persistent extrahepatic enhancement [13].

Table 1 Demographics, baseline characteristics, and oncologic histories of the entire cohort

Characteristic	No. of patients (%)
Sex (male/female)	143/104
Median (range) age (y)	62 (20–92)
Primary tumor (%)	
Colorectal	72 (29.1)
Hepatocellular	64 (25.9)
Neuroendocrine	31 (12.6)
Cholangiocarcinoma[a]	26 (10.5)
Other[b]	54 (21.9)
Microspheres (%)	
Resin	181 (73.3)
Glass	66 (26.7)
Median (range) administered activity (GBq)	1.93 (0.39–14.45)
Treatment (%)	
Whole liver	174 (70.4)
Lobar/segmental only	73 (29.6)
Injection position (%)	
CHA or PHA	101 (40.9)
More distal hepatic artery	146 (59.1)
Previous liver-directed treatment (%)	
Any	113 (45.7)
Transarterial (chemo)embolization	58 (23.5)
Partial liver resection	51 (20.6)
RFA	30 (12.1)
External beam radiotherapy	13 (5.3)
Radioembolization	8 (3.2)
Previous systemic treatment (%)	
Any	173 (70.0)
Chemotherapy[c]	148 (59.9)
Antiangiogenic agents	104 (42.1)
Bevacizumab	80 (32.4)
Sorafenib	24 (9.7)
Anti-EGFR agents	37 (15.0)
ECOG performance status (%)	
0	113 (45.7)
1	117 (47.4)
2	16 (6.5)
3	1 (0.4)

Anti-EGFR agents anti-epidermal growth factor receptor agents

[a] Four patients with mixed type cholangiohepatomas were added to the cholangiocarcinoma group

[b] Uveal melanoma (8 patients); renal cell (7 patient); sarcoma (6 patients); breast (6 patients); pancreatic (4 patients); gallbladder (4 patients); urothelial (4 patients); oesophageal (3 patients); ovarian (3 patients); thymic (2 patients); non–small cell lung (2 patients); cervical (2 patients); Hodgkin's lymphoma (1 patient); small-cell lung (1 patient); unknown primary (1 patient)

[c] Most patients were chemorefractory except those patients with chemo-resistant tumors (hepatocellular and renal cell carcinoma, etc.)

Radioembolization

Dose calculations and treatments were performed in compliance with international consensus guidelines [7–9]. Systemic targeted agents bevacizumab, sorafenib, and anti-epidermal growth factor receptor (EGFR) agents were withheld at least 4 weeks, 3 days, or 1 week before RE treatment, respectively. A detailed technical and nursing procedure log, radiation safety report, radioactivity laboratory log, radionuclide authorized user report, and interventional radiology report were documented in the permanent electronic medical record of every patient. Procedural specifics recorded included timing of events (*i.e.*, total procedure, administration times, etc.); documentation of adverse events, such as pain, nausea, and vomiting; and periprocedural medication use. Archived angiographic images and the interventional radiologist's report provided details on changes in flow dynamics, and the radiation safety report documented the actual delivered radiation activity.

For statistical analysis, stasis was defined as slowing of flow during or at the end of the administration procedure as documented in the physician's report and archived cinematic images. The degree of stasis was defined as follows: grade 0 = no flow abnormalities; grade 1 = minor decrease in pace of flow after full administration of the prescribed dose of microspheres; grade 2 = major decrease (near stasis) of flow after full administration of the prescribed dose of microspheres; grade 3 = periodic stasis of flow during administration, requiring pausing for antegrade flow to resume, but the full prescribed dose of microspheres administered; and grade 4 = stasis of flow during administration to an extent that the full prescribed dose of microspheres could not be delivered.

After delivery of the microspheres, 95 % of patients were discharged within 3 h with a 10-day oral methylprednisolone taper regimen starting at 20 mg/d, a 30-day course of a proton pump inhibitor (PPI [pantoprazole 40 mg daily]), and analgesic and antiemetic agents as needed. Symptoms refractory to PPI therapy were additionally treated with at least 1 week of oral sucralfate. Five percent of patients were hospitalized overnight because of symptoms related to postembolization syndrome (*i.e.* pain, nausea, vomiting) or for management of comorbidities.

Standard follow-up consisted of clinical and laboratory follow-up at 2, 4, 8, and 12 weeks, and at additional intervals prescribed by the medical oncologist thereafter. Patients with severe or persistent gastrointestinal symptoms, including pain, nausea, anorexia, early satiety, or melena, were referred for endoscopic examination. Each ulcer discovered during endoscopic examination was subject to a biopsy. Patients with biopsy-proven microsphere-

induced gastroduodenal ulceration were included in this analysis. Only one biopsy-negative ulceration was encountered at 9 months after treatment in a patient with a previous history of peptic ulcer disease, and this patient was not included in the analysis.

Root Cause and Statistical Analyses

A root cause analysis on the occurrence of gastroduodenal ulceration was performed. The DSA, planar/SPECT, and CACT images were retrospectively evaluated to identify the culprit vessel leading to nontarget RE in each individual case in which gastroduodenal ulceration was diagnosed. When a possible culprit vessel was identified, it was matched with the endoscopic report of the location of the ulceration for confirmation.

Multiple pretreatment and procedural variables possibly associated with the occurrence of gastroduodenal ulceration in the RE population were selected. A commercial statistical software package (SPSS for Windows, version 19.0; SPSS, Chicago, IL) was used for data analysis. All continuous variables proved to have a nonnormal distribution (normal probability plots with Kolmogorov–Smirnov test); median and range are presented for these variables. Univariate analysis was performed first to test the association with the occurrence of gastroduodenal ulceration. Nonparametric Mann–Whitney test was used for continuous variables, and Fisher exact test was used for categorical variables. Statistically significant variables ($p < 0.05$) were then analysed using multivariate binary logistic regression. A forward stepwise selection method was used for variable entry in the model with a p value of < 0.10 for retention to identify important factors at the 0.05 level of statistical significance. Hosmer–Lemeshow test was used to check goodness-of-fit. A two-sided p value < 0.05 was considered statistically significant.

Results

Of the 247 consecutive patients, a total of 278 RE treatment procedures were performed with glass microspheres in 66 patients (predominantly for hepatocellular carcinoma) and with resin microspheres in the remaining 181 patients (predominantly for bilobar metastatic disease) (Table 1). Whole liver treatment was performed in 174 patients in a single session ($n = 151$ patients) or two-staged sessions ($n = 23$ patients) in patients with poor performance status (Eastern Cooperative Oncology Group [ECOG] 1 or 2). Seventy-three patients underwent single lobe or segmental treatment only, and 8 patients underwent treatment to the same target volume twice. The median interval between pretreatment vascular mapping and actual microsphere administration was 11 days (range 1 to 125). Median time for injection of microspheres was 18 min (range 4 to 92). In some patients with grade 4 stasis in whom not all of the prescribed dose could be injected, intra-arterial glycerol trinitrate (GTN) was used to facilitate the injection (7 patients [2.8 %]). Pain during the injection of microspheres was experienced by 48 patients (19.4 %) and was usually described as dull pain in the right upper quadrant or sharp pain in the mid-chest that worsened during injection of the microspheres. The pain was relieved by fentanyl in most cases and resolved before transfer to the recovery room. Stasis during the injection of the microspheres was noted in 30 patients (12.1 %), all of whom were treated with resin microspheres.

Eight patients (3.2 %; three men and five women; median age 52 years [range 33 to 65]) developed biopsy-proven microsphere-induced gastroduodenal ulceration (Table 2). After RE, they had persistent epigastric pain with nausea, vomiting, and dyspepsia that did not respond to medication (pantoprazole [40 mg twice daily] or sucralfate [1 g four times daily]). The onset of symptoms ranged from 0 to 4 months after RE. Initial endoscopies were performed 1 to 6 months after RE (median 2 months) because of persistent symptoms that were refractory to medical management. All biopsy specimens showed an ulcer that was negative for malignancy, helicobacter pylori, and fungus but positive for resin microspheres (Fig. 1). The ulceration was located in the antrum (3 patients), the pylorus (3 patients), or the duodenal bulb (2 patients) (Table 3). The size of the ulceration ranged from 0.5 to 2 cm or was "diffuse" and unmeasured (3 patients). Symptoms persisted a minimum duration of 4 months in some patients, but persisted for > 4 years in others. The ulcer in four patients completely resolved on conservative therapy. One patient experienced recurrent gastric haemorrhage that required multiple transfusions and argon plasma coagulation procedures until death 4.5 months later. Two patients remain PPI-dependent, although their endoscopic examinations showed healed ulcers. In another patient, pyloric stricture developed after healing of the ulceration, thus requiring intermittent dilatation.

These patients who developed ulceration had all been treated with resin microspheres for either metastatic colorectal carcinoma (5 patients), breast carcinoma (1 patient), hemangiopericytoma (1 patients), or neuroendocrine carcinoma (1 patient). Most patients had undergone both systemic and liver-directed treatments, including multiple lines of chemotherapy; targeted agents, including bevacizumab; liver resections; and radiofrequency ablation (RFA) (Table 2). All patients underwent whole liver treatments (median administered dose 1.58 GBq [range 0.99–2.12]), and all but one patient received administration

Table 2 Demographics of patients with gastroduodenal ulceration

Patient no. & sex/age (y)	Cell type	Previous liver-directed treatments	Previous antiangiogenesis agents	Previous anti-EGFR agents	Previous systemic chemotherapy
1 F/46	Metastatic colorectal carcinoma	–	Bevacizumab	–	Yes
2 F/47	Metastatic hemangiopericytoma	Resection, RFA	–	–	–
3 M/62	Metastatic colorectal carcinoma	RFA	Bevacizumab	Cetuximab	Yes
4 M/52	Metastatic colorectal carcinoma	Resection, RFA	Bevacizumab	–	Yes
5 M/52	Metastatic colorectal carcinoma	Resection, RFA	Bevacizumab	–	Yes
6 F/33	Metastatic breast carcinoma	–	Bevacizumab	–	Yes
7 F/52	Metastatic colorectal carcinoma	Resection, RFA	Bevacizumab	Cetuximab	Yes
8 F/65	Metastatic neuroendocrine carcinoma	Resection	–	–	–

Anti-EGFR agents anti-epidermal growth factor receptor agents

Table 3 Clinical characteristics of patients with gastroduodenal ulceration

Patient no. & sex/age (y)	Culprit artery	Ulcer characteristics					Survival (mo)
		Size (cm)	Location	Complications	Onset of symptoms after RE (mo)	Durationof symptoms (mo)	
1 F/46	Accessory RGA identified	2	Antral	Hospitalization	0	5	>58
2 F/47	RGA reconstituted from CA/PDA identified 3 y later	2	Pyloric	–	1	>53	>54
3 M/62	–	1	Pyloric	Stricture	0	>44	>44
4 M/52	SDA suspected	Diffuse	Antral	–	2	>42	>44
5 M/52	SDA suspected	1	Bulb	–	0	6	33
6 F/33	SDA suspected	Diffuse	Anterior gastric wall	Haemorrhage	0	4.5	4.5
7 F/52	SDA suspected	Diffuse	Bulb	–	4	10	14
8 F/65	PDA branch identified	0.5	Pyloric	–	0	4	>15

CA cystic artery; *PDA* pancreaticoduodenal artery

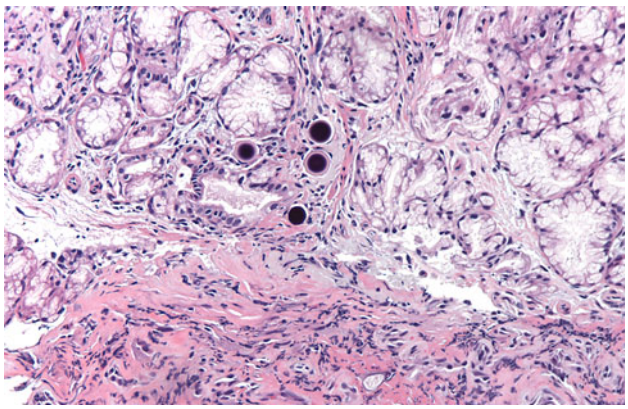

Fig. 1 All biopsy specimens showed an ulcer that was negative for malignancy, helicobacter pylori, and fungus but positive for resin microspheres (dark round corpora aliena [patient no. 2])

from a proximal catheter-tip position (CHA or PHA). Complications during administration of the microspheres were frequent in these eight patients due to high-grade stasis (six of eight patients) and pain (three of eight patients). Although GTN was used in two patients, the total prescribed dose could not be fully delivered in four of the eight patients (Table 4).

In all patients, all visible hepaticoenteric vessels, including at least the GDA and RGA, were coil embolized at the time of preparatory angiography. Vessels that recanalized and collateral vessels that developed by the time of treatment, including pancreaticoduodenal and supraduodenal branches, were coil embolized at the time of treatment angiography (Table 4). Review of the angiographic images showed a specific hepatic arterial anatomic variant in seven of eight patients (87.5 %). A distal origin of the GDA was found either as a trifurcation with the left and right hepatic arteries (LHA and RHA; 5 patients) or as an even more distal origin from the RHA (2 patients). In the total treated population, this distal GDA origin variant had a prevalence of only 31 of 247 patients (12.6 %).

All relevant baseline variables and procedural variables were included in univariate and multivariate risk

Table 4 Treatment characteristics of patients with gastroduodenal ulceration

Patient no. & sex/age (y)	Coiled arteries during preparatory angiography	Coiled arteries during treatment angiography	Treated territory/ artery infused[a]	Administered activity (GBq)	Stasis grade[c]	Prescribed dose injected (%)[d]	Pain at administration	Glycerol trinitrate given
1 F/46	GDA, RGA, FA from MHA	PDA	Whole liver/CHA	0.99	4	75	Yes	Yes
2 F/47	GDA, RGA	SDA	Whole liver/CHA	1.48	0	100	–	–
3 M/62	GDA, RGA, PDA		Whole liver/CHA	1.78	3	100	–	–
4 M/52	GDA, RGA, PDA	SDA	Whole liver/CHA	1.97	4	93	Yes	–
5 M/52	GDA, RGA, PDA, aLHA from LGA, CA	SDA	Whole liver/CHA	1.68	3	100	–	–
6 F/33	GDA, RGA, PDA	SDA	Whole liver/PHA	1.46	4	92	Yes	–
7 F/52	GDA, RGA, PDA, aLHA from LGA	PDA	Whole liver/PHA	2.12	0	100	–	–
8 F/65	GDA, RGA, PDA		Whole liver/LHA[b]	1.04	4	89	–	Yes

[a] FA = falciform artery; aLHA = accessory left hepatic artery

[b] RHA was occluded, with collateral blood supply from the LHA

[c] Grade 0 stasis = no flow abnormalities; grade 1 stasis = slow flow after complete administration; grade 2 stasis = near stasis after complete administration; grade 3 = stasis during injection but administration could be completed; and grade 4 = stasis during injection leading to incomplete administration

[d] Corrected for hepatopulmonary shunt and retained activity in the administration system

assessment (Table 5). Patients who developed ulceration after RE were younger and had undergone liver-directed treatments (resection, RFA) and bevacizumab more frequently. The injection of the microspheres lasted longer, and stasis was encountered more frequently. Out of all significant risk factors, age ($p = 0.040$), proximal injection of the microspheres in the CHA or PHA ($p = 0.043$), distal origin of the GDA ($p = 0.004$), and stasis during injection ($p = 0.004$) proved to be independent risk factors for the development of gastroduodenal ulceration after RE in multivariate analysis.

Gastroduodenal ulceration occurred in 6 of 30 patients (20 %) who had stasis during microsphere administration. Like ulceration, stasis only occurred in patients who were treated with resin microspheres. Because stasis proved to be an important risk factor for ulceration, it was further investigated. Administration procedures that were complicated by stasis (30 patients in total) lasted longer (39 min [range 11 to 76]) *vs.* 16 min [range 4 to 92]; $p < 0.001$) and involved pain during injection more frequently (15 of 30 [50 %] *vs.* 33 of 217 patients (15.2 %); $p < 0.001$). However, procedural pain itself did not correlate with development of ulceration ($p = 0.179$). The grade of stasis was further refined and is listed in Table 6. Greater grade of stasis was associated with longer administration times ($p = 0.002$) because extra time was required between aliquots to allow antegrade flow to resume. In seven patients with grade 4 stasis, GTN was also used to facilitate the administration. Pain and probability of ulceration were not found to be associated with greater grade of stasis even though all six cases of ulceration in the "stasis group" occurred in conjunction with greater grades of stasis. In univariate analysis, stasis was significantly associated with the use of resin microspheres ($p < 0.001$), previous use of bevacizumab ($p < 0.001$), and previous systemic chemotherapy ($p = 0.005$). On multivariate analysis, however, only previous use of bevacizumab proved to be an independent risk factor for stasis ($p = 0.008$).

Patients who were treated with resin microspheres, compared with glass microspheres, had a distinctly different treatment profile. They underwent whole liver treatment more frequently ($p < 0.001$), underwent treatment more frequently from a proximal injection site ($p < 0.001$), and underwent treatment predominantly for metastases ($p < 0.001$). Less activity was administered ($p < 0.001$) with longer administration times ($p < 0.001$) and more pain ($p < 0.001$) and stasis ($p < 0.001$). Although every case of ulceration occurred after treatment with resin microspheres, the use of resin microspheres did not correlate significantly with the occurrence of ulceration in either univariate or multivariate analysis. In the assessment of stasis, the use of resin microspheres correlated in univariate analysis only because several risk factors were

Table 5 Correlation between baseline variables, procedural data, and gastroduodenal ulceration

Variable	No ulcer	Ulcer	Univariate *p*	Multivariate *p*
Sex (male/female)	140/99	3/5	0.287	
Age (y)[a]	62 (20–92)	52 (33–65)	**0.013**	**.040**
Liver tumor (%)			0.054	
Primary[b]	90 (37.7)	0 (0)		
Secondary[b]	149 (62.3)	8 (100)		
Microspheres (%)			0.113	
Resin	173 (72.4)	8 (100)		
Glass	66 (27.6)	0 (0)		
Administered activity in GBq[a]	1.92 (0.39–14.45)	1.58 (0.99–2.12)	0.066	
Treatment (%)			0.109	
Whole liver	166 (69.5)	8 (100)		
Lobar/segmental	73 (30.5)	0 (0)		
Injection position (%)			**0.009**	**0.043**
CHA/PHA	94 (39.3)	7 (87.5)		
More distal hepatic artery	145 (60.7)	1 (12.5)		
Distal origin of the GDA (%)	24 (10)	7 (87.5)	**<0.001**	**0.004**
Previous liver-directed treatment (%)				
Any	107 (44.8)	6 (75)	0.147	
Transarterial (chemo)embolization	58 (24.3)	0 (0)	0.204	
Partial liver resection	46 (19.2)	5 (62.5)	**0.011**	0.162
Radiofrequency ablation	25 (10.5)	5 (62.5)	**0.001**	0.190
External beam radiotherapy	12 (5.0)	1 (12.5)	0.355	
Radioembolization	8 (3.3)	0 (0)	1.0	
Previous systemic treatment				
Any	167 (69.9)	6 (75)	1.0	
Chemotherapy	142 (59.4)	6 (75)	0.481	
Antiangiogenesis agents	98 (41)	6 (75)	0.073	
Bevacizumab	74 (31)	6 (75)	**0.015**	0.369
Sorafenib	24 (10)	0 (0)	1.0	
Anti-EGFR agents	35 (14.6)	2 (25)	0.342	
ECOG performance (%)			0.147	
0	107 (44.8)	6 (75)		
1–3	132 (55.2)	2 (25)		
Stasis (%)	24 (10)	6 (75)	**<0.001**	**0.004**
Pain during injection (%)	45 (18.8)	3 (37.5)	0.179	
Injection time in minutes[a]	18 (4–92)	37 (17–51)	**0.004**	0.083
Interval ^{99m}Tc-MAA – ^{90}Y (d)[a]	11 (1–125)	9 (1–80)	0.589	

Bold numbers indicate two-sided significance < 0.05

[a] Median and range are given

[b] Primary liver tumors include hepatocellular and cholangiocarcinomas

interrelated. The use of bevacizumab was strongly correlated to the use of resin microspheres and proved to be a stronger risk factor for stasis than the use of resin microspheres. Bevacizumab was used in 75 of 181 (41.4 %) of patients treated with resin microspheres, mostly in patients with metastatic colorectal carcinoma, and in only 5 of 66 (7.6 %) of patients treated with glass microspheres ($p < 0.001$). Because ulceration only occurred in patients treated with resin microspheres, multivariate subset analysis in that specific cohort yielded the same results.

Individual cases were scrutinized retrospectively to identify the culprit vessel that led to the extrahepatic deposition of microspheres. All pretreatment imaging findings (DSA, ^{99m}Tc-MAA planar/SPECT, CACT) had been prospectively interpreted as being negative for extrahepatic gastrointestinal distribution before treatment.

Table 6 Stasis during RE administration

Stasis grade[a]	Patient number	Median (range) dose injected (%)[b]	Median (range) injection time (min)	No. of patients with pain during injection (%)	No. of patients who received glycerol trinitrate (%)	No. of patients with biopsy proven ulcer (%)
0	217	100	16 (4–92)	32 (15)	0 (0)	2 (1)
1	5	100	20 (11–28)	0 (0)	0 (0)	0 (0)
2	3	100	32 (12–46)	3 (100)	0 (0)	0 (0)
3	5	100	41 (35–59)	2 (40)	0 (0)	2 (40)
4	17	82 (52–93)	44 (15–76)	11 (65)	7 (41)	4 (24)
Total	247	100 (52–100)	18 (4–92)	48 (19)	7 (3)	8 (3)

[a] Grade 0 stasis = no flow abnormalities; grade 1 = slow flow after complete administration; grade 2 stasis = near stasis after complete administration; grade 3 = stasis during injection but complete administration; and grade 4 = stasis during injection leading to incomplete administration

[b] Corrected for hepatopulmonary shunt and retained activity in the administration system

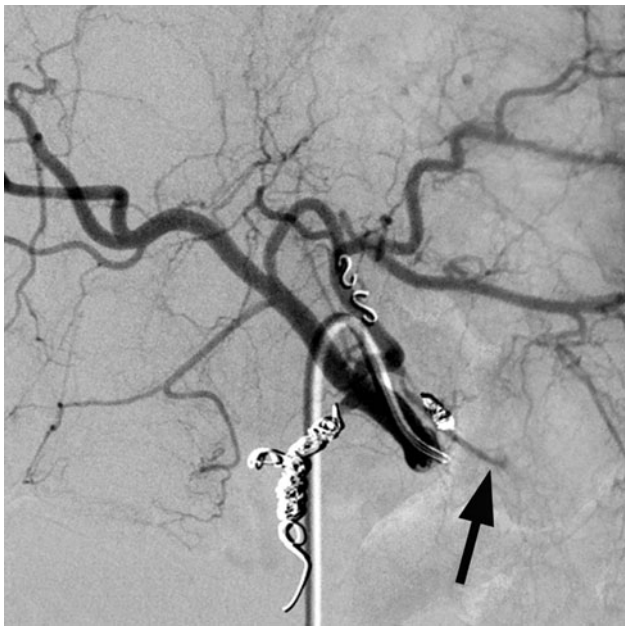

Fig. 2 Accessory RGA originating from proximal LHA reconstituted the distal RGA (*arrow*) as seen on DSA in patient no. 1 [13]. Note trifurcation of CHA into GDA, LHA, and RHA. Stasis and pain were encountered during RE administration, and only 75 % of the prescribed dose could be delivered despite intra-arterial GTN infusion. The patient developed an antral ulcer that healed after 5 months of medical therapy

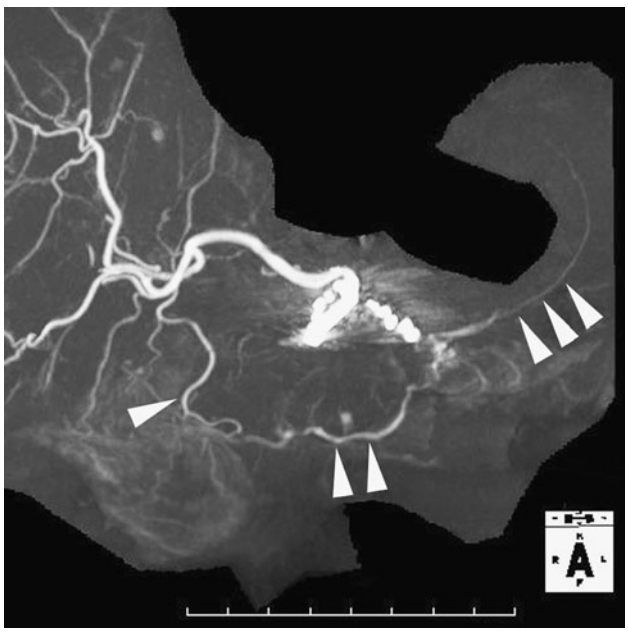

Fig. 3 Angiography performed on patient no. 2 at 38 months after RE during chemoembolization treatment of recurrence showed a supraduodenal branch of the superficial ramus of the CA (*single arrowhead*) supplying collateral flow to reconstitute pancreaticoduodenal branches (*double arrowheads*), which then reconstituted the RGA (*triple arrowheads*), as seen on an oblique thin-slab maximum-intensity projection of CACT performed with injection of contrast into the CHA. Note the metallic artifact from embolization coils in the GDA, PDA, and RGA with no flow distal to the coils. This patient developed a pyloric channel ulcer 8 weeks after treatment and has had intermittent symptoms for 4 years

Retrospective review of the procedural images identified a probable or possible culprit vessel in seven of the eight patients who developed gastroduodenal ulceration (Table 3). In one patient, an accessory RGA originating from the proximal LHA reconstituted the distal RGA as seen on DSA (Fig. 2) [10]. In a second patient, subsequent angiography performed 38 months after RE during chemoembolization showed a supraduodenal branch of the superficial ramus of the cystic artery (CA) supplying collateral flow to reconstitute pancreaticoduodenal branches, which then reconstituted the RGA, as seen on CACT (Fig. 3). In a third patient, a proximal branch of a pancreaticoduodenal artery (PDA) originating from the CHA remained patent after coil embolization (Fig. 4). In three other patients, the evidence was less clear, with possible culprit vessels being small supraduodenal branches found

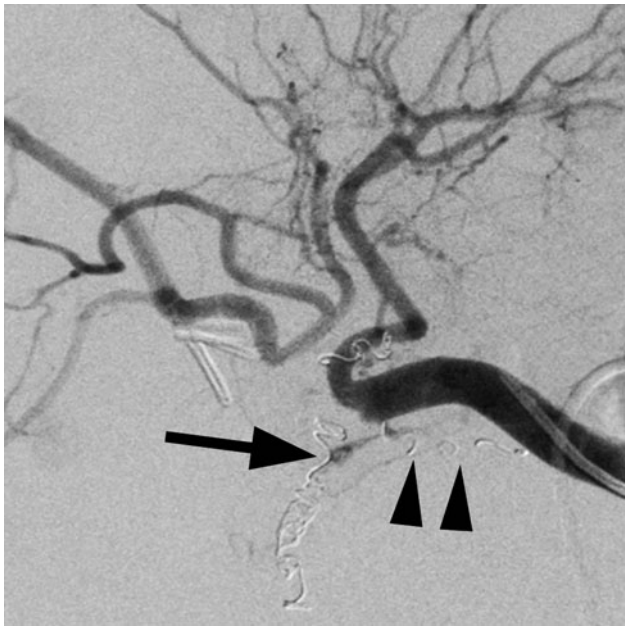

Fig. 4 The GDA and RGA were successfully coil embolized in this patient with an occluded RHA. However, a proximal branch (*arrow*) was incompletely occluded by coil embolization of a pancreaticoduodenal artery originating from the CHA (*arrowheads*). Whole liver treatment was delivered from the LHA, but even after administration of GTN, stasis allowed delivery of only 89 % of the prescribed dose. This patient developed a 5-mm pyloric ulcer that healed after 4 months of medical therapy

retrospectively on DSA only (Fig. 5). In one patient, a supraduodenal artery arising from the CA was not successfully coil embolized (extrahepatic ^{99m}Tc-MAA was noted on scintigraphy) because of a dissection of the right hepatic artery that required a bare stent to re-establish flow. It was probably only partially excluded using a balloon-expandable stent-graft (iCAST, Atrium Medical, Hudson, NH), and likely allowed hepatofugal deposition of microspheres (Fig. 6). In one patient, no evidence of hepaticoenteric communications was found whatsoever.

Discussion

The root cause analysis performed uncovered several factors associated with increased risk for development of gastroduodenal ulceration after RE. These included young age, proximal administration site, distal origin of the GDA, past surgical resection or RFA, previous exposure to bevacizumab, prolonged microsphere administration time, and stasis of flow during administration. Reflecting on interrelations of these factors, only stasis, proximal administration site, distal origin of the GDA, and young age proved to be independent risk factors by multivariate analysis. Despite the fact that ulceration after RE only occurred after the use of resin microspheres in our cohort, this did not prove to be a statistically significant independent risk factor.

Two proposed mechanisms of nontarget deposition of microspheres may lead to gastroduodenal ulceration after RE. The first is a series of events leading to stasis of blood flow in the distal hepatic arteries, causing retrograde flow of microspheres in the proximal hepatic artery and reflux into hepaticoenteric branches proximal to the catheter tip. This is only known to occur with resin microspheres. The second mechanism is antegrade flow of microspheres into unrecognized hepaticoenteric branches distal to the site of administration. To limit the occurrence of both mechanisms, the hepatic artery is usually "skeletonised," especially before treatment with resin microspheres, by coil embolizing recognized hepaticoenteric communications, such as the GDA and RGA. However, in the case of resin microspheres, stasis during administration can still result in reflux, possibly into branches further proximal than the GDA and RGA. In addition, hepaticoenteric channels may initially demonstrate hepatopetal flow, which reverses to hepatofugal after intrahepatic resistance increases as a consequence of microsphere-induced stasis and may thus evade angiographic detection. Furthermore, hepaticoenteric vessels, such as an accessory RGA, may be missed despite prophylactic embolization of the GDA and the RGA [13]. In fact, collateral hepaticoenteric channels, many of which are not visible during initial angiography, may actually be induced to hypertrophy after coil embolization of the GDA and RGA and to develop into prominent arterial supply to the gastroduodenal region by the time of the treatment session [14], thus potentially sustaining the risk of nontarget deposition by the first mechanism and increasing the risk of the second mechanism occurring.

A major proportion of these smaller hepaticoenteric vessels originate from the PHA or proximal LHA or RHA and are part of the hilar peribiliary plexus [15]. In the present study, a new and interesting observation was made that the majority of patients who had ulcerations exhibited a hepatic vascular anatomic variant with a distal origin of the GDA, either as a trifurcation with the LHA and RHA or more distal with an origin from the RHA. The same finding was previously reported in three separate case reports without recognition of its possible importance [16–18]. This variant anatomy proved to be an independent risk factor for the occurrence of gastroduodenal ulceration in univariate and multivariate analysis. It also adds to the argumentation to administer the microspheres selectively. Blood supply to the bile ducts is a network formed by contributions from the GDA, the PHA, the RHA, and the CA. Typically a marginal or SDA connects the GDA to the CA. In the presence of the distal origin of the GDA variant, the PHA is nonexistent and the marginal artery is typically

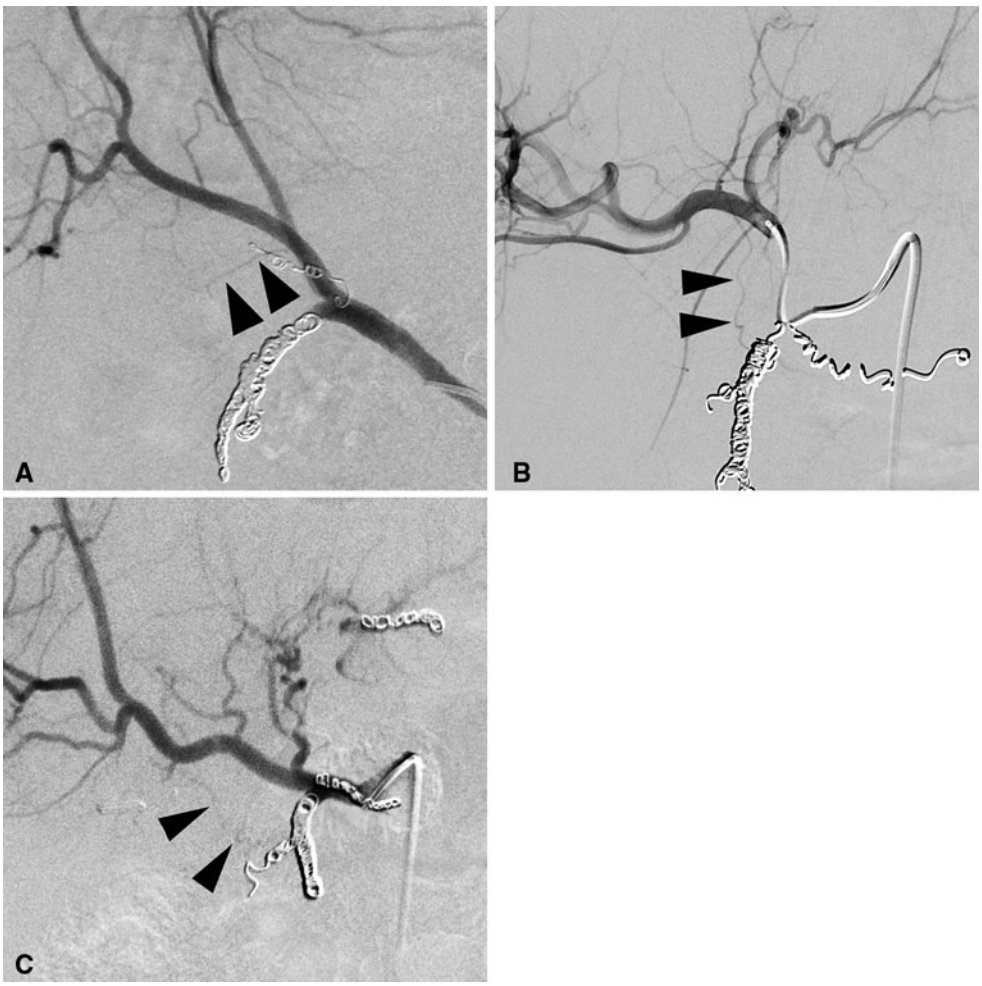

Fig. 5 In 3 patients (**A–C**) the evidence was less clear with possible culprit vessels being small supraduodenal branches (*arrowheads*) found retrospectively on DSA images only. None of these vessels were visible before coil embolization

absent, but extra branches to the bile ducts originate from the RHA [19]. These small contributors may potentially be a source of hepatofugal flow, especially in the case of intrahepatic stasis.

Because proximal injection, stasis, and distal origin of the GDA were found to increase risk of ulceration, a sequential lobar approach with the catheter tip in the more distal LHA and RHA, although possibly increasing the risk of incomplete tumor treatment, should decrease nontarget deposition in branches originating proximally. This was confirmed when extrahepatic distribution of ^{99m}Tc-MAA as discovered by SPECT imaging could be eliminated by moving the microcatheter to a more distal position, even when the culprit vessels could not be identified angiographically [20]. In addition, exclusively administering microspheres distally can result in a high safety profile even without prophylactic coil embolization [21]. In one of our patients who developed an ulcer, however, whole liver treatment distal to the SDA would have required at least five separate administrations or complex redistributive coil embolization [22] because the SDA originated from a segmental RHA. Overall, the findings from our root cause analysis have resulted in changes in our treatment practices to selective administrations only with earlier termination for near-stasis when resin microspheres are used. In addition, we now coil embolize hepaticoenteric vessels only when they are distal in origin to minimize formation of subtle collateralization.

Limitations of the present study include its retrospective design and relatively low number of events (*i.e.*, gastroduodenal ulceration). However, our sample size and completeness of prospective data collection are higher than in any other single-center study reported in literature, whereas the percentage of events is comparable with other studies [2]. A true prospective study design would likely yield much lower absolute numbers, thus making it virtually unfeasible to perform a root cause analysis. Furthermore, endoscopies were performed on patients with persistent

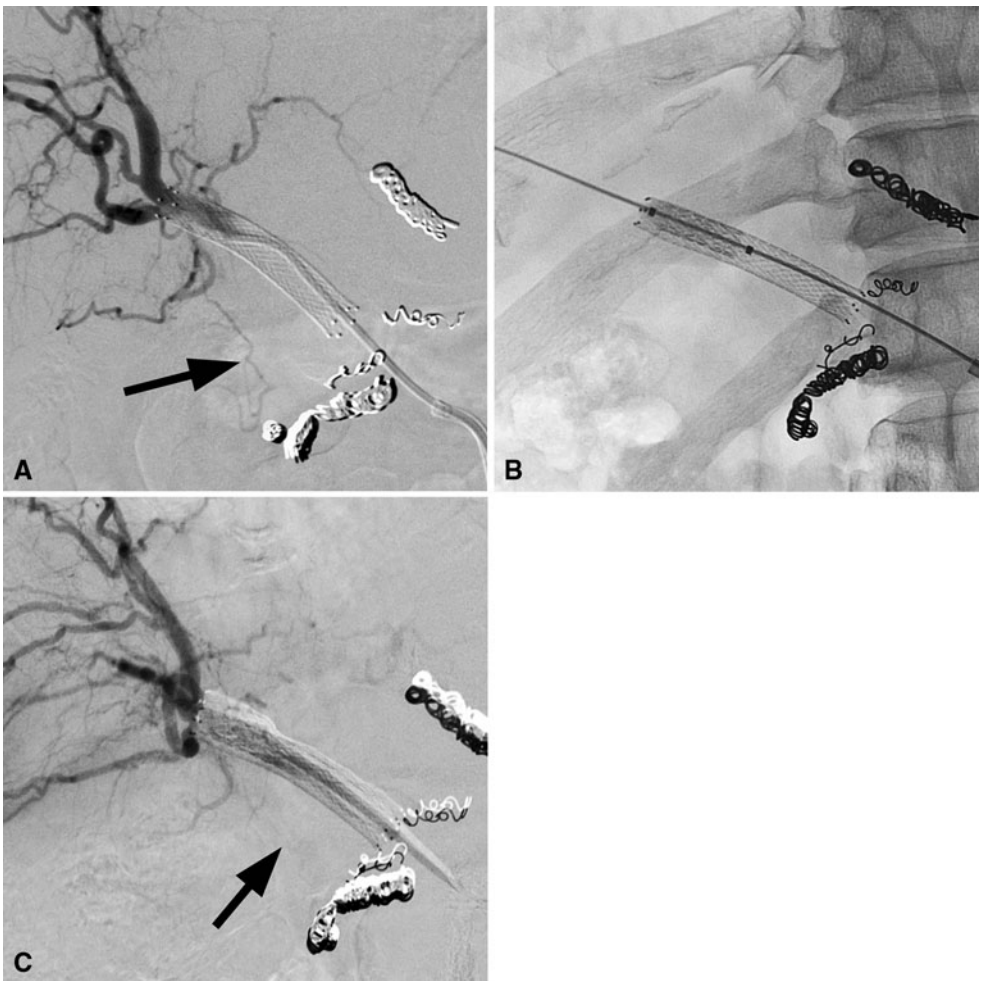

Fig. 6 Patient no. 5 had an iatrogenic dissection of the RHA requiring a bare stent to re-establish flow into distal branches. **A** A supraduodenal branch of the cystic artery was identified before treatment (*arrow*). **B** Because the cystic artery could not be catheterized through the stent interstices, a balloon-expandable stent-graft was deployed to cover its origin. **C** Follow-up angiography showed only a hint of persistent filling of the supraduodenal artery (*arrow*). This patient had a 1-cm duodenal bulb ulcer that healed after 6 months of medical therapy

symptoms only, *i.e.*, prescribed by the treating physician and not on a routine scheduled basis, thus making it likely that some clinically occult nontarget depositions were missed.

In conclusion, the most important root causes identified for the occurrence of gastroduodenal ulceration after RE are related to proximal administration from the CHA or PHA and stasis of hepatic arterial flow during administration. In addition, distal origin of the GDA and previous exposure to bevacizumab are independent risk factors. Skeletonisation by coil embolization of hepaticoenteric anastomoses is not fail-safe and may promote the development of stealthy collateral vessels. To minimize the risk of gastroduodenal ulceration, we conclude that treatments should be performed as selectively as possible to treat the target volume. Patients being treated with resin microspheres who have been exposed to bevacizumab require special attention to flow dynamics during the injection procedure, and a low threshold should be set for suspending administration.

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Conflict-of-interest statement Daniel Sze is on the medical or scientific advisory boards for Surefire Medical, Inc., Treus Medical, Inc., RadGuard Medical, Inc., and Jennerex Biotherapeutics, Inc.; on speaker's bureau for W. L. Gore, Inc.; and is a consultant for Biocompatibles, Inc. and Sirtex, Inc.

References

1. Bilbao JI, de Martino A, de Luis E et al (2009) Biocompatibility, inflammatory response, and recannalization characteristics of nonradioactive resin microspheres: histological findings. Cardiovasc Intervent Radiol 32:727–736
2. Murthy R, Brown DB, Salem R et al (2007) Gastrointestinal complications associated with hepatic arterial yttrium-90 microsphere therapy. J Vasc Interv Radiol 18:553–561
3. Ogawa F, Mino-Kenudson M, Shimizu M et al (2008) Gastroduodenitis associated with yttrium 90-microsphere selective internal radiation: an iatrogenic complication in need of recognition. Arch Pathol Lab Med 132:1734–1738
4. Carretero C, Munoz-Navas M, Betes M et al (2007) Gastroduodenal injury after radioembolization of hepatic tumours. Am J Gastroenterol 102:1216–1220
5. Naymagon S, Warner RR, Patel K et al (2010) Gastroduodenal ulceration associated with radioembolization for the treatment of hepatic tumours: an institutional experience and review of the literature. Dig Dis Sci 55:2450–2458
6. Kennedy AS, Coldwell D, Nutting C et al (2006) Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. Int J Radiat Oncol Biol Physiol 65:412–425
7. Coldwell D, Sangro B, Wasan H et al (2011) General selection criteria of patients for radioembolization of liver tumours: an international working group report. Am J Clin Oncol 34:337–341
8. Dezarn WA, Cessna JT, DeWerd LA et al (2011) Recommendations of the American Association of Physicists in Medicine on dosimetry, imaging, and quality assurance procedures for 90Y microsphere brachytherapy in the treatment of hepatic malignancies. Med Phys 38:4824–4845
9. Kennedy A, Nag S, Salem R et al (2007) Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys 68:13–23
10. Lewandowski RJ, Sato KT, Atassi B et al (2007) Radioembolization with 90Y microspheres: angiographic and technical considerations. Cardiovasc Intervent Radiol 30:571–592
11. Salem R, Lewandowski RJ, Gates VL et al (2011) Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol 22:265–278
12. Louie JD, Kothary N, Kuo WT et al (2009) Incorporating cone-beam CT into the treatment planning for yttrium-90 radioembolization. J Vasc Interv Radiol 20:606–613
13. Meer AB, Louie JD, Abdelmaksoud MH et al (2011) Intrahepatic collateral supply to the previously embolized right gastric artery: a potential pitfall for nontarget radioembolization. J Vasc Interv Radiol 22:575–577
14. Abdelmaksoud MH, Hwang GL, Louie JD et al (2010) Development of new hepaticoenteric collateral pathways after hepatic arterial skeletonization in preparation for yttrium-90 radioembolization. J Vasc Interv Radiol 21:1385–1395
15. Northover JM, Terblanche J (1979) A new look at the arterial supply of the bile duct in man and its surgical implications. Br J Surg 66:379–384
16. Sjoquist KM, Goldstein D, Bester L (2010) A serious complication of selected internal radiation therapy: case report and literature review. Oncologist 15:830–835
17. South CD, Meyer MM, Meis G et al (2008) Yttrium-90 microsphere induced gastrointestinal tract ulceration. World J Surg Oncol 6:93
18. Thamboo TP, Wai CT, Lim LG, Wang SC (2008) Late gastric ulceration and cytomegalovirus infection following selective internal radiation therapy (SIRT) of the liver. Pathology 40:303–305
19. Parke WW, Michels NA, Ghosh GM (1963) Blood supply of the common bile duct. Surg Gynecol Obstet 117:47–55
20. Barentsz MW, Vente MA, Lam MG et al (2011) Technical solutions to ensure safe yttrium-90 radioembolization in patients with initial extrahepatic deposition of (99m)technetium-albumin macroaggregates. Cardiovasc Intervent Radiol 34:1074–1079
21. Hill S, Amesur NB, Zajko AB et al (2012) Reconsidering the necessity for prophylactic embolization of the gastroduodenal artery and right gastric artery prior to radioembolization of the liver with Yttrium-90 microspheres. J Vasc Intervent Radiol 23:S160
22. Bilbao JI, Garrastachu P, Herraiz MJ et al (2010) Safety and efficacy assessment of flow redistribution by occlusion of intrahepatic vessels prior to radioembolization in the treatment of liver tumours. Cardiovasc Intervent Radiol 33:523–531