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Radioembolization with Yttrium-90 Microspheres (SIRT) in Pancreatic Cancer Patients with Liver Metastases: Efficacy, Safety and Prognostic Factors

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Key Words
Liver metastases · Pancreatic cancer · Radioembolization · Yttrium-90

Abstract
Objective: To analyze the clinical efficacy of ^{90}Y radioembolization in liver metastases from pancreatic cancer, to describe treatment toxicities and to identify biomarkers as predictors of outcome. ***Methods:*** Data from 19 pancreatic cancer patients (9 females/10 males) who had received ^{90}Y radioembolization for metastatic liver disease between 06/2004 and 01/2011 were analyzed retrospectively. ***Results:*** The median age at ^{90}Y radioembolization was 63 years (range 43–77). In 16 patients, previous palliative gemcitabine-based chemotherapy was given for metastatic disease. Objective response in the liver after ^{90}Y radioembolization was 47%. Median local progression-free survival in the liver was 3.4 months (range 0.9–45.0). Median overall survival (OS) was 9.0 months (range 0.9–53.0) and 1-year survival was 24%. Cox regression models for baseline biomarkers at ^{90}Y radioembolization revealed correlations of increased carbohydrate antigen 19-9 ($p = 0.02$) and C-reactive protein ($p = 0.03$) with shorter OS. Short-term adverse events (nausea, vomiting, fatigue, fever and abdominal pain) did not exceed grade 3. As long-term adverse events, liver abscesses, gastroduodenal ulceration, cholestasis and cholangitis, ascites and spleen infarction were observed. ***Conclusion:*** ^{90}Y radioembolization is able to induce an encouraging local response rate of liver metastases of pancreatic cancer patients. Most short-term toxicities are manageable; however, patients should be followed up carefully for severe long-term toxicities.

Introduction

Patients with metastatic pancreatic cancer still have limited treatment options and outcome is poor. Gemcitabine remains a backbone in the standard of care for these patients and is able to induce a median overall survival (OS) of about 5–7 months [1]. Erlotinib as a single agent received European Medicine Agency approval for the treatment of metastatic disease in combination with gemcitabine based on a modest improvement in median

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OS of 0.4 months [2]. The promising data of the recently introduced FOLFIRINOX combination chemotherapy regimen showed a median OS of about 11 months; however, novel active treatment options are still needed for this patient population [3].

An interdisciplinary treatment approach to liver metastases including surgery, chemotherapy, radiation therapy and local therapeutic methods such as radiofrequency ablation, chemo- and radioembolization has evolved as a treatment option for several solid tumor entities. Yttrium-90 radioembolization (or selective internal radiation therapy, SIRT) has evolved as a feasible liver-directed therapy in primary liver cancer [4] and hepatic metastases from colorectal cancer [5], neuroendocrine tumors [6–8], cholangiocarcinoma [9, 10], breast cancer [11, 12] and other tumors [13]. Only very little experience exists with ^{90}Y radioembolization for liver metastases of pancreatic cancer patients. The published data are limited to a few cases picked out of a pooled patient cohort with various tumor entities [13–15]. In this article, we report on 19 patients with pancreatic cancer treated with ^{90}Y radioembolization for liver metastases. It is the first analysis that focuses on metastatic pancreatic cancer patients who underwent ^{90}Y radioembolization as a salvage therapy. Systemic pretreatment for pancreatic cancer varied according to tumor stage at first diagnosis and the physician in charge before admission to our center for ^{90}Y radioembolization. However, most of the patients had previously received a standard palliative gemcitabine-based regimen.

Therefore, the aim of the present retrospective single-center study was to analyze the efficacy and safety of liver-directed treatment with SIRT in patients with liver metastases from pancreatic cancer. Response rates, survival data and side effects in this patient cohort were evaluated. Furthermore, clinical characteristics, radiological findings and laboratory tests were examined for prognostic or predictive values influencing response and survival.

Materials and Methods

Patient Selection

The current analysis was a retrospective cohort study of 19 patients with histologically proven exocrine pancreatic cancer and liver metastases who underwent ^{90}Y radioembolization between June 2004 and January 2011 at our university center.

All patients fulfilled the inclusion criteria for ^{90}Y radioembolization [16]: (1) age >18 years; (2) signed informed consent; (3) chemotherapy-refractory pancreatic cancer with liver metastases; patients with limited extrahepatic disease were not excluded if the hepatic metastases were assessed to be the predominant and presumably life-limiting factor and the extrahepatic lesions continued to be stable over the disease course; (4) preserved liver function defined by a serum bilirubin-level ≤2.0 mg/dl and the absence of ascites; (5) ECOG performance status 0–2, and (6) estimated life expectancy >3 months.

Patients were excluded if they had (1) signs of liver failure, e.g. bilirubin-level >2.0 mg/dl or ascites; (2) complete portal vein occlusion, and (3) evidence of excessive hepatopulmonary shunting (>20% in ^{99m}Tc macro-aggregated albumin scan) or angiographically demonstrable and non-occludable gastrointestinal shunting [17].

Irrespective of prior treatment, ^{90}Y radioembolization was administered to all 19 patients as a salvage therapy as liver metastases were considered to be the life-limiting factor for the patients. The indication and the time point for ^{90}Y radioembolization were determined by the patient's oncologist in consultation with an interventional radiologist and an expert from the Department of Nuclear Medicine.

Pretherapeutic Examinations

Before SIRT, all patients underwent imaging examinations with whole-body FDG-PET/CT scan and contrast-enhanced MRI of the liver to assess the extent of metastatic liver infiltration and the presence of extrahepatic disease. For laboratory testing, C-reactive protein (CRP), lactate dehydrogenase (LDH) and the serum tumor markers carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) were determined.

If the patients qualified for ^{90}Y radioembolization up to this point, they received a mapping angiography with visceral catheterization to evaluate their vascular anatomy, the presence of aberrant gastrointestinal vessels and the magnitude of hepatopulmonary shunting. Therefore, approximately 100 MBq of ^{99m}Tc-macro-aggregated albumin were administered to the left and right hepatic arteries in order to estimate the shunt fraction of ^{90}Y microspheres to the lung vasculature. Prophylactic coil embolization of the gastroduodenal artery was performed in all patients (except for those after Whipple surgery); embolization of the right gastric and other extrahepatic arteries was only performed if it was deemed necessary by the interventional radiologist.

Radioembolization Technique

Resin microspheres (SIR spheres®, Sirtex Medical Limited, Sydney, N.S.W., Australia) labeled with the radioactive isotope (^{90}Y) were selectively delivered to the tumor-supplying vessels. Regarding the detailed technical approach, we refer to the just previously published standards of practice in transarterial radioembolization [18]. In our patient cohort, 1.0–2.5 GBq were applied in a single administration of microspheres. The body surface area method was used to determine the dosage [19]. Since pancreatic cancer patients have an increased risk for ascending cholangitis (particularly after Whipple surgery and loss of the papilla function), all patients received peri-interventional antimicrobial prophylaxis with intravenous ciprofloxacin 200 mg on days 1 and 2 and oral ciprofloxacin 500 mg on day 3.

Response and Safety Assessment

The first follow-up visit was scheduled 3 months after ^{90}Y radioembolization and included physical examination, laboratory tests (tumor markers, CRP and LDH), FDG-PET/CT and MRI of the liver. Radiological tumor response was assessed using standard

RECIST criteria (version 1.0) on the MRI and CT scans [20]. Metabolic response was assessed by FDG-PET. The maximum standardized uptake value was used for PET-based assessment of metabolic response and patients with a decline >30% were judged as responders [21]. Further follow-up visits including the abovementioned examinations were scheduled every 3 months in survivors. All adverse effects were graded using Common Terminology Criteria for Adverse Events (CTC-AE) developed by the National Cancer Institute (version 4.0).

Statistical Analysis

Data were summarized by adequate measures of location and spread for continuous variables and by proportions for discrete variables, e.g. response rates. Survival probabilities for OS and (local and systemic) progression-free survival (PFS) were assessed by the Kaplan-Meier method. All time-to-event data were calculated starting from the day of SIRT until the day of documented disease progression or death (or in case of censoring the date of last contact with the patient). Univariate Cox proportional hazard models were used to explore the impact of independent variables on OS and PFS. Tumor and serum markers are considered as continuous covariates so that there is no loss of information due to dichotomization. For such a model, the hazard ratio (HR), its 95% confidence interval (CI) and the (two-sided) p value resulting from the Wald test are reported. Due to the large number of tests performed, p values are reported rather than tests performed with adjustment for multiple testing at the 0.05 level of statistical significance. All statistical analyses were conducted with the statistical software R (version 2.13.2).

Results

Patient and Tumor Characteristics

Baseline patient demographics and tumor characteristics are summarized in table 1. According to the primary tumor location, 15 patients (79.0%) underwent Whipple surgery or left-sided pancreatic resection with curative intent or for exploratory reason (classified as probably resectable on the basis of radiological imaging). Four patients (21.0%) were classified as nonresectable at the time of the fist diagnosis due to radiologically visible metastatic disease. After surgery, 9 patients (47.4%) received adjuvant chemotherapy (1 patient in combination with radiotherapy). One single patient underwent neoadjuvant chemoradiotherapy with gemcitabine and cisplatin. For metastatic disease, 16 patients (84.2%) were treated with palliative chemotherapy: 8 patients (42.1%) with gemcitabine alone and 6 patients (31.6%) with gemcitabine and erlotinib. Two patients (10.5%) received other than gemcitabine-based chemotherapeutic regimens or experimental treatments, as specified in the legend of table 1. Three patients (15.8%) did not receive any previous systemic therapy for metastatic disease before SIRT [22].

Table 1. Baseline patient and tumor characteristics, prior surgical procedures and systemic treatments before ^{90}Y radioembolization (n = 19)

Characteristics	n	%
Sex		
Male	10	52.6
Female	9	47.4
Age at radioembolization, years		
Median	62.9	
Range	43–77	
Primary tumor site		
Head and papilla	12	63.2
Body and tail	7	36.8
Prior pancreatic surgery		
Whipple surgery[a]	11	57.9
Left-sided pancreatic resection[b]	4	21.0
No surgery	4	21.0
Adjuvant chemotherapy		
Yes	9	47.4
No	10	52.6
Liver metastases		
Synchronous	9	47.4
Metachronous	10	52.6
Metastatic sites at the time of radioembolization		
Liver only	7	36.8
Liver predominant[c]	12	63.2
One liver lobe	5	26.3
Both liver lobes	14	73.7
Prior palliative chemotherapy before radioembolization		
Yes	16	84.2
Gemcitabine	8	42.1
Gemcitabine and erlotinib	6	31.6
Other[d]	2	10.5
No	3	15.8
Prior radiation of the primary tumor site		
Yes	2	10.5
No	15	79.0
Unknown	1	5.3

[a] Curative: 8 patients (42.1%), exploratory: 3 patients (15.8%).
[b] Curative and exploratory: 2 patients (10.5%), respectively.
[c] Extrahepatic metastasis: bone: 2 patients (10.5%), lung: 1 patient (5.3%), peritoneal carcinosis: 5 patients (26.3%), spleen and lienal vein infiltration: 3 patients (15.8%), lymph nodes: 12 patients (63.2%, regional and distant lymph node: 6 patients each, 31.6% each).
[d] Other: FOLFIRINOX, vaccination, XELIRI + bevacizumab, gemcitabine/oxaliplatin.

Survival Data and Efficacy

Survival data were available in all 19 patients. The median OS, calculated from the time point of ^{90}Y radioembolization, was 9.0 months (range 0.9–53.0; fig. 1a); the 1-year survival rate was 24.0%. A total of 15 patients died

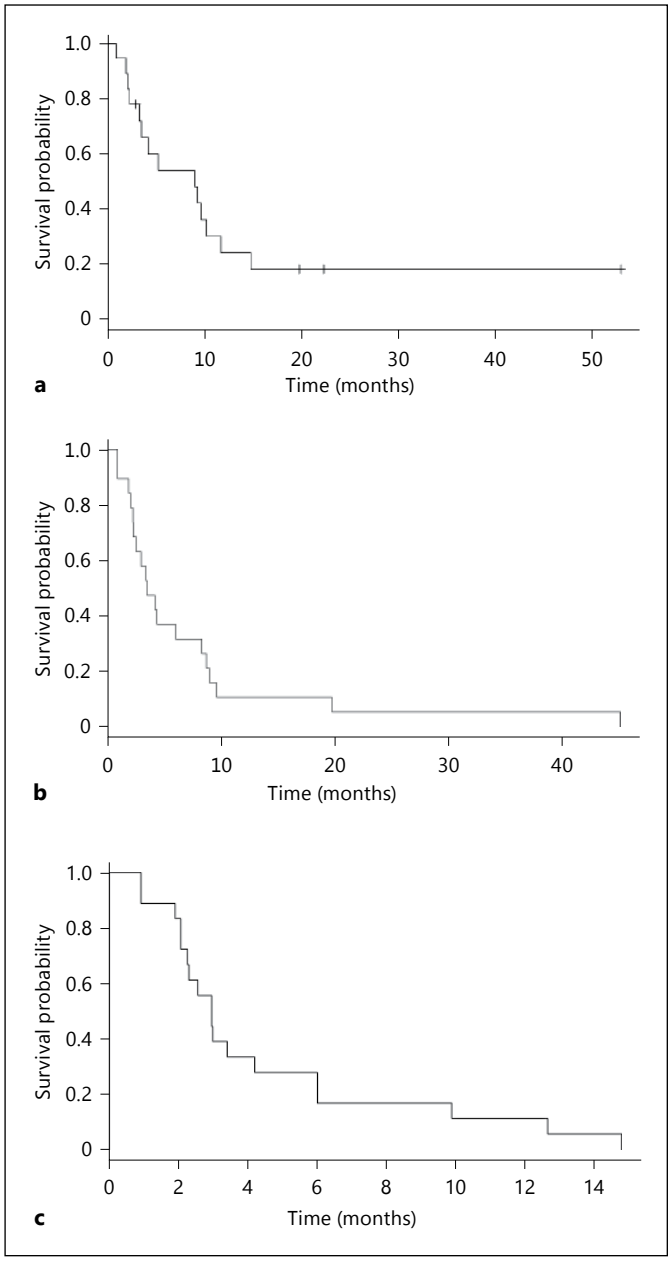


Fig. 1. a Kaplan-Meier plots of OS following radioembolization with ^{90}Y resin microspheres in pancreatic cancer patients with liver metastasis. **b**, **c** Kaplan-Meier plots of the study cohort after radioembolization for PFS in the liver (**b**; local) and systemically regarding all tumor manifestations (**c**; systemic).

during the observation period. Thirteen of the 19 study patients were evaluable for objective response assessment by imaging (using MRI and FDG-PET/CT according to RECIST) after a median follow-up of 2.6 months for the first radiologic assessment (range 2.1–4.4; table 2a). Five patients died before the first follow-up assessment. In 1 patient, the radiological assessment was omitted due to clinical suspicion of cancer progression; the patient died 1 month later. The local overall response rate in the liver was 47% (95% CI: 0.25–0.70). However, new extrahepatic tumor manifestations evolved after ^{90}Y radioembolization in several patients (table 2). Further analysis revealed a median PFS in the liver (PFS local) of 3.4 months (range 0.9–45.0) and a median systemic PFS regarding all metastatic manifestations (PFS systemic) of 2.6 months (range 0.9–14.8; table 3; fig. 1b, c). No stable disease was recorded.

Three patients showed an outstanding long OS after ^{90}Y radioembolization, namely 20, 22 and 53 months.

Table 2. Response evaluation of lesions in the liver by RECIST and evaluation of extrahepatic metastatic disease after a median follow-up of 2.6 months (range 2.1–4.4)

a Six patients (Nos. 3, 7, 14, 16, 18, 19) were excluded due to death before the first follow-up assessment or loss to follow-up

Patient No.	Response: liver	New extrahepatic lesions	Overall tumor response
1, 2, 11, 13	PR	no	PR
4	PD	no	PD
5, 8, 9, 12, 15	PR	yes	PD
6, 10, 17	PD	yes	PD

b Summary of response rates: liver and extrahepatic metastases

Response at first follow-up (after median 2.6 months) (n = 13/19)	Response: liver		Response: systemic	
	n	%	n	%
PR	9	64.3	4	35.7
SD	0	0	0	0
PD	4	35.7	9	64.3

PR = Partial response; SD = stable disease; PD = progressive disease.

Table 3. Median (range) time after ^{90}Y radioembolization and initial diagnosis: OS and PFS in the liver (local) and at all disease sites (systemic)

	Time, months	
	radioembolization	initial diagnosis
OS	9.0 (0.9–53.0)	18.9 (4.8–79.0)
PFS (local)	3.4 (0.9–45.0)	
PFS (systemic)	2.6 (0.9–14.8)	

Table 4. Univariate Cox proportional hazard modeling: OS and PFS (local and systemic) by patient and tumor characteristics, radiological findings and laboratory values

Variable	OS				PFS (local)				PFS (systemic)			
	n	HR	95% CI	p	n	HR	95% CI	p	n	HR	95% CI	p
Sex	19	0.79	0.275–2.288	0.668	19	1.04	0.412–2.648	0.927	18	1.57	0.583–4.258	0.371
At initial diagnosis												
Age	19	1.00	0.932–1.080	0.932	19	1.00	0.939–1.075	0.897	18	1.02	0.953–1.090	0.575
Tumor size (TNM)	19	4.45	0.567–34.84	0.156	19	1.04	0.291–3.722	0.950	18	2.80	0.629–12.50	0.176
Grading	18	1.07	0.369–3.081	0.905	18	0.58	0.196–1.693	0.316	17	1.64	0.580–4.620	0.352
Synchronous metastasis	19	1.34	0.453–3.986	0.595	19	0.92	0.360–2.352	0.862	18	1.60	0.592–4.333	0.353
At radioembolization												
Age	19	0.99	0.923–1.065	0.821	19	1.00	0.934–1.067	0.958	18	1.01	0.948–1.081	0.707
Liver-only metastasis	18	2.92	0.343–0.912	**0.071**	18	1.97	0.719–5.394	0.188	17	2.48	0.849–7.266	**0.097**
Prior surgery of primary	19	0.59	0.123–2.826	0.508	19	0.35	0.105–1.148	**0.083**	18	0.51	0.162–1.626	0.257
Tumor and serum markers												
CEA	18	1.32	0.934–1.877	0.115	18	1.14	0.830–1.558	0.425	17	1.18	0.881–1.576	0.270
CA 19-9	18	1.40	1.062–1.836	**0.017**	18	1.17	0.968–1.408	0.105	17	1.11	0.923–1.346	0.261
CRP	19	1.71	1.066–2.757	**0.026**	19	1.41	0.942–2.104	**0.095**	18	1.39	0.974–1.988	**0.069**
LDH	18	1.06	0.212–5.280	0.945	18	1.12	0.288–4.355	0.870	17	0.87	0.232–3.262	0.835

p values <0.10 are printed in bold. The numbers of patients listed correspond to the numbers of observations of 19 (rest deleted due to missing data).

In 1 of these patients, radiological follow-up investigations confirmed the disappearance of all hepatic tumor manifestations and the patient is currently still doing well without evidence of disease. In the 2 other patients, ^{90}Y radioembolization led to a long-standing reduction in tumor growth and metabolism before local tumor progression and distant recurrence.

Survival and Response by Baseline Characteristics – Univariate Cox Model

Several patient and tumor characteristics, and radiological and laboratory findings were analyzed regarding their prognostic value for OS and PFS (table 4). The following variables were included: sex, age, tumor size, tumor grading and metastatic pattern at initial diagnosis of pancreatic cancer; age and metastatic pattern at the time of ^{90}Y radioembolization, prior surgery of the primary cancer and levels of the serum and tumor markers CEA, CA 19-9, LDH and CRP. Univariate Cox analysis revealed a significant correlation of elevated baseline CA 19-9 (p = 0.02; HR 1.40, 95% CI: 1.06–1.84) and CRP (p = 0.03; HR 1.71, 95% CI: 1.07–2.76) with shorter OS after ^{90}Y radioembolization, but no significant correlation for pretreatment CEA (p = 0.12; HR 1.32, 95% CI: 0.93–1.88) and LDH levels (p = 0.95; HR 1.06, 95% CI: 0.21–5.28). Patients with metastasis limited to the liver showed a longer OS compared to patients with liver-predominant metastasis (p = 0.07; HR 2.9, 95% CI: 0.34–0.91). Patients with metastases confined to the liver and no extrahepatic tumor manifestation were categorized as 'liver only'. Patients were categorized into the 'liver-predominant' group if hepatic metastasis was assessed as a life-limiting factor requiring treatment by the attending physician and extrahepatic metastasis were present but tumor burden was low and stable over the last months. All other variables seem to have no prognostic significance for OS or PFS (local and systemic).

Acute and Delayed Toxicity

Short-term toxicities, including general symptoms such as fever, nausea, vomiting, fatigue and abdominal pain, occurred frequently within the first 10 days after ^{90}Y radioembolization. They were manageable and reversible in all patients and did not exceed CTC-AE grade 3 (table 5).

Long-term toxicities occurred weeks or even months after ^{90}Y radioembolization. 1 patient developed upper gastrointestinal bleeding due to gastric ulceration and needed subsequent gastrectomy. Histopathological ex-

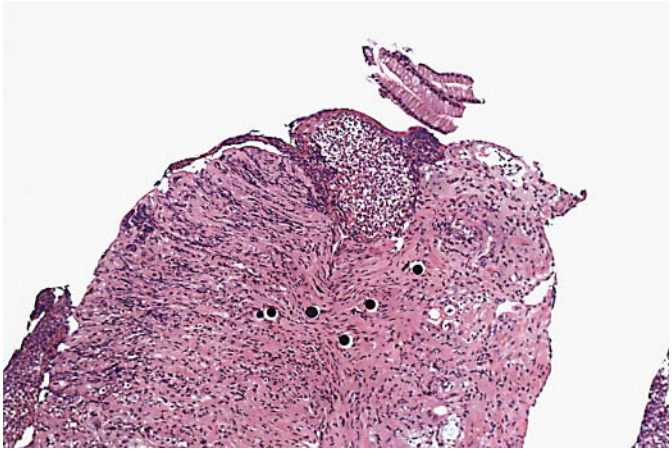
Table 5. Procedure- and radiation-related morbidity after ^{90}Y radioembolization (short- and long-term toxicities)

Toxicities	CTC-AE					
	all grades	grade 1	grade 2	grade 3	grade 4	grade 5
Short term (n = 11/19)						
Fever	11 (100%)	8 (72.7%)	3 (27.3%)	–	–	–
Nausea	11 (100%)	6 (54.5%)	5 (45.5%)	–	–	–
Vomiting	0	–	–	–	–	–
Fatigue	11 (100%)	3 (27.3%)	7 (63.6%)	1 (9.0%)	–	–
Abdominal pain	11 (100%)	3 (27.3%)	8 (72.7%)	–	–	–
Long term (n = 14/19)						
Gastric ulceration	1 (7.1%)	–	–	–	1 (7.1%)	–
Liver abscesses	2 (14.1%)	–	–	1 (7.1%)	–	1 (7.1%)
Cholangitis	1 (7.1%)	–	–	1 (7.1%)	–	–
Ascites	*3 (21.4%)*					
Spleen infarction	*1 (7.1%)*	*1 (7.1%)*	–	–	–	–
RILD	*2 (14.1%)*	–	–	–	–	*2 (14.1%)*

Data were available from 11 and 14 patients, respectively. Possibly related toxicities are italicized.

amination revealed resin microspheres in the gastric wall (fig. 2) and thus suggested radiation-induced gastric ulceration, a known serious complication of ^{90}Y radioembolization [23, 24]. Another 2 patients developed liver abscesses. One of them was successfully treated with intravenous antibiotics after liver puncture and bacterial identification, the other patient died in an external hospital due to infection complications (grade 5 toxicity). In the latter, the suspicion of liver abscesses on ultrasound had been expressed by the physician in charge before the patient died. One patient developed cholangitis due to bile duct stenosis, which was considered a side effect of ^{90}Y radioembolization. In 3 patients, ascites was detected within the first 3 months of follow-up, but its extent and cause were not evaluable in detail. In 1 patient, an asymptomatic spleen infarction was recorded as an incidental finding at the radiological response assessment.

Five patients died before the first follow-up. Three patients might have died from complications after ^{90}Y radioembolization: 1 patient from liver abscesses (see above) and 2 patients from liver failure. In the latter two, the detection of severe ascites and a sharp rise in liver enzymes gave rise to the suspicion of a potential radiation-induced liver disease (RILD). RILD is characterized by anicteric nonmalignant ascites, hepatomegaly and elevation of transaminase and bilirubin levels, and occurs in about 4% after radioembolization [19]. It is the most severe toxicity from microspheres. The body surface area



Color version available online

Fig. 2. Gastric biopsy in macroscopically visible gastric ulceration with histopathological evidence of resin microspheres in the gastric wall (HE, ×10).

approach has shown the lowest incidence of RILD. The risk of RILD rises with the radiation dose administered, but it results from a multifactorial setting and is not simply correlated to the total radiation dose delivered. However, there was no possibility to prove this suspicion and the observed liver failure also could have been attributable to the underlying tumor progression. In 2 patients, no information about cause of death or clinical condition after radioembolization was evaluable due to lacking medical care.

Discussion

A considerable amount of promising data has been published in the last years regarding the use of radioembolization with ^{90}Y microspheres for the treatment of primary liver cancer [4, 25] or liver metastases from colorectal cancer [26, 27], neuroendocrine tumors [7] and other tumors, such as cholangiocellular carcinoma [28] and breast cancer [11]. Up to now, almost no data exist on the use of ^{90}Y radioembolization in pancreatic cancer patients, which explains why no comparable data on survival and response rates, efficacy and toxicity were found in the review of the literature. One study was published by Cao et al. [15], who reported a case series on 7 pancreatic cancer patients of whom 3 had reached a partial response or stable disease.

In the current study, we present the largest series of pancreatic cancer patients who received ^{90}Y radioembolization for metastatic liver disease up to date. Though data were analyzed retrospectively, detailed information about the patients' medical history, previous treatment (including surgery, chemotherapy, radiotherapy and local treatment methods) as well as follow-up data were available for evaluation. In our patient cohort, we observed a median OS of 9.0 months after ^{90}Y radioembolization, which represents an unexpectedly long OS in metastatic pancreatic cancer patients after first-line treatment [29]. Although ^{90}Y radioembolization is a liver-directed treatment option we differentiated local and systemic response evaluation. Both the response rate (overall response rate in the liver 47%) and the local PFS (3.4 months) in our patient cohort revealed a high degree of concordance with those of other tumor entities [7, 11, 12]. However, with respect to extrahepatic tumor manifestations, systemic tumor response evaluation turned out to be significantly worse (table 2).

Therefore, we investigated clinical, radiological and laboratory factors regarding their prognostic and predictive value for response and survival (table 4). Performance status, tumor and serum markers, disease burden and metastatic pattern have been described to be prognostic and predictive factors for survival in pancreatic cancer patients [30]. Furthermore, kinetics of the tumor markers CEA and CA 19-9 as well as the serum parameters CRP and LDH have been closely investigated and reported to have prognostic value for survival after second-line treatment in advanced pancreatic cancer patients recently [31]. In the current SIRT study, we identified the tumor marker CA 19-9 and the serum marker CRP as potential prognostic biomarkers for OS. In addition, patients with metastases limited to the liver showed a tendency to live longer than patients with extrahepatic disease. Interestingly, CEA and LDH were not of prognostic value for OS.

Most experience regarding safety and toxicity of ^{90}Y radioembolization can be derived from studies with hepatocellular carcinoma, colorectal cancer and neuroendocrine carcinoma patients [4, 7, 30]. In general, a differentiation into acute (early or short-term) and chronic (delayed or long-term) toxicities is performed. Acute toxicities are generally reported as procedure-related events and occur 1–14 days after radioembolization [16]. They include general symptoms such as fever, nausea, vomiting, fatigue and abdominal pain, and are often referred to as the postembolization syndrome. Delayed toxicities are considerable radiation-induced complications occurring weeks or months after radioembolization and are frequently caused by unintended deposition of ^{90}Y microspheres into organs other than the liver. Accordingly, radiation damage results in gastric ulceration [23, 24], pneumonitis [32], cholecystitis [33] or pancreatitis. The occurrence of liver abscesses [34] or cholangitis due to bile duct stenosis [35] has been described as a possible complication of ^{90}Y radioembolization. RILD remains a rare but serious adverse event [19, 36, 37].

Our patient cohort presented with a very low incidence of severe acute toxicities (only CTC-AE grades 1 and 2 and only 1 patient with fatigue CTC-AE grade 3), which were all manageable and completely reversible (table 5). However, the frequency and severity of observed long-term toxicities in our patient population was rather unexpected and high. We suspect that long-term toxicities after SIRT are not systemically tracked, potentially misinterpreted as signs of tumor progression and presumably underestimated. We also hypothesize that the rate of delayed toxicities in pancreatic cancer patients may be higher than in other patients receiving ^{90}Y radioembolization. Especially infectious complications such as liver abscesses might occur due to the loss of papilla function after Whipple surgery, which our data, however, could not approve at that point.

Despite limitations of the present study as a retrospective single-center data analysis in a selected patient cohort with different pretreatments and a nonstandardized follow-up, we suggest that ^{90}Y radioembolization may be a reasonable treatment option for hepatic metastases from pancreatic cancer. We showed that increased baseline levels of CA 19-9 and CRP correlate with shorter OS and appear to serve as prognostic factors for survival after ^{90}Y radioembolization. However, further prognostic and predictive factors need to be identified in order to allow better patient selection and improve outcome. In addition to

prognostic factors, the importance of pretreatment, especially Whipple surgery, as risk factors for morbidity and mortality after SIRT remains unclear. In prospectively planned studies, pancreatic cancer patients with liver-only metastases should be selected for radioembolization. CA 19-9 and CRP may serve as valuable selection criteria. Combination with peri-interventional chemotherapy regimens as applied with SIRT in other malignancies should be evaluated. Despite well-tolerable short-term toxicities, long-term toxicities may be severe and concerning. Therefore, systematic and careful follow-up consultations are needed in order to understand especially long-term toxicities in detail.

Disclosure Statement

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