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REVIEW

Current status of transarterial radioembolization

Andreas H Mahnken

Andreas H Mahnken, Department of Diagnostic and Interventional Radiology, University Hospital, Philipps-University, 35043 Marburg, Germany

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Correspondence to: Andreas H Mahnken, MD, MBA, MME, Department of Diagnostic and Interventional Radiology, University Hospital, Philipps-University, Baldingerstrasse, 35043 Marburg, Germany. mahnken@med.uni-marburg.de
Telephone: +49-6421-5866231
Fax: +49-6421-5868959

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Abstract

Unresectable primary and secondary liver malignancies present a major problem in the treatment of solid tumors. Transarterial radioembolization (TARE) is an increasingly used technique for treating various types of malignant liver tumors. This approach is appealing, as the mechanism of action is independent from other loco-regional treatments and potentially complementary to systemic therapies. There are two commercially available products in use for TARE: ^{90}Y-resin and ^{90}Y-glass microspheres. Currently available data indicates TARE so be safe and effective in hepatocellular carcinoma (HCC) and metastatic liver disease. In HCC the results compare well with chemoembolization, while the role of TARE in combination with kinase inhibitors has yet to be established. Current data on TARE in metastatic liver disease is promising, but there is a strong need for prospective randomized trials comparing TARE and modern chemotherapeutic regimen to support the growing role of TARE in metastatic liver disease.

Key words: Hepatocellular carcinoma; Selective internal radiation therapy; Radioembolization; Liver; Neoplasm; Metastasis

Core tip: Transarterial radioembolization (TARE) with ^{90}Y microspheres is a targeted therapy indicated for unresectable primary and secondary liver malignancies. Current data proves its safety and effectiveness, but its definitive role in the treatment of hepatocellular carcinoma and metastatic liver disease within interdisciplinary treatment algorithms is still to be established. There is a strong need for randomized controlled trials comparing TARE to transarterial chemoembolization in primary liver cancer and to modern chemotherapeutic regimen in metastatic liver disease.

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INTRODUCTION

Transarterial radioembolization (TARE) describes a group of treatment options currently in use for the treatment

of primary and secondary liver tumors. Primary and secondary malignant liver neoplasms are common. Hepatocellular carcinoma (HCC) is the most common primary malignant hepatic neoplasm with about 782000 new cases per year, with a particularly high incidence in the Western Pacific Region[1]. In addition, the liver is the most common site for metastases from different solid tumors, most importantly colorectal cancer (CRC). Patients with colorectal liver metastases (CRLM) present a particularly relevant group of patients. With 1361000 estimated new cases of CRC per year and a frequency of 15%-25% of all CRC patients presenting synchronous metastatic disease and one third of patients eventually developing metachronous metastatic liver disease it also is the largest group of potential patients[2-4]. About 20%-30% of patients with metastatic liver disease are thought to be candidates for resection. However, reported resection rates of liver metastases are only around 5%-15%[5,6]. Thus there is a large number of patients in need of alternative therapies.

There are substantial differences in the treatment strategies for primary and secondary malignancies of the liver. While loco-regional treatments are a mainstay in primary liver cancers[7], transcatheter techniques such as conventional or drug-eluting beads transarterial chemoembolization (cTACE/DEB-TACE) are not commonly used in metastatic liver disease. With ^{90}Y-based TARE there is a new and increasingly accepted treatment option for both primary and secondary malignancies to the liver.

The goal of this review is to provide an overview on the current status of TARE. As this is not a systematic review it may contain personal biases of the author.

CONCEPT AND HISTORY OF RADIOEMBOLIZATION

Radiation based tumor treatment is long known and has a clear rationale, as radiation is: (1) known to be cytocidal; and (2) independent from chemical or other energy based ablation techniques. Practically there are some limitations for the use of radiation for the treatment of liver tumors: Most importantly > 70 Gy are needed for the destruction of solid liver tumors[8], whereas the tolerance of normal liver tissue is only about 30 Gy[9]. Thus a selective delivery of radiation is the key for a safe and successful radiation therapy in hepatic malignancies. As all transcatheter techniques aim on a selective delivery of the anticancer treatment, it was an obvious choice to combine transcatheter delivery techniques with radiation based cancer treatments. Consequently the concept of TARE was introduced several decades ago and over time a variety of radioactive substances were used for treatment, particularly 131I-lipiodol[10]. While the term TARE is currently associated with the application of ^{90}Y-microspheres, other radioactive microspheres based on 166 Ho and 188 Re and are under investigation[11,12].

Initial reports on TARE date back to the 1960s, when ^{90}Y microspheres have first been reported for embolizing the prostate gland in dogs. Clinical data from the early days of radioembolization reported its use in inoperable pancreas, liver, lung and bone tumors[13,14]. While initial intravenous applications showed poor outcomes[15], early clinical series with intra-arterial administration of ^{90}Y microspheres *via* the proper hepatic artery reported promising results. It was observed that hypervascularized tumors benefitted most from this type of therapy[16]. Several dose-escalation studies in animals and humans followed these early reports, indicating doses of up to 150 Gy to be safe, if pre-procedural work-up included a pre-treatment angiogram with occlusion of arteries with hepatofugal flow[17,18]. Although early applications of ^{90}Y-TARE were first reported in the mid-1960s it took until the 1990s to establish this technique as a tool in clinical routine.

COMMERCIALLY AVAILABLE DEVICES

Two distinctively different types of ^{90}Y-microspheres are commercially available: (1) SIR-Spheres® (Sirtex Medical Europe, Bonn, G); and (2) TheraSphere® (BTG International, London, United Kingdom) (Table 1). TheraSphere® were approved in 1999 in the United States for the treatment of unresectable HCC, while SIR-Spheres® were approved in 2002 in the United States for treating CRLM. In many countries both products are commercially available, labeled for treating hepatic neoplasms in general. All other products suited for TARE are either investigational or not in clinically relevant use.

INDICATIONS AND CONTRAINDICATIONS

TARE may be considered for the treatment of unresectable primary or secondary liver malignancies or in patients unfit for surgery. There is an increasing amount of data necessitating more differentiated indications.

In general appropriateness of TARE needs to be determined in a multidisciplinary tumor board. Independent from the underlying disease candidates for TARE should have a life expectancy greater than 3 mo, with an Eastern Cooperative Oncology Group (ECOG) status $\leqslant$ 2.

In metastatic liver disease TARE is most commonly used as a salvage therapy in almost any kind of primary tumors. Based on early clinical trials TARE is accepted in CRLM either alone after failure of first-line chemotherapy, as salvage option in combination with 5-fluoruracil (5-FU), leucoverin, oxaliplation or irinotecan. It may also be applied as an adjuvant treatment to first- or second-line chemotherapy ideally within a clinical trial[19-23]. Several ongoing studies are likely to broaden accepted indications for TARE. Only recently the results of the SIRFLOX trial were published, indicating a potential use of TARE in a first line setting[24]. A neoadjuvant indication before resection may also be considered[25].

So far TARE is not yet named in the current treatment recommendations derived from the Barcelona Clinic Liver Cancer (BCLC) staging system. Despite the amount of data on TARE in HCC there is a lack of prospective

Table 1 Characteristics of commercially available ^{90}Y-particles

Feature	SIR-Spheres®	TheraSphere®
Isotope	^{90}Y	^{90}Y
Half life (h)	64.2	64.2
Material	Resin	Glass
Diameter (μm)	20-60	20-30
Activity per particle (Bq)	50	2500
Spheres per 3 GBq	40-80 × 10^6	1.2 × 10^6
Specific Gravity (g/mL)	1.6	3.2
Embolic effect	Mild	Negligible
Contrast injection	During infusion	No
FDA approved indication	CRC liver metastases with intrahepatic floxuridine	HCC

FDA: Food and Drug Administration; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma.

randomized trials comparing TARE with other accepted treatment options such as TACE or sorafenib. Consequently in many institutions TARE is limited to patients who failed TACE. However, TARE may be considered instead of TACE in patients fulfilling the criteria for TACE according to the BCLC staging system[26]. Moreover, TARE should be considered an option in patients with portal vein thrombosis (PVT)[27].

The use of TARE is limited by only few absolute contraindications. These include inadequate functional liver reserve with an elevated total bilirubin > 2.0 mg/dL and reduced albumin < 3 g/dL, pathological lung shunting fraction potentially causing a lung dose of ⩾ 30 Gy in a single application and foreseen non-target embolization that cannot be avoided by adequate transarterial embolization[28]. From an early trial with SIR-spheres® treatment with capecitabine within 3 mo prior to TARE is deemed an absolute contraindication for the use of resin spheres.

Patient preparation and procedural details are described in several practice guidelines[29-31]. These aspects include vascular anatomy of the liver, pre-procedural imaging as well as dosimetry. The latter is of particular interest as it varies depending on the type of spheres used for treatment. Moreover, dose has to be taken into account when comparing outcome and complications.

CURRENT RESULTS IN PRIMARY LIVER CANCER

There is a general consensus to accept ^{90}Y-TARE as a safe and effective treatment. In fact TARE results in a significantly longer survival when compared with a control group without loco-regional treatment[32]. However, there is a substantial variation in response rates and survival. Recent data indicate any response rates [partial response (PR), complete response (CR), stable disease (SD)] according to EASL in the range of 79%-94% with an overall survival of 15-16.4 mo[33-35]. Liver function as determined by Child-Pugh score was shown to be a strong predictor for outcome with CHILD. A patients having a markedly better prognosis, when compared with CHILD B patients with a median survival of 17.2-17.4 mo *vs* 6-7.7 mo[33,34]. The presence of PVT is another predictor of outcome with significantly reduced time-to-progression (TTP), while evidence regarding overall survival is contradictory[33,34]. Although most HCC patients die of liver failure due to intrahepatic tumor, extensive extrahepatic disease negatively impacts prognosis with 5.4-7.4 mo overall survival in current series from Europe and the United States[33,36].

According to the BCLC staging system and treatment recommendations TACE is the first-line treatment of choice. To assess the role of TARE it therefore is important to compare outcome of TACE and TARE. Unfortunately there is only a single randomized controlled clinical trial (RCT) addressing this issue. This very small RCT comparing TARE and DEB-TACE in only 24 patients failed to show a difference in progression free survival, TTP and overall survival[37]. Typical candidates for TARE often come with more advanced stages of disease and are often considered poor candidates for TACE. Comparison of a large case series on TACE analyzed by BCLC stage[38] and corresponding data on TARE[39] showed median overall survivals of 17.4 mo (95%CI: 13.9-18.8) and 16.9 mo (95%CI: 12.8-22.8) in intermediate BCLC stage B patients. From these data one may assume TARE to be more or less equivalent with TACE. However, a coarse comparison of both methods is problematic as results vary and strongly depend on the stage of disease (Tables 2 and 3).

A recent meta-analysis even concluded that microsphere embolization in patients with unresectable HCC provides better response to therapy and improved survival when compared with TACE[40]. As this meta-analysis mixes TARE with other techniques, data has to be analyzed in more detail and forest plots from the same meta-analysis prove TARE to be more effective than TACE in terms of overall survival [HR = 0.73 (0.60-0.88)] and TTP [HR = 0.61 (0.41-0.89)]. However, a more recent case control series comparing TARE *vs* TACE failed to show significant differences[26]. While CR rate was higher in the TARE groups, there were no differences in objective response rates and most importantly survival, with an overall survival of 15 mo after TARE and 14.4 mo after TACE. A subgroup analysis according to BCLC stage favored TARE over TACE in stage BCLC A/B, while in BCLC C patients TACE resulted in a slightly better survival. However, none of these trends was statistically significant. A more detailed analysis of two substantial patient series using either cTACE[38] or ^{90}Y-glass microspheres[33] revealed median overall survivals of: 40 (15-46) mo *vs* 26.9 (17-30.2) mo in BCLC A, 17.4 (13.9-18.8) mo *vs* 17.2 (13.5-29.6) mo in BCLC B and 6.6 (4-9.3) mo *vs* 7.3 (6.5-10.1) mo in BCLC C. Therefore a prospective randomized controlled trial is needed, which according to Salem *et al*[41] would require more than 1000 patients as difference in outcome between TACE and TARE is expected to be relatively small.

In terms of quality of life, TARE might be somewhat better than TACE, particularly in terms of embolotherapy

Table 2 Summary of studies on ^{90}Y-transarterial radioembolization in hepatocellular carcinoma with more than 50 patients

Ref.	Patients (*n*)	Particle type	Stage	Design	Response (%)					Median survival (mo)
					CR	PR	SD	AR	PD	
Lau *et al*[73]	71	Resin	CHILD A/B	Retrospective	0	27	65	92	8	9.4
Carr[74]	65	Glass	Okuda Ⅰ/Ⅱ	Prospective	3	28	40	71	29	Okuda Ⅰ = 21.6; Okuda Ⅱ = 10
Geschwind *et al*[75]	80	Glass	CHILD A/B	Retrospective	NA	NA	NA	NA	NA	CHILD A = 18.9; CHILD B = 8.2
Hilgard *et al*[34]	108	Glass	CHILD A/B	Retrospective	3	37	53	94	6	16.4 (CHILD A = 17.4; CHILD B = 6)
Salem *et al*[33]	291	Glass	CHILD A/B	Prospective	23	34	NA	NA	NA	CHILD A = 17.2; CHILD B = 7.7
Sangro *et al*[39]	325	Resin	BCLC A-D	Retrospective						12.8 (BCLC A = 24.4; BCLC B = 16.9; BCLC C = 10)
Mazzaferro *et al*[35]	52	Glass	CHILD A/B	Prospective	9.6	30.8	38.4	78.8	21.2	15

CR: Complete response; PR: Partial response; SD: Stable disease; AR: Any response; PD: Progressive disease; NA: Not available; BCLC: Barcelona Clinic Liver Cancer.

Table 3 Summary of studies comparing different treatments to ^{90}Y-transarterial radioembolization in hepatocellular carcinoma

Ref.	Patients (*n*)	Particle type	Stage	Design	Response (%)					Median survival (mo)
					CR	PR	SD	AR	PD	
D'Avola *et al*[32]	35	Resin	CHILD A/B	Retrospective	NA	NA	NA	NA	NA	16
	43	Control			NA	NA	NA	NA	NA	8
Lewandowski *et al*[43]	43	Glass	UNOS T3	Retrospective	47	39	14	100	0	18.7
	43	TACE			17	54	26	97	3	35.7
Kooby *et al*[76]	27	Resin	Okuda Ⅰ-Ⅲ	Retrospective	0	11	56	87	33	6
	44	TACE			0	4	60	64	36	6
Salem *et al*[41]	123	Glass	BCLC A-D	Retrospective	NA	NA	NA	72	NA	20.5
	122	TACE			NA	NA	NA	69	NA	17.4
Lance *et al*[77]	38	Glass	CHILD A/B	Retrospective	NA	NA	NA	NA	NA	8
	35	TACE			NA	NA	NA	NA	NA	10.3
Moreno-Luna *et al*[26]	55	Glass	CHILD A/B	Retrospective	12	39	39	91	9	15
	61	TACE			4	47	34	85	15	14.4
Gramenzi *et al*[47]	63	Resin	BCLC B/C	Retrospective	14	54	14	72	28	13.2
	74	Sorafenib			0	10	42	52	48	14.4

CR: Complete response; PR: Partial response; SD: Stable disease; AR: Any response; PD: Progressive disease; NA: Not available; TACE: Transarterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer; UNOS: United Network for Organ Sharing.

specific quality of life scores[42]. However, there was no significant difference in overall quality of life, likely due to the small number of patients included.

A different topic is the choice of loco-regional therapy for downstaging or bridging to transplant. In fact there are several studies assessing the effectiveness of TARE for these indications. In a comparative data analysis comparing TARE and TACE downstaging to UNOS T2 was achieved in 31% of TACE and 58% of ^{90}Y-TARE patients. In this particular analysis TARE was also beneficial in terms of survival[43]. Two case series showed TARE to be effective as a bridging treatment while on the waiting list for transplantation[44,45]. Both of the latter case series also indicated the potential of TARE to downstage patients to meet the transplant criteria. Other case series confirmed the potential of TARE to downstage HCC patients to become eligible for other treatments such as resection, ablation or transplantation[46]. This, however, has to be considered anecdotal and prospective trials addressing this topic are missing.

Only recently Gramenzi *et al*[47] questioned the use of TARE in HCC by comparing TARE and sorafenib in a retrospective single center analysis. Their key finding is a comparable overall survival of both groups with 14.4 (4.3-24.5) mo in sorafenib and 13.2 (6.1-20.2) mo in TARE patients, with 1-, 2- and 3-year overall survival rates of 52.1%, 29.3% and 14.7% *vs* 51.8%, 27.8% and 21.6% respectively. Interestingly TARE showed better response rates and was the only technique providing a sufficient downstaging that allowed for liver transplantation in some patients. These data are highly relevant, but require further confirmation.

In view of currently available data TACE has still to be considered the first line method in HCC patients eligible for transarterial therapies. The lack of RCTs proving TARE to be more effective than TACE is a key drawback. The costs of treatment also need to be considered. The only cost effectiveness study on TARE in HCC concludes that the costs of TARE may be justified in BCLC C patients, while TARE appears not to be cost effective in BCLC A patients. Unfortunately there is no recommendation for BCLC B patients, who represent the majority of patients eligible for transarterial therapies[48].

In view of the poor outcome after systemic chemotherapy, TARE is also used for treating intrahepatic cholangiocaracinoma (ICC). A recent systematic review on the use of TARE in ICC treatment identified 12 studies covering 73 patients. PR and SD at 3 mo were reported in 28% and 54% of patients, respectively. In a pooled analysis the overall weighted median survival was 15.5

mo. In seven patients downstaging to surgery was achieved[49]. The combination of TARE and chemotherapy as a strategy for downstaging ICC to achieve resectability has recently been identified and initial data are encouraging[50]. However, when comparing different loco-regional treatments for ICC, TARE may not be the most effective approach. In a comparative analysis TARE was second to hepatic artery infusion chemotherapy (HAI), but more effective than cTACE or DEB TACE in terms of response to treatment as well as overall survival, which was best for HAI (22.8 mo) followed by ^{90}Y-TARE (13.9 mo), cTACE (12.4 mo) and DEB-TACE (12.3 mo). While HAI provided best survival, but also had the highest grade Ⅲ/Ⅳ toxicity[51]. Despite the lack of randomized controlled trials, loco-regional treatment appears to be somewhat more effective when compared with the current standard chemotherapy with oxaliplatin and gemcitabine[52]. In ICC TARE seems to be best suited for patients who are not eligible for HAI.

CURRENT RESULTS IN LIVER METASTASES

There is a vast amount of data on TARE in metastatic liver disease. With CRLM being the most common type of metastatic liver disease a large amount of data is focused on this entity. Currently the integration of TARE in multidisciplinary treatment algorithms is subject of discussion[53].

An early RCT compared early treatment with radioembolization combined with HAI with floxuridine (FUDR) to HAI with FUDR alone. In these patients with unresectable CRLM objective response rate and TTP were significantly longer in the HAI plus TARE group when compared to HAI alone, with 44% and 15.9 mo compared to 17.6% and 9.7 mo respectively[19].

Several prospective trials have examined TARE in combination with systemic chemotherapy *vs* systemic chemotherapy alone (Table 4). In an early study, a first line setting with TARE combined with systemic 5-FU proved superior to 5-FU alone in terms of objective response rate (73% *vs* 0%), TTP (18.6 mo *vs* 3.6 mo) and overall survival (29.4 mo *vs* 12.8 mo)[21]. As 5-FU alone is an outdated chemotherapeutic regimen, prospective studies assessed TARE with more recent chemotherapeutic regimen. In a first line setting TARE combined with FOLFOX4 achieved a 90% PR rate[23], while TARE with irinotecan in a second line setting after failure of previous chemotherapy reported 87% any response with 48% PR and 39% SD[22]. Only recently the SIRFLOX study, an RCT in 530 patients, reported the results of mFOLFOX 6 with or without bevacizumab compared with TARE + mFOLFOX 6 with or without bevacizumab. While there was no difference in progression free survival, there was a significant difference in progression free survival in the liver, favoring the combination with TARE (20.5 mo) over chemotherapy alone (12.6 mo; $P = 0.002$). Objective response rates were somewhat better in the combination therapy when compared to chemotherapy alone (68.1% *vs* 76.4%; $P = 0.113$)[24].

Clinically TARE is most often used in a salvage setting. In a phase Ⅱ study on 50 patients with isolated or predominant liver disease with progression after at least three lines of systemic chemotherapy TARE achieved disease control in 24% of patients with a progression-free-survival of 3.7 mo and an overall survival of 12.6 mo[54]. An RCT on 46 chemorefractory patients comparing systemic 5-FU to 5-FU plus TARE showed an significantly improved time to progression of liver disease (5.5 mo *vs* 2.1 mo; $P = 0.003$), but failed to show an significant improvement in overall survival (10.0 mo *vs* 7.3 mo; $P = 0.80$)[20]. A recent systematic review on TARE in unresectable, chemorefractory CRLM included 979 patients from 20 studies. After failure of 2 to 5 (median: 3) lines of chemotherapy TARE achieved CR, PR and SD in 0% (range: 0%-6%), 31% (range: 0%-73 %) and 40.5% (range: 17%-76 %) of patients, respectively. The median time to intra-hepatic progression was 9 mo (range: 6-16) and median overall survival was 12 mo (range: 8.3-36)[55]. A large multicenter data analysis proved overall survival being strongly dependent on previous treatment with median survivals (95%CI) receiving ^{90}Y-TARE as a 2nd-, 3rd-, and ⩾ 4th line of treatment after chemotherapy of 13.0 mo (95%CI: 10.5-14.6), 9.0 mo (95%CI: 7.8-11.0), and 8.1 mo (95%CI: 6.4-9.3), respectively ($P < 0.001$)[56]. A recent cost-effectiveness study on TARE using ^{90}Y-resin microspheres compared to best supportive care reported a cost per QALY gained of £28216. The authors concluded that TARE using ^{90}Y-resin microspheres offers a clinically effective and cost-effective treatment option[57].

While aforementioned data was obtained from ^{90}Y resin spheres, there is only little data on ^{90}Y-TARE with glass sphere. In 72 patients with unresectable CRLM after failure of at least one line of chemotherapy time to intrahepatic progression was 15.4 mo with a median survival of 14.5 mo after first ^{90}Y treatment. ECOG stage 0, tumor replacement < 25% of liver volume, lack of extrahepatic tumor and response to therapy were identified as positive prognostic markers[58]. A recent phase Ⅱ multicenter trial reported slightly worse results for treating liver metastases were, with an 8.8 mo median overall survival in CRLM[59].

There also is encouraging data on TARE in liver metastases from various other tumor entities such as metastatic breast cancer, uveal melanoma or neuroendocrine tumors (NET) (Table 5 and Figure 1). Among these, NET take a special role as these tumors are well arterialized and thus an ideal target for transarterial therapies similarly to HCC. Treatment goral in these patients is control of symptoms as well as survival. The biggest series so far comprises data from 148 patients from ten institutions. This series reported very high response rates with any response in 95.1% of patients and progressive disease in only 4.9% of the patients. The median OS of 70 mo after initial TARE was higher than other studies (Table 5)[60]. This may be due to the variable biology of NET, with pancreatic NET being associated with a markedly poorer prognosis when

Table 4 Summary of randomized controlled clinical trials comparing different treatments to ^{90}Y-transarterial radioembolization using resin spheres in colorectal liver metastases

Ref.	Patients (*n*)	Protocol	Design	Setting	Response (%)					Progression free survival (mo)	Median survival (mo)
					CR	PR	SD	AR	PD		
Gray *et al*[19]	36	TARE + HAI FUDR	RCT - Phase Ⅲ	Early	6	44	28	78	14	15.9 (liver)	17
	34	TARE - HAI FUDR		line	0	22	48	70	30	9.7 (liver)	15.9
Van Hazel *et al*[21]	11	TARE + 5-FU/LV	RCT - Phase Ⅱ	1. line	0	91	9	100	0	18.6	29.4
	10	5-FU/LV			0	0	60	60	40	3.6	12.8
Hendlisz *et al*[20]	21	TARE + 5-FU	RCT - Phase Ⅲ	Salvage	0	10	80	90	10	4.5	10
	23	5-FU			0	0	36	36	64	2.1	7.3
Gibbs *et al*[24]	267	TARE + FOLFOX ± Bevacizumab	RCT - Phase Ⅲ	1. line	4.5	71.9	NA	NA	NA	10.7/20.5 (liver)	NA
	263	FOLFOX ± Bevacizumab			1.5	66.5	NA	NA	NA	10.2/12.6 (liver)	NA

CR: Complete response; PR: Partial response; SD: Stable disease; AR: Any response; PD: Progressive disease; NA: Not available; RCT: Randomized controlled clinical trial; HAI: Hepatic artery infusion; FUDR: Floxuridine; TARE: Transarterial radioembolization; 5-FU: 5-fluoruracil; LV: Leucoverin.

Table 5 Summary of studies on ^{90}Y-transarterial radioembolization in liver metastases from various tumor types with more than 10 patients published within the last 5 years

Ref.	Patients (*n*)	Particle type	Entity	Setting	Design	Response (%)					Median survival (mo)
						CR	PR	SD	AR	PD	
Saxena *et al*[78]	48	Resin	NET	Salvage	Retrospective	15	40	23	78	22	35
Cao *et al*[79]	58	Resin	NET	Mixed	Retrospective	11.7	27.5	27.5	66.7	33.3	36
Paprottka *et al*[80]	42	Resin	NET	Mixed	Retrospective	0	22.5	75	97.5	2.5	NA
Memon *et al*[81]	40	Glass	NET	Mixed	Retrospective	1.2	62.7	32.5	96.4	3.6	34.4
Peker *et al*[82]	30	Resin	NET	Mixed	Retrospective	3	37	43	83	17	39
Haug *et al*[83]	58	Resin	Breast	Salvage	Retrospective	0	25	63	88	12	10.8
Cianni *et al*[84]	52	Resin	Breast	Salvage	Retrospective	0	56	35	91	9	11.5
Saxena *et al*[85]	40	Resin	Breast	≥ 1.line CTX	Retrospective	5	26	39	70	30	13.6
Gonsalves *et al*[86]	32	Resin	Uveal Melanoma	Salvage	Retrospective	3	3	56	62	38	10
Michl *et al*[87]	19	Resin	Pancreas	mixed	Retrospective	0	64.3	0	64.3	45.7	9

CR: Complete response; PR: Partial response; SD: Stable disease; AR: Any response; PD: Progressive disease; NA: Not available; CTX: Chemotherapy; NET: Neuroendocrine tumor.

compared to non-pancreatic NET. However, there are no RCTs on any these entities and further data is needed to confirm these encouraging results.

SIDE EFFECTS AND ADVERSE EVENTS

The so called post-(radio)embolization syndrome with fatigue, nausea, vomiting, anorexia, fever and abdominal discomfort is the most frequent side effect of TARE. It may occur in up to 55% of patients and is self-limiting, lasting no longer than two weeks[61]. A passing elevation of liver enzymes, namely in alkaline phosphatase, alanine transferase and bilirubin are normal side effects of this treatment.

The most common relevant complication of TARE is gastrointestinal (GI) ulceration, caused by non-target embolization of ^{90}Y-microspheres into the GI tract. Thorough pre-interventional imaging work-up and coiling of vessels with hepatofugal flow are key to minimize the risk of GI complications to less than 4%[62]. Proton pump inhibitors are the treatment of choice in GI ulcers. In case of treatment failure surgery may be required.

Eventually radiation leads to fibrosis presenting with imaging signs of portal hypertension. Fortunately, these findings hardly ever have clinical consequences[63]. In patients with HCC signs of portal hypertension are commonly seen on pre-interventional imaging as most of these patients suffer from underlying cirrhosis. However, liver dysfunction potentially progresses to radiation induced liver disease (RILD), which may occur in up to 20% of patients[59,64]. RILD is defined as icteric or anicteric, non-malignant ascites combined with an increase in alkaline phosphatase to at least twice the upper normal level within four months after treatment. So far there is no reliable treatment. Only recently administration of defibrotide (Gentium, Como, Italy) which is used for the treatment of veno-occlusive disease has been suggested[65]. Thus preventing RILD is most important. Consequently selection of patients by liver function is crucial as deranged baseline hepatic function, presence of liver cirrhosis and administered radiation dose are the most important risk factors for developing RILD. The routine administration of ursodeoxycholic acid and low-dose steroids has been shown to significantly reduce the risk of RILD[64]. In addition sequential lobar treatment seems to be safer than single session whole liver treatment[66].

Biliary toxicity with biloma, abscess and radiation induced cholecystitis occurs in ⩽ 2% of patients[67]. Fortunately, many imaging findings indicative of biliary complications do not manifest clinically.

Finally, radiation pneumonitis, a restrictive lung

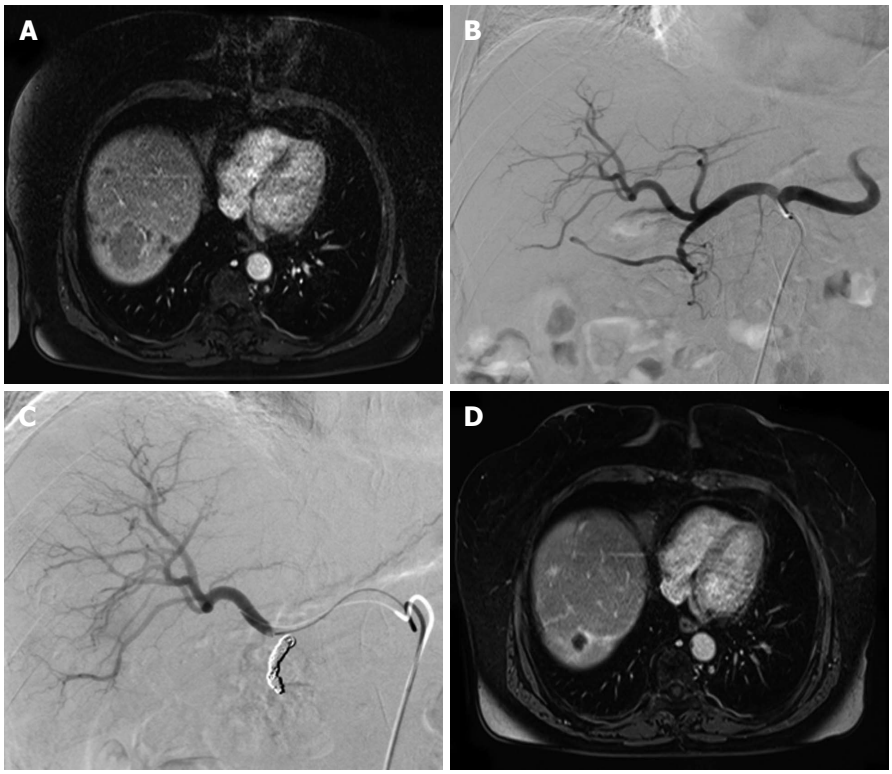

Figure 1 Case study of a 64-year-old female patient suffering from liver metastases from a midgut neuroendocrine tumor. A: Contrast enhanced MRI shows a large liver metastasis in the right hemiliver; B: Prior to TARE an angiogram of the hepatic arteries was obtained; C: The gastroduodenal artery was occluded with multiple microcoils; D: Contrast enhanced MRI obtained 24 mo after therapy shows a maintained partial response of the liver metastasis. MRI: Magnetic resonance imaging; TARE: Transarterial radioembolization.

dysfunction, is a relevant, but very rare adverse event[68]. It can reliably be avoided if dosimetry and pre-interventional work-up are performed properly with computation of lung shunting fraction from ^{99m}Tc-MAA imaging[69]. Lung doses need to be below 30 Gy for a single treatment and less than 50 Gy for repeated TARE. Radiation induced pneumonitis is usually managed with a steroid based therapy.

FUTURE PERSPECTIVES

A steadily growing amount of data shows TARE to be an effective monotherapy in the treatment of HCC. The obvious next step is the adjuvant or neoadjuvant combination of systemic and loco-regional therapies, specifically sorafenib and TARE. From theory both techniques run complementary ways of action. So far there data on the combination of sorafenib and TARE is scarce. In the only prospective study on this type of combination therapy, 39% of patients could not complete the prescribed dose of sorafenib due to side effects. Moreover, an objective response rate of 25% does not support the use of this type of combination therapy[70]. Initial data from a RCT comparing TARE with ^{90}Y-resin microspheres followed by sorafenib with sorafenib only so far only reported safety data from the first 40 patients. These preliminary results indicate a similar tolerance for both treatment arms[71]. Outcome data from ongoing RCTs such as SORAMIC (NCT01126645), SARAH (NCT01482442) or SIRveNIB (NCT01135056) using SIR-spheres® or STOP-HCC using TheraSphere® (NCT01556490) have not yet been published.

While TARE is considered a bridging technique to transplantion, the combination of sorafenib and TARE seems problematic. A RCT in 20 patients undergoing TARE with or without sorafenib prior to transplantation indicated more acute rejections and peri-transplant complications in the treatment arm receiving TARE plus sorafenib. In addition, none of the patients could tolerate the prescribed dose of sorafenib. Half of the patients discontinued sorafenib completely because of side effects[72]. Thus caution on this type of combination therapy appears to be prudent until more data is available.

For metastatic disease RCTs comparing TARE and modern chemotherapeutic regimen are needed, as currently available data compared SIR-spheres® with outdated chemotherapeutic regimen or lacking survival data (Table 4), while there are no comparative data at all for TheraSphere®. The latter is currently addressed in an ongoing phase Ⅲ trial evaluating treatment with ^{90}Y-glass spheres and second-line chemotherapy after failure of first-line chemotherapy in comparison to second-line chemotherapy alone for CRLM (EPOCH; NCT01483027). The FOXFIRE global trial is an ongoing phase Ⅲ study assessing the value of additional ^{90}Y-resin spheres in a first line setting with FOLFOX6m (NCT01721954). There are further trials evaluating the role of TARE in uveal melanoma (SIRUM NCT01473004) or the combination of

TARE and pasireotide and everolimus in neuroendocrine tumors (NCT01469572).

The use of TARE beyond the liver has been described sporadically for the lung and the spleen and is currently evaluated in a pilot trial for renal cancer (RESIRT, ACTRN 12610000690055).

CONCLUSION

In conclusion, TARE represents a potent technique for treating liver malignancies. The current data justifies its clinical use in HCC and CRLM, while its role outside a salvage setting needs to be identified for liver metastases from other tumor entities. Considering ongoing trials and the increasing clinical experience, a rapid increase in TARE procedures has to be expected.

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