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REVIEW ARTICLE

Ytrrium-90 transarterial radioembolization in patients with gastrointestinal malignancies

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Abstract

Transarterial radioembolization (TARE) with yttrium-90 (Y90) is a promising alternative strategy to treat liver tumors and liver metastasis from colorectal cancer (CRC), as it selectively delivers radioactive isotopes to the tumor via the hepatic artery, sparring surrounding liver tissue. The landscape of TARE indications is constantly evolving. This strategy is considered for patients with hepatocellular carcinoma (HCC) with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy is possible. In patients with liver metastases from CRC, TARE is advised when other chemotherapeutic options have failed. Recent phase III trials have not succeeded to prove benefit in overall survival; however, it has helped to better understand the patients that may benefit from TARE based on subgroup analysis. New strategies and treatment combinations are being investigated in ongoing clinical trials. The aim of this review is to summarize the clinical applications of TARE in patients with gastrointestinal malignancies.

Keywords Radioembolization · Yttrium-90 · Colorectal neoplasms · Liver neoplasms

Introduction

Primary liver malignancies and liver metastases constitute a major cause of morbi-mortality in patients with cancer. Local control is an important goal and when surgery is not feasible and/or indicated, other less-invasive local therapies may be delivered to patients. Conventional transarterial chemoembolization (c-TACE), and more recently, DEB-TACE (drug-eluting bead transarterial chemoembolization), consist of selective embolization through the hepatic artery and injection of Lipiodol chemotherapeutic agents. Transarterial radioembolization (TARE) or selective internal radiation therapy (SIRT) is also an endovascular procedure that involves the delivery of yttrium-90 (Y90) and other radioisotopes inside a glass matrix or on the surface of microspheres through the hepatic artery (Fig. 1). This procedure allows the radiation to be focused on the tumor region and minimizes damage to the surrounding liver tissue. It can be delivered at lobar, segmental, or local liver levels [1].

The concept of hepatic artery therapies for hepatic malignancies dates back to the 1950s, when it was demonstrated that hepatic malignancies are fed by the arterial blood supply. In contrast, most normal liver cells are fed through the portal vein. In 1961, Miller Tr. described a technique to deliver radiation to liver tumors by a catheter that was inserted through the femoral artery and placed into the hepatic artery via the gastroduodenal artery [2]. Later, in 1965, Ariel et al. reported the delivery of Y90 from the coeliac trunk in patients with primary liver cancer. Y90 was administrated in ceramic microspheres ± 50 microns in diameter. The results were acceptable, achieving tumor shrinkage and good palliation with minimal complications [3]. In 1967, Simon et al. described the use of Y90 for hepatic neuroendocrine tumors with poor outcomes because of toxicity [4]. Eventually, in 1973,

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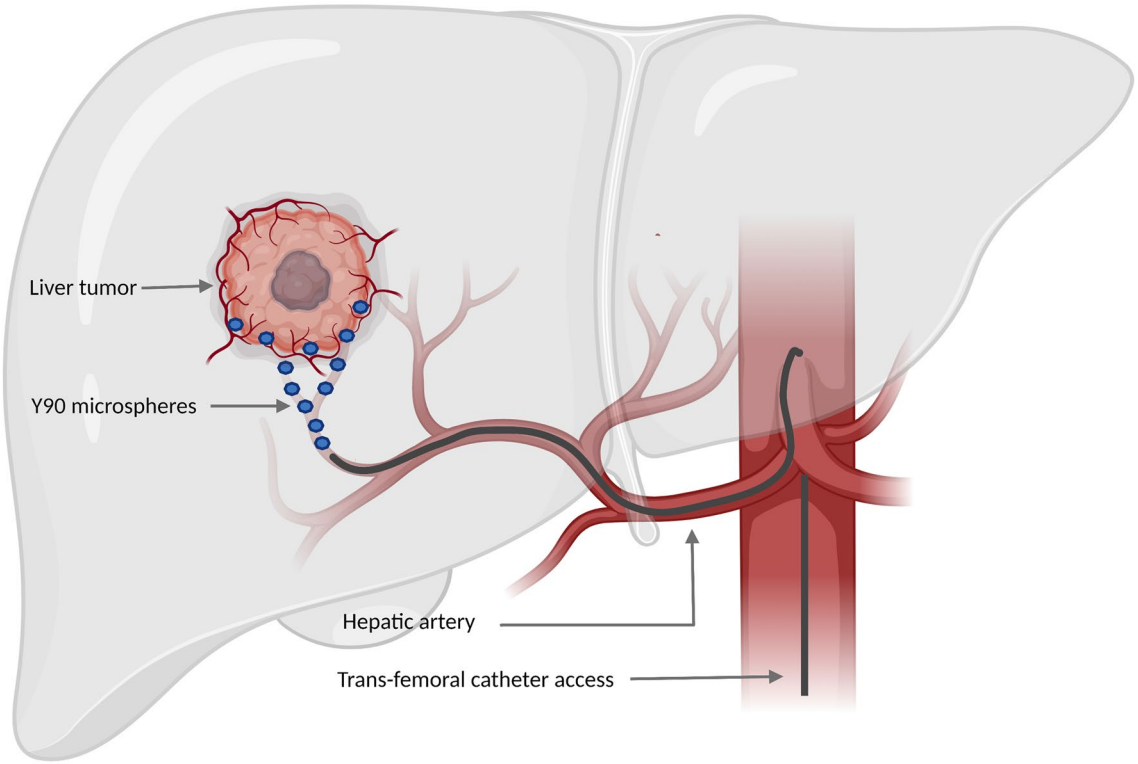

Fig. 1 Scheme of the Y90 TARE procedure. TARE is performed typically in a 2-stage process. The first step involves trans-femoral catheter access to the hepatic artery to identify tumor feeding vessels and prophylactic occlusion of extrahepatic vessels, and lung-shunt assessment with 99mTc-MAA/gammacamera. One to 3 weeks later, after reassessment of vessel occlusion, delivery of Y90 microspheres through the hepatic artery is performed. Y90, yttrium-90; TARE, transarterial radioembolization

25 patients with metastases from CRC were treated with Y90-resin microspheres. The tumor size decreased in 17 patients. These promising results supported the role of TARE for hepatic malignancies and boosted further investigation [5].

The design and size of the microspheres progressed in subsequent studies. The aim was to determine the relationship between the optimal size of the microspheres and adequate liver distribution. Meade VM et al. reported that microspheres of 15 and 32.5 µm were more frequently deposited in the tumor than in healthy tissue. In contrast, 50 µm microspheres were equally distributed in normal and tumor tissue. Eventually, in 1999 the FDA approved the use of glass microspheres for unresectable HCC [6, 7]. Three types of microspheres are currently available: resin microspheres (SIR-Spheres) coated with Y90, glass microspheres (TheraSphere) in which Y90 is an intrinsic component, and microspheres based on the radionuclide holmium-166 (QuiremSpheres) [8]. Differences between resin and glass microspheres are depicted in Table 1 [9, 10]. Holmium-166 microspheres are paramagnetic and emit gamma radiation besides beta radiation, which makes them cuantifiable on both single-photonemission CT (SPECT) and MRI for precise assessment of the dose distribution [11].

Table.1 Comparison between yttrium-90 microspheres

Characteristics	SIR-Spheres®	TheraSphere®
Material	Resin	Glass
Particle size (µm)	20–60	20–30
Number of spheres per vial (range in million)	40–80	1.2–8
Specific gravity (g dl21)	Low, 1.6	High, 3.6
Embolic effect	Moderate	Mild
Activity per sphere (Bq)	40–70	2.500
Activity available (GBq)	3	3, 5, 7, 10, 15, 20

As indications for Y90 TARE are expanding, clinicians must be aware of the main contraindications of the treatment. Hepatopulmonary shunt is not an absolute contraindication for radioembolization but the radiation dose to lungs must not exceed 30 Gy in a single setting and the cumulative dose must not exceed 50 Gy. The grade of shunt is calculated through the arterial injection of technetium-99 m-labeled macroaggregated albumin (Tc-99 m MAA) [12]. The mapping with Tc-99 m MAA also aims to determine the arterial anatomy of the liver and the identification of any aberrant hepatic artery. This allows calculating

the dose to be delivered and avoiding non-target regions. Other contraindications for Y90 TARE include Child–Pugh C cirrhosis, encephalopathy, and biliary obstruction. Relative contraindication is ascites, bilirubin > 2 mg/dL, or pregnancy [8]. Unlike for TACE, portal vein thrombosis is not a contraindication for TARE. When combining treatment with systemic therapy, caution must be taken with several agents. For instance, some authors suggest starting oxaliplatin at a lower dose on the first cycle. Gemcitabine is a radiosensitizer and, when combined with Y90, there is an increased risk of hepatotoxicity. Bevacizumab, an antiangiogenic monoclonal antibody, can induce delayed wound healing and vascular fragility, at a 4-week interval since the last bevacizumab infusion is recommended [13].

Y90 TARE is a relatively safe procedure. However, knowledge of potential complications is essential. The post-radioembolization syndrome (PRS) is observed in 20–70% of the patients in the firsts weeks post-TARE and includes nausea/vomiting, abdominal pain, fatigue, and/or cachexia and do not usually require hospitalization. There are also complications due to aberrant microsphere deposition including hepatic disfunction (radiation-induced liver disease, fibrosis or portal hypertension), cholangitis or cholecystitis, radiation pneumonitis (less than 1%), gastroenteritis/gastrointestinal ulcera due to hepaticoenteric arterial communications, among others. However, grade ≥ 3 complications are reported in less than 9% of patients and rarely require intervention [14].

Although the TARE technique was not a popular treatment for many years, recent studies have reported the safety of TARE with Y90 for liver malignancies, and supported the use of this alternative treatment for patients who are not candidates for curative treatments. However, there has been no consensus on the use of TARE as standard care. This review aims to summarize the evidence for TARE and its application in clinical practice in patients with gastrointestinal malignancies.

Y90 radioembolization in hepatocellular carcinoma

HCC accounts for about 90% of all primary liver cancers and is the second cause of cancer-related death globally [15]. The prognosis of HCC depends on tumor burden and underlying liver disease. The median survival following diagnosis is around 6–20 months [16]. The HCC treatment strategy requires a multidisciplinary team involving oncologists, surgeons, hepatologists, radiologists, and nuclear medicine specialists. Curative options for very early or early HCC stages include surgery, liver transplantation, or ablation. However, they represent only 30% of all cases. Most cases are classified as intermediate or advanced stage at diagnosis. TACE is the treatment of choice for intermediate HCC (BCLC stage B) and systematic treatment for advanced HCC (BCLC stage C). Various local therapies, such as TARE, have been advocated for intermediate and advanced stages. TARE has been reported to be a safe and well-tolerated procedure with promising results [15, 17].

TARE as a radical treatment

Radioembolization can be delivered in the form of "lobectomy" radiation in patients with multifocal but unilobar disease. In addition to the effect of the radiation delivered, RE may also cause atrophy of the lobe treated in an attempt to achieve hypertrophy of the contralateral lobe, the future liver remnant (FLR). It has been established that for successful resection the FLR volume should be 20–40% of the total liver volume. In 2008, Jakobs reported that radioembolization of the right lobe led to left lobe hypertrophy [18, 19].

Subsequent studies reported a grade of hypertrophy following radioembolization lobectomy of 21–57% depending on the time of measurement and underlying diseases. In the presence of hepatitis B infection, the liver showed a greater degree of hypertrophy than with hepatitis C infection or alcoholic liver cirrhosis [20, 21].

Radiation can also be delivered at a segmental level, causing "segmentectomy". This allows a more selective administration of Y90 in an attempt to achieve regression or atrophy of the treated segment. It has been reported as a potentially curative option in early stages, especially for HCC located in liver areas not suitable for ablation [18, 22]. In 2011, Riaz described radiation segmentectomy in 84 patients with unresectable HCC not suitable for surgery or radiofrequency ablation. The median TTP was 13.6 months and overall survival (OS) was 26.9 months (OS at 1, 2, and 3 years was 74%, 55%, and 27%, respectively) with necrosis of > 50% reported in 81% of all patients. The toxicity rate was low. Fatigue was the most common side effect (52%). Biochemical toxicity ranged from 2 to 6% [22]. A study of 102 patients with unresectable solitary HCC less than 5 cm in size and without PVT not suitable for radiofrequency ablation demonstrated the benefit of radiation segmentectomy. The complete response, partial response (PR), and stable disease (SD) rates were 47, 39 and 12%, respectively. The median TTP was 33.1 months. Thirty-two percent underwent transplantation and pathological investigation showed 100 and 50–99% necrosis in 52 and 48%, respectively. Patients aged under 65 years, those with an ECOG of 0 or with a Child–Pugh A score had longer survival [23].

TARE for downstaging and bridging approaches

Successful downstaging to within Milan criteria allows a curative option to be offered to HCC patients. It has been

suggested that TARE could downstage the patients to fit within the Milan criteria. The success rate of TARE for downstaging ranges from 22 to 78.9%, the lowest rates being reported in patients with ipsilateral portal vein invasion [18]. In a systematic review including 13 studies and 950 patients, Parikh et al. reported no significant differences in downstaging or the recurrence rate between TACE and TARE. The highest success rates of downstaging were reported in multimodal locoregional therapy. Post-transplantation recurrence was higher in those patients with previous downstaging than in those initially diagnosed within Milan criteria [24]. Combining TARE with sorafenib in patients with HCC and PVT has been suggested as a promising downstaging approach, achieving acceptable survival rates when compared with no intervention or palliative sorafenib [25].

TARE/SIRT using Y90 microspheres for bridging to transplantation has also been studied in patients with BCLC-A. The median time to liver transplantation is 1 year. Disease progression occurs in 10–23% of patients while waiting for transplantation. Local therapies have been used to maintain tumor burden within the Milan criteria. The literature suggests that TARE could be the preferable option for this purpose. The PREMIERE trial was a prospective randomized phase 2 study that studied the efficacy of C-TACE versus Y90 TARE in patients with unresectable BCLC stage A/B, Child–Pugh A/B HCC. The rate of transplantation was higher in the TARE group (87% vs 70%) [26]. Other studies have also highlighted the role of TARE as bridging therapy [27, 28]. A retrospective study of 3601 patients within Milan criteria concluded that bridging therapy did not improve post-liver transplantation survival or recurrence. Post-liver transplantation recurrence was associated with the lack of alphafetoprotein response to locoregional therapy and the need for locoregional therapy treatments [29].

TARE for intermediate stages. TARE versus TACE

The intermediate stage constitutes a wide range of patients and is a heterogeneous group in terms of tumor burden and liver factors. For this group, TACE has been considered as the first-line treatment. However, TARE has also been reported as an acceptable alternative to TACE with better tolerability. The PREMIERE trial was an investigator-initiated phase 2 trial in which 45 patients with HCC BCLC-A or -B were randomized to Y90 therapy or c-TACE. Median TTP was significantly longer for the Y90 therapy group (> 26 vs. 6.8 months, $p = 0.0012$; HR 0.122; 95% CI 0.027–0.557; $p = 0.007$). However, there were no differences in median OS (17.7 months for the c-TACE group vs. 18.6 months for the Y90 group (95% CI 7.4–32.5) [26]. A recent meta-analysis of 5 studies with 553 patients comparing TACE vs TARE for unresectable HCC found that significantly more patients in the TARE group were alive at 2 years (27 vs. 18%). However, at 4 years, the survival rates were similar (4%), with no difference between groups. No statistical differences in complete or partial radiological responses were found. Pain was more common with TACE and fatigue with TARE, and there were no differences in other post-treatment symptoms between the groups. Furthermore, TARE was an outpatient procedure while TACE required a one-night hospital stay [26]. In 2017, a meta-analysis comparing DEB-TACE vs TARE was performed with an adjusted indirect meta-analytic method out of studies comparing conventional (c)TACE versus 90Y TARE or DEB-TACE for HCC. A total of 736 patients from 14 studies were included. The meta-analysis showed a survival benefit for drug-eluting bead transarterial chemoembolization (D-TACE) at 1 year over TARE (79% vs. 55%) with no statistically significant benefit for 2- and 3-year survival, although this could be explained partially by a strong trend to advanced Child–Pugh scores and BCLC stages in the TARE group [30]. Individual retrospective studies generally showed a delay in tumor progression and comparable survival to those reported for sorafenib and TACE [31, 32].

The 2019 update of the Indian National Association for study of the liver consensus on prevention, diagnosis, and management of HCC considers TARE as a good treatment option for patients in whom TACE is not feasible or relatively contraindicated and also in those in whom TACE has failed. They concluded that TARE is contraindicated in BCLC-D patients, those with Child C status, patients with prior external beam radiotherapy, extrahepatic metastases, or hepatopulmonary shunt of more than 20% [33]. ESMO guidelines consider TARE for patients with liver-confined disease and preserved liver function in whom neither TACE nor systemic therapy is possible [15].

TARE and portal vein thrombosis

Portal vein thrombosis (PVT) is present in 44% of HCCs at death and is considered a poor prognostic factor in most classification systems and a limitation to perform a curative treatment [34]. Overall survival when PVT is present may be as poor as 2–4 months; however, without PVT, OS ranges from 10 to 24 months. In the presence of PVT, TACE remains relatively contraindicated, due to the possibility of ischemic necrosis derived from the embolic effect on the hepatic artery and the compromised blood supply of the PV with PVT. However, the use of glass particles such as Y90 glass microsphere does not induce significant macroscopic arterial embolization [35, 36].

In 2004, Salem et al. reported the injection of Y90 microspheres in a cohort of 15 patients with PVT of first order or related segmental portal vein branches. It was a safe and well-tolerated procedure [37]. Subsequent studies supported the safety and good tolerability of TARE (Y90) for HCC

with portal vein thrombosis. In 2008, Kulik et al. demonstrated the safety of TARE with Y90 glass microspheres in 108 unresectable HCC patients. Thirty-seven of them (35%) had PVT. They found no difference in terms of complications related to treatment or liver failure between thrombosis affecting small branch or no PVT when compared to thrombosis in the main branch of the portal vein [38]. In 2010, Salem et al. reported a time-to-progression (TTP) of 7.9 months in 291 patients with locally advanced HCC treated with TARE. Child–Pugh B patients with PVT had the worst outcomes with a median OS of 5.6 months [39]. In 2013, a phase 2 study that included 52 patients with BCLC intermediate and advanced HCC receiving Y90 with lobar delivery and found no significant difference in TTF (7 vs. 13 months) or median OS between patients with or without PVT [40]. Other studies reported a 22% of downstaging for surgery or transplantation in patients with HCC and ipsilateral PVT [41]. She et al. reported better OS in patients with major vascular invasion receiving TARE when compared with TACE [42]. Other studies even reported thrombus regression in patients with advanced HCC [43]. In a single-center cohort study of 75 patients with HCC and PVT, Cardarelli-Leite et al. reported that ablative TARE is a safe option with longer survival than conventional TARE [44].

Prognostic scores to predict response to Y90 TARE and define the patients with PVT that will benefit from TARE is crucial. Spreafico et al. reported that bilirubin levels, extension of PVT, and tumor burden were independent variables correlated to OS in patients with HCC and PVT treated with TARE. They described three prognostic categories: favorable, intermediate, and poor prognosis with a median OS of 32.2, 14.9, and 7.8 months, respectively [45].

A meta-analysis comparing TARE and sorafenib in patients with HCC and PVT recently concluded that TARE is more effective in patients with PVT with higher OS at 6-month (76% [95% CI 64–85%] vs. 54% [95% CI 45–62%]) and 1-year (47% [95% CI 38–57%] vs. 24% [95% CI 18–30%]). Furthermore, TARE delayed tumor progression and had lower incidence of grade 3/4 AEs than sorafenib (9% [95% CI 3–27%] vs. 28% [95% CI 17–43%]) [46].

TARE for advanced stages. TARE vs systematic therapy

The role of SIRT with Y90 embolization compared to systemic therapy was studied in the SARAH and SIRveNIB trials (Table 2). The SARAH trial was a randomized phase 3 trial that enrolled 467 patients from 25 centers in France with locally advanced HCC or in whom TACE was not effective. It failed to demonstrate a benefit from TARE over sorafenib (OS was 8 months for TARE and 9.9 months for sorafenib; HR, 1.15 [95% CI 0,94–1,41]; $p = 0.18$). However, overall response rate was higher with TARE than with sorafenib (19% vs. 12%; $p = 0.04$). Grade ≥ 3 AEs were more common in the sorafenib group than in the TARE group (63% vs. 40%) [47]. The phase 3 SIRveNIB trial showed no significant differences in OS between TARE and sorafenib (8.8 vs. 10.0 months) in 350 Asia–Pacific patients with locally advanced HCC. TARE was also associated with a higher tumor response rate (TRR) (16.5% vs. 1.7%) and less grade 3 side effects (27.7% vs. 50.6%) [48]. The palliative treatment substudy of the SORAMIC phase II trial assessed whether the addition of TARE to sorafenib improved survival in 424 patients with advanced HCC patients. However, median OS was similar in both groups (12.1 months in the SIRT + sorafenib arm versus 11.4 months in the sorafenib arm; HR 1.01; 95% CI 0.81–1.25; $p = 0.95$) [49]. In the per-protocol population, non-significant better median OS was found in favor of the combination group (14.0 months (95% CI 11.5–17.0) in the SIRT + sorafenib arm, and 11.1 months (95% CI 9.8–13.8) in the sorafenib arm; HR, 0.86 (95% CI 0.67–1.11; $p = 0.25$). Interestingly, subgroup analyses showed benefit of SIRT + sorafenib for patients without cirrhosis; cirrhosis of nonalcoholic etiology, or aged 65 years or younger. A recent meta-analysis including these three major trials found that median OS with SIRT, whether or not followed by sorafenib, was non-inferior to sorafenib (10.2 and 9.2 months [HR 0.91; 95% CI 0.78–1.05]) [50]. The STOP-HCC Phase 3 trial is currently underway across North America, Europe, and Asia, and is assessing the efficacy of TARE + sorafenib vs sorafenib in unresectable HCC. It is thought that it will help to establish the role of TARE in unresectable HCC [51].

Liver metastases from colorectal cancer

In recent years, the prognosis of patients with colorectal cancer (CRC) liver metastases has improved due to the appropriate selection of patients for surgery, a more effective systematic chemotherapy approach and advances in ablative techniques. When liver metastasectomy is performed, the five-year survival rate after resection ranges from 24 to 58% with a mortality rate of less than 5% [52]. Other local therapies such as radiofrequency ablation, TACE, or TARE have also been proposed for unresectable liver metastases from CRC with acceptable results.

TARE as first-line treatment for CRC liver metastases

In 2004, a phase 2 randomized trial including 21 patients with untreated CRC liver metastases with or without extrahepatic metastases found a longer time to disease progression in the TARE plus chemotherapy group when compared with chemotherapy alone (18.6 vs. 3.6 months, $p < 0.005$, respectively). Median OS was higher in the

Table 2 Main phase II and III clinical trials involving yttrium-90 transarterial radioembolization in patients with hepatocellular carcinoma and liver metastases from colorectal cancer

Clinical trial	Patients	N	Design	Treatment	ORR	PFS	OS	G ≥ 3 AEs
Hepatocellular carcinoma								
SARAH	HCC BCLC C. HCC not eligible for local therapies after a cured HCC. HCC with two unsuccessful TACE	467	Multicentre, open label, randomised, controlled	sorafenib 400 mg BID vs TARE with Y90-resin microspheres	19% versus 12%; $p=0.04$	4.1 versus 3.7 months. HR, 1.03 (95% CI 0.85–1.25); $p=0.76$	8.0 versus 9.9 months. HR, 1.15 (95% CI 0.94–1.41); $p=0.18$	41% versus 63%
SIRveNIB	Locally advanced HCC BCLC stage B or C without extrahepatic disease, and not amenable to curative treatments	360	Open-label, investigator-initiated, phase III trial	Y90-resin microspheres TARE vs sorafenib 400 mg BID	16% versus 1%; $p<0.01$	5.8 versus 5.1 months. HR, 0.89 (95% CI 0.7–1.1); $p=0.31$	8.8 versus 10.0 months. HR, 1.1 (95% CI 0.9–1.4); $p=0.36$	27% versus 50%; $p<00.001$
SORAMIC, palliative treatment substudy	HCC BCLC B not eligible for TACE and C	424	phase II, open label, multicentre, randomized controlled	Y90-resin microspheres + sorafenib 400 mg BID versus sorafenib 400 mg BID			12.1 versus 11.4 months.HR, 1.01 (95% CI 0.81–1.25); $p=0.953$	64% versus 53%; $p=0.036$
Colorectal cancer liver metastases								
SIRFLOX	Patients with treatment-naïve CRC liver metastases	530	Multicentre, open label, randomised, controlled	TARE + mFOLFOX6 vs mFOLFOX6	76% versus 68%; $p=0.113$	mPFS: 10.7 vs 10.2 months. HR, 0.93; (95% CI 0.77–1.12); $p=.43$, mhPFS: 20.5 versus 12.6 months, HR, 0.69 (95% CI 0.55–0.90) $p=0002$	22.6 versus 23.3 months, $p=0.61$	85% versus 73%
FOXFIRE Global	Chemotherapy-naive patients with CRC liver metastases not suitable for curative therapy	1103	Combination of 3 randomized, phase III trials	FOLFOX plus single treatment TARE	72% vs 63%; = .001	11.0 versus 10.3 months, HR,0,90 (95% CI 0.79–1.02) $p=0.11$	22.6 versus 23.3 months, HR, 1.04 (95% CI 0.90–1.19; $p=0.61$	74% versus 67%
EPOCH	Patients with CRC and liver metastasis who progressed on oxaliplatin- or irinotecan-based first-line therapy	428	Randomized, open-label, multicenter, phase III Trial	Second-line chemotherapy with TARE versus second-line chemotherapy	34% versus 21% $p=0.001$	mPFS: 8.0 versus 7.2 months. HR 0.69 (95% CI 0.54–0.88); $p=0.001$, mhPFS: 9.1 versus 7.2 months. HR 0.59 (95% CI 0.46–0.77); $p<0.001$)	14.0 versus 14.4 months. HR, 1.07 (95% CI 0.86–1.32); $p=0.722$	68% versus 49%

AEs adverse events, *BCLC* barcelona clínic liver cáncer, *CI* confidence interval, *CRC* colorectal cáncer, *HCC* hepatocellular carcinoma, *HR* hazard ratio, *mPFS* median progression-free survival, *mhPFS* median hepatic progression-free survival, *ORR* overall response rate, *OS* overall survival, *TARE* transarterial radioembolization, *TACE* transarterial chemoembolization

combined treatment group (29.4 vs. 12.8 months, $p=0.02$). No difference in the quality of life was observed between the two groups [53].

Due to the promising efficacy of the combination, three phase III trials were designed (SIRFLOX, FOXFIRE, and FOXFIRE-global) to compare the efficacy of selective internal radiation therapy (SIRT) with Y90 combined with FOLFOX6 chemotherapy (± an-ti-VEGF and/or anti-EGFR therapy) as a first-line treatment in patients with unresectable liver-dominant metastatic CRC with or without extrahepatic disease (Table 2). The SIRFLOX trial [54] included 530 patients and showed that although the addition of SIRT to FOLFOX did not improve PFS (10.7 vs. 10.2 months), it significantly delayed liver disease progression (20.5 vs. 12.6 months), with no impact on survival. A pooled analysis of the three phase III trials was published in 2017. A total of 1103 patients were included. The median PFS in the SIRT/FOLFOX group was 11.0 and 10.3 months in the FOLFOX group (HR 0.90; 95% CI 0.79–1.02, $p=0.11$). In the liver-only subgroup analysis, median PFS was 11.1 months for the FOLFOX group and 11.9 months for the FOLFOX/SIRT group (HR 0.86, 95% CI 0.73–1.01, $p=0.066$). Cumulative incidence of radiological first progression within the liver was lower in the FOLFOX/SIRT group (HR 0.51 (95% CI 0.43 − 0.62); $p<0.0001$). Objective responses in the liver were more frequently observed in the FOLFOX/SIRT arm (OR 1.78; 95% CI 1.37–2.31, $p<0.0001$), but no difference in patients undergoing liver resection was observed (OR 1.07; 95% CI 0.78–1.48, $p=0.67$). Median OS, the primary endpoint, was not significantly different in the FOLFOX/SIRT versus FOLFOX arm (22.6 vs. 23.3 months, respectively. HR 1.04, 95% CI 0.90–1.19; $p=0.61$) [55]. Toxicity was higher in the SIRT/FOLFOX group, particularly SIRT-related expected toxicities and neutropenia. Serious adverse events were reported in 54% versus 43% of the patients, respectively. Ten patients in the combination group and 3 patients in the FOLFOX group experienced a treatment-related death. The addition of SIRT to FOLFOX significantly reduced HRQOL quality of life for up to 3 months following SIRT; however, this difference was not clinically relevant [56].

Gibs et al. analyzed the effect of primary tumor location on survival within the SIRFLOX and FOXFIRE trials. When SIRT was added to chemotherapy a significant improvement in OS was observed for right-sided primary tumors but not for left-sided primary tumors (HR 0.67; 95% CI 0.48–0.92) [57, 58]. Wasan et al. reported that KRAS mutation was a prognostic factor for shorter OS, but did not predict benefit from the combination strategy [59].

TARE with chemotherapy for CRC liver metastasis in the second-line setting

The EPOCH study is a phase III trial that aimed to assess the benefit of TARE in combination with second-line chemotherapy in 428 patients with metastatic CRC (Table 2). The co-primary endpoints were PFS and hepatic PFS. The median PFS was 8.0 (95% CI 7.2- 9.2) and 7.2 (95% CI 5.7–7.6) months in the combination group and chemotherapy alone group, respectively. The HR for PFS was 0.69 (95% CI 0.54–0.88; $p=0.0013$). The median hepatic PFS was 9.1 (95% CI 7.8–9.7) and 7.2 (95% CI 5.7–7.6) months, respectively, with a HR of 0.59 (95% CI 0.46–0.77; $p<0.0001$). Overall response rate was also higher in the combination group (34 and 21%; $p=0.0019$). However, median OS was similar in both arms (14.0 (95% CI 11.8–15.5) and 14.4 months (95% CI 12.8–16.4; $p=0.7229$; HR 1.07 (95% CI 0.86–1.32). Subgroup analysis found that tumors with KRAS mutation, left-sided primary tumors, hepatic tumor burden 10%–25%, less than 3 lesions, and addition of a biologic agent and resected primary tumor were associated with longer hepatic PFS. Chemotherapy-related adverse events were comparable between the groups and Y90 did not compromise the ability to receive additional chemotherapy [60]. The small benefit in PFS and the absence of benefit in OS, together with an overall excess in toxicity and substantial cost (approximately $31,000 and $48,000 in US dollars for unilobar and for bilobar TARE, respectively [61]), do not support the addition of TARE to second-line chemotherapy, at least in unselected patients [62].

TARE for disease refractory to chemotherapy

The ESMO currently advises the use of TARE for patients with unresectable CRC liver metastases in which other chemotherapeutic options have failed [63]. This was based on a small phase III trial that randomized patients with chemorefractory disease to receive TARE/FU or FU and found a longer median time to tumor progression (4.5 vs. 2.1 months, respectively; $p=0.03$). Median OS did not reach statistical significance (10 vs. 7.3 months, respectively ($p=0.8$) [64].

Other retrospective studies and single-arm trials also provided interesting efficacy and safety data in the chemorefractory setting [65–69]. In a multicenter phase II clinical trial including 50 patients who had received 4 or more lines of chemotherapy, Cosimelli et al. reported a median survival of 12.6 months. Two patients (4%) were sufficiently downstaged for curative resection. In addition, procedure-related toxicity was low [67]. In 2015, Sofocleous et al. described liver disease progression-free survival of 4.7 months with a median OS of 12.7 months and a high proportion with SD at 4–8 and 12–16 weeks (80 and 61%, respectively) in

53 patients with chemorefractory disease [69]. The MORE study, a retrospective analysis of 606 patients with unresectable colorectal liver, reported a median OS after TARE of 13.2 months in patients treated with RE as a monotherapy in the second-line setting. When RE was used in the third and fourth-line setting, OS was 9.1 and 8.1 months, respectively. The study concluded that TARE provided favorable survival even in patients who received 3 or more previous lines of chemotherapy [70]. For patients with chemorefractory disease, KRAS mutation could be a negative prognostic factor [71–74]. Other relevant prognostic factors include neutrophil-to-lymphocyte ratio, CEA, CA 19,9, KDH, HMGB1, and VEGF [75–79].

TARE for oligometastatic disease

Oligometastatic disease is characterized by the existence of metastases at up to 2 or 3 sites and 5 lesions, although occasionally more than 5 lesions. According to ESMO guidelines, the treatment of these patients should have curative intent. This includes surgery and other local ablative therapies [63, 80]. In this scenario, the main advantages of TARE vs TACE are the ability of TARE to achieve hypertrophy of the future liver remanent and its safety in the presence of PVT [81]. However, further research is required to reach a consensus on which local ablative option to use and which patients would benefit.

Y90 radioembolization in biliary tumors

Intrahepatic cholangiocarcinoma (ICC) is an uncommon type of primary liver cancer with a dismal prognosis at advanced stage [82]. In recent years, TARE has been proposed as an option for patients with unresectable ICC in whom systematic treatment has failed. In a systematic review of 12 studies and 298 patients with unresectable ICC that progressed to prior treatment, Al-Adra et al. reported a median OS of 15.5 months with in patients treated with TARE. Partial response was observed in 28% and SD in 54% of patients at 3 months. In 7 patients the disease downstaged for surgical resection [83]. Of note, the OS reported is slightly superior to the OS reported for systemic chemotherapy (cisplatin–gemcitabine) (11.7 months) and after TACE (13.4 months) [84, 85]. Other authors have also reported the ability of TARE to bring patients within resectability criteria [86, 87]. The safety and efficacy of TARE in unresectable ICC has been reported in other studies. Yanhua et al. found a median OS of 14.0 months in a pooled analysis of 16 studies. Partial response and SD were observed in 11.5% and 61.5% of patients, respectively. In terms of toxicity, fatigue and abdominal pain were the most common side effects but they were mild, and with little clinical impact. No significant differences were found between resin and glass matrix microspheres [88]. In contrast, in a prospective observational study performed in 10 sites that included 61 patients with unresectable and chemotherapy-refractory ICC, a median OS of 8.7 months was reported [89]. Similar outcomes for TARE when compared with TACE in patients with unresectable ICC have been reported [90]. Regarding prognostic factors, Köhler et al. reported that the worst results after TARE were observed in patients who had previously undergone surgical resection (OS of 4 months). Previous systematic chemotherapy, and bilobar disease were also associated with lower survival [91]. The combination of chemotherapy and TARE for unresectable ICC has been proposed as a safe alternative with acceptable results. A phase Ib trial of gemcitabine–TARE combination in 8 patients with unresectable hepatic metastases from pancreatic cancer and unresectable ICC reported a DCR of 100% [92].

TARE has also been proposed as a first-line treatment when administrated in combination with chemotherapy. The MISPHEC phase 2 clinical trial studied the efficacy of the combination of chemotherapy (cisplatin and gemcitabine) and Y90 TARE in 41 patients with unresectable treatment-naive ICC. OS was 75% at 12 months and 45% at 24 months. Interestingly, 22% were downstaged to surgical resection [93].

Y90 radioembolization in pancreatic cancer

Small prospective [94] or retrospective studies have addressed the role of TARE to treat hepatic metastases from pancreatic cancer. In one of the largest retrospective studies, 33 patients with chemorefractory pancreatic cancer were treated with TARE and found an OS of 8.1 months. Partial responses were observed in 42% of patients [95]. In other recent retrospective study, 26 patients with advanced and chemorefractory pancreatic cancer were treated with TARE and found a median OS of 7.0 months (1.0–84.1 months). One patient had a PR and 9 had SD [96]. Other authors found similar results in smaller cohorts [97–100]. No unexpected toxicities were reported.

Y90 radioembolization in neuroendocrine tumors

In December 2012, the International Consensus Conference on neuroendocrine liver metastases (NLM) concluded that surgery is the only potentially curative treatment option [101]. For unresectable liver metastases, SIRT and TACE may have a palliative role. It has been reported a response rate of 55% with SIRT and a DCR of 88.9% at 3 months. However, studies comparing SIRT vs TACE are required

Table.3 Recruiting clinical studies with transarterial radioembolization with yttrium-90 in patients with gastrointestinal malignancies

NCT	Title	Treatment
Liver tumors		
NCT04668872	Biopsy after radioembolization to identify changes in tumor cells from the radiation	SOC Y90 TARE
NCT03889093	Radioembolization of primary and secondary liver malignancies and the effect on the immune system	SOC Y90 TARE
NCT04315883	Yttrium-90 (TARE-Y90) in children, adolescents, and young adults with liver tumors	SOC Y90 TARE
NCT04517643	TheraSphere® for treatment of metastases in liver	Personal dosimetry-based treatment planning for TARE
Hepatocellular carcinoma		
NCT03731910	Short-term MRI for treatment response evaluation/prediction of HCC treated with TARE	SOC Y90 TARE
NCT03896646	Radioembolization for HCC Patients with personalized yttrium-90 dosimetry for curative intent (RAPY90D)	Y90 glass microspheres TARE using personalized dose measurements
NCT03199274	Perflutren protein-type a microspheres and contrast-enhanced ultrasound in improving response to radioembolization therapy in patients with liver cancer	Perflutren protein-type A microspheres IV; CEUS over 60 min at 1–6 h and at 7 and 14 days after Y90 TARE
NCT04605731	Durvalumab and tremelimumab after TARE for the treatment of unresectable, locally advanced liver cancer	SOC Y90 TARE on day-14. Durvalumab and tremelimumab day 1, every 4 weeks for 12 months
NCT04150874	Contrast-enhanced ultrasound for the evaluation of changes in tumor blood flow surrounding HAE	IV administrative of Lumason® microbubbles, prior to TARE
NCT04390724	Optimizing Y90 therapy for radiation lobectomy	Group 1: Y90 standard of care, Group 2: Y90 Dose determined by results from Group 1
Colorectal áncer liver metastases		
NCT04108481	Immunotherapy with Y90-radioembolization for metastatic colorectal cancer (iRE-C)	Durvalumab + Y90 TARE
Cholangiocarcinoma		
NCT04301778	Durvalumab in combination with a CSF-1R inhibitor (SNDX-6532) following chemo- or radioembolization for patients with IC	Durvalumab and SNDX-6352 following SOC Y90 TARE
NCT02512692	90Y TARE plus gemcitabine and cisplatin in unresectable IC	Y90 TARE + cisplatin/gemcitabine
Neuroendocrine tumors		
NCT04789109	CapTem plus radioembolization for NET liver metastases (CapTemY90)	Capecitabine + temozolomide + SIR-Spheres

We performed a systematic research on clinicaltrials.gov of "radioembolization" and "cancer" with the filter "recruiting", and selecting those involving gastrointestinal malignancies, up to September 2021

CEUS contrast-enhanced ultrasound, *IC* intrahepatic cholangiocarcinoma, *NET* neuroendocrine tumors, *TARE* transarterial radioembolization, *SOC* standard of care, *Y90* yttrium-90

[101–103] Recently, a retrospective review including 248 patients with NLM found no difference between TARE vs TACE in terms of OS (35.9 vs. 50.1 months, $p = 0.3$, respectively) or PFS (15.9 vs. 19.9 months, $p = 0.37$). However, the DCR was greater for TACE vs TARE (96% vs. 85%, $p < 0.01$). TARE was associated with shorter hospital stay [104]. In a recent systematic review and meta-analysis, a total of 870 patients with unresectable NLM from 11 studies and 7 abstracts were included. The DCR was 86% at 3. The median OS was 28 months. The median OS for patients with carcinoid, pancreatic, and unclassified origin of NETs were 56, 31, and 28 months, respectively. Seventy percent of those patients with carcinoid syndrome improved symptoms after TARE [105].

Conclusions and future directions

TARE is a promising approach to treat patients with GI malignancies including HCC, liver metastasis from CRC, and others, although the best clinical scenario for the treatment is still to be determined. New treatment approaches, new indications, new combination strategies with chemotherapy, radiotherapy and

immunotherapy are being studied at this moment in clinical trials (see Table 3) to define the role and optimal patient selection for radioembolization.

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