RADIOEMBOLIZATION FOR HEPATIC MALIGNANCIES. A REVIEW.

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ABSTRACT

INTRODUCTION

Primary liver malignancies and liver metastases from colorectal cancer have a poor prognosis at diagnosis and constitute a major cause of death.

Embolization techniques are generally the treatment of choice for hepatic malignancies that cannot be treated with curative options. 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. This has been considered the standard treatment for patients with unresectable hepatocellular carcinoma (HCC). Transarterial radioembolization (TARE) is also an endovascular procedure delivered through hepatic artery that involves the administration of yttrium-90 (Y90) and other radioisotopes inside a glass matrix or on the surface of resin microspheres. This procedure allows the radiation to be focused on the tumour 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 1961, Miller described a technique to deliver radiation to liver tumours by means of a catheter that was inserted through the femoral artery and placed into the hepatic artery via the gastroduodenal artery [2]. Later, in 1965, Ariel 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 tumour shrinkage and good palliation with minimal complications [3]. In 1967, Simon et al. described the use of Y90 for hepatic neuroendocrine tumours with poor overall outcomes because of toxicity [4]. Eventually, in 1973, 25 patients with colorectal cancer metastases were treated with Y90 resin microspheres. The tumour size decreased in 17 patients. These promising results supported the role of radioembolization for hepatic malignancies and boosted further investigation [5].

Meanwhile, the design and size of the microspheres progressed in various studies, the aim of which was to determine the relationship between the optimal size of the microspheres and adequate liver distribution. Meade et al. reported that microspheres of 15 and 32.5 um were more frequently accommodated by tumour than by healthy tissue. In contrast, 50 μm microspheres were equally distributed in normal and tumour tissue. Eventually, in 1999 the FDA approved the use of glass microspheres for unresectable HCC [6,7]. Three types of Y90 microspheres are currently available: resin microspheres (SIR-Spheres) coated with Y90, glass microspheres (TheraSphere) in which Y90 is an intrinsic component and, finally, microspheres based on the radionuclide holmium-166 (QuiremSpheres) [8].

Radioembolization treatment requires a multidisciplinary assessment of the patient along with a mapping procedure. The mapping procedure aims to determine the arterial anatomy of the liver along with any aberrant hepatic artery anatomy. This allows calculation of the dose to be delivered and avoidance of non-target zones. Moreover, mapping allows assessment of hepatopulmonary shunting. 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-99m-labelled macroaggregated albumin (Tc-99m MAA) [9].

Although the radioembolization technique was relegated as an option for many years, in recent decades many studies have reported the safety of radioembolization for liver malignancies as long as it is well tolerated, and have supported the use of this promising option for patients who are not candidates for curative treatments. These studies have resulted in increasing interest in this technique. However, up until now there has been no consensus on the use of TARE as standard care.

The aim of this review is to summarize the evidence for TARE and its application in clinical practice.

HEPATOCARCINOMA

Introduction

HCC accounts for about 90% for all primary liver cancers and is the second most common cause of cancer-related death globally [10]. Several risk factors have been involved in the development of HCC: hepatitis B virus infection (50%), hepatitis C virus infection (20%), haemochromatosis or cirrhosis of almost any cause. The incidence varies across regions, with the highest incidence in Africa and Asia. In these areas, chronic hepatitis B and exposure to aflatoxin B1 are the main risk factors. Conversely, chronic hepatitis C and alcohol prevail in North America and Europe [11].

The HCC treatment strategy requires a multidisciplinary team involving oncologists, surgeons, hepatologists, radiologists and nuclear medicine specialists. The modified BCLC staging system is currently the most widely used algorithm for HCC; it includes prognostic variables and treatment strategies. It is a dynamic system that has been reviewed and modified in recent years. The BCLC staging system classifies HCCs into four categories: very early/early, intermediate, advanced and terminal stages. However, it has some limitations regarding the value of resection in a subgroup of patients that could benefit from this approach (intermediate stage and multi-nodular lesions) and the value of loco-regional therapies for some BCLC stage C patients. Moreover, the Milan/Mazzaferro criteria for liver transplantation are not completely taken into account in this algorithm [12,13] (**Figure 1**). For this reason, the AHPBA/AJCC consensus in 2010 concluded that no single staging system must be used and advised using BCLC staging in patients with advanced liver disease and those who were not candidates for surgical options (resection or transplantation), and AJCC/UICC classification for patients undergoing resection [14].

The prognosis of HCC depends on tumour burden and underlying liver disease. The median survival following diagnosis is around 6-20 months [15]. 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 being diagnosed at intermediate or advanced stages (70%). TACE is considered the first-line treatment for intermediate HCC (BCLC stage B), and systematic treatment (sorafenib as first-line 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. Despite this, the 2018 ESMO guidelines do not recommend TARE as first-line therapy for HCC in intermediate and advanced stages [14]. Furthermore, in recent years, various authors have reported the role of TARE in maintaining patients within Milan criteria while awaiting a transplant (bridging) or for downstaging (treating tumours so that they become eligible for transplantation) [10].

In view of the results published in recent years, TARE seems to be a promising option for selected HCC patients. Consensus on the use of TARE is therefore needed.

The use of TARE in HCC:

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. Overall survival (OS) when PVT is present is only 2-4 months; however without PVT, OS ranges from 10-24 months. PVT is a limitation for curative treatment [12]. Initially, radioembolization techniques seemed a good option for patients with PVT who were not candidates for TACE.

In 2004, Salem described the injection of yttrium-90 microspheres in a cohort of 15 patients with PVT of first order or related segmental portal vein branches. It was shown to be a safe and well-tolerated procedure [16]. Successive studies supported the safety and good tolerability of TARE (Y90) for HCC with portal vein thrombosis.

In 2008, in a phase 2 study, Kulik demonstrated the safety of TARE with Y90 glass microspheres in 108 unresectable HCC patients with an incidence of PVT of 35% and found no difference in terms of complications related to treatment or liver failure between thrombosis affecting small branch or no PVT when compared with main branch. The partial response for the entire cohort was 42.2% [17].

Subsequently, other studies reported the safety and benefits of TARE in patients with advanced HCC and PVT. In 2010, Salem et al. reported an overall time-to-progression (TTP) of 7.9 months in a total of 291 locally advanced HCC patients treated with radioembolization. Survival varied according to the Child-Pugh score, A or B (17.2 vs 7.7 months). Child-Pugh B patients with PVT had the worst outcomes with a survival of 5.6 months. The best results were for Child-Pugh A patients with or without PVT. The author thus highlighted the impact of Child-Pugh status on TTP and survival [18].

In 2013, in a phase 2 study that included 52 patients receiving Y90 with lobar delivery with BCLC intermediate and advanced HCC, Mazzaferro et al. reported a median TTP of 11 months and there was no significant difference between patients with or without PVT (7 versus 13). The median OS was 15 months with no significant difference between PVT and non PVT. In a multivariate analysis, tumour response affected TTP and survival. The authors therefore concluded that Y90 is safe for patients with PVT [19].

Following a study with 18 patients with HCC and ipsilateral portal vein thrombosis, Pracht et al. concluded that TARE is a safe procedure with a disease control rate of 88.9%. Downstaging for surgery or transplantation was achieved in 4/18 patients (22%). Median progression-free survival was 11 months after treatment. Survival rates at 6 months and 1 year were 88.5 $\pm$ 14.7% and 70.3 $\pm$ 21.1% months respectively [20].

Similarly, Shae et al. reported better OS in patients with major vascular invasion receiving TARE when compared with TACE [21].

Recently, other studies have supported the benefits of TARE in patients with advanced stage HCC (stage C BCLC) even in the presence of PVT. PVT did not alter the survival in patients undergoing Y90 radioembolization. Moreover, thrombus regression was noted [22]. Similarly, in a single centre cohort study of 75 patients with HCC and PVT, Cardarelli reported that ablative TARE is a safe option with longer survival than conventional TARE [23].

Finally, although TARE has been described as a safe procedure for patients with PVT, the need for a prognostic score to predict response to yttrium-90 radioembolization has been advocated for patients with PVT. In this way, the score would help to identify good candidates for TARE. Spreafico et al. thus reported that bilirubin levels, extension of PVT and tumour burden were independent variables correlated to OS in patients with HCC and PVT treated with TARE. They described three prognostic categories: favourable, intermediate and poor prognosis with a median OS of 32.2, 14.9, and 7.8 months respectively [24].

In conclusion, the literature supports the use of TARE in the presence of PVT with benefits in terms of OS and even tumour regression, but adequate selection is crucial.

TARE vs TACE

Many investigators have studied the effectiveness of TARE vs TACE across HCC stages. It is obvious that TACE has a beneficial effect on short-term results, but its effectiveness for long-term outcomes is unsatisfactory.

Several studies have reported the non-inferiority of TARE compared with other local therapies (TACE) and even compared it with systematic therapy (sorafenib) [25]. TARE has thus been proposed as a local therapy for various HHC scenarios.

The intermediate stage constitutes a wide range of patients and is a heterogenous group in terms of tumour 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.

A meta-analysis of 5 studies with 553 patients comparing TACE vs TARE for unresectable HCC found that more patients in the TARE group were alive at 2 years and that the difference was significant (27 vs 18%). However, at 4 years, the survival rates were similar (4%), with no significant difference between groups, and at 5 years only 1% of patients were alive.
No statistical differences in complete or partial radiological response or disease progression were found. Pain was more common with TACE and fatigue with TARE; there were no differences in other post-treatment symptoms between the groups. TTP was more favourable for TARE. Furthermore, TARE was an outpatient procedure while TACE required a one-day hospital stay [25].

In the same way, other authors failed to demonstrate the superiority of TARE regarding overall survival in the long term.
In 2017, a meta-analysis including 736 patients demonstrated a survival benefit for 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 in part by a strong trend to advanced Child-Pugh scores and BCLC stages in the TARE group [26].

Similarly, retrospective cohort studies have concluded that TARE is comparable to TACE in terms of survival rates [27].
In contrast, other authors have reported a better overall survival and response for patients undergoing TARE.
In 2014, in a meta-analysis comparing C-TACE vs Y90 microsphere embolization for HCC that included 13 trials and a total of 1834 patients, Ni found TARE to be associated with significantly higher overall survival and complete tumour response rate with no significant differences in partial response, stable disease or complications [28].
Similarly, Yang conducted a meta-analysis of TARE vs TACE for HHC and reported a better overall survival rate at 2 years versus TACE, although no significant differences were observed at 1 year. A better response to TARE was also observed [29].

Regarding costs, although TARE is more expensive than TACE, TARE is a single therapy while most patients receiving TACE are also on other therapies [30].

The 2019 update of the Indian National Association for study of the liver consensus on prevention, diagnosis and management of hepatocellular carcinoma considers TARE a good 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, extra hepatic metastases or hepatopulmonary shunt of more than 20% [31].

To summarize, some studies have failed to demonstrate the inferiority of TARE compared with TACE. However, other authors have pointed out the benefit of TARE in terms of survival and response. TARE therefore seems to be a good option for patients in whom TACE is not feasible, but more studies are still required to define the role of TARE in this scenario.

TARE for advanced stages. TARE vs systematic therapy.

Although sorafenib is considered the standard treatment for advanced HCC, the role of selective internal radiotherapy with yttrium-90 embolization was also studied in a randomized phase 3 trial (SARAH trial in France) that included 467 patients with locally advanced HCC not responsive to other therapies or in whom TACE was unsuccessful. It failed to demonstrate a benefit for TARE over sorafenib (overall survival 8 months for TARE vs 9.9 months for sorafenib) although the tumour response rate was higher with TARE than with sorafenib (complete response 3% vs 1%). Toxicity (grade 3 side effects) was more common in the sorafenib group than in the TARE group (63% vs 40.7%) [32].

Similarly, SIRveNIB failed to prove the superiority of TARE over sorafenib. It included 350 Asia-Pacific patients and showed no significant differences in OS between TARE and sorafenib (8.8 months vs 10.0 months), with TARE associated with a higher tumour response rate (TRR) (16.5% vs 1.7%) and fewer grade 3 side effects (27.7 vs 50.6%) [33].

The fact that these two trials have failed to demonstrate superiority in overall survival of TARE over sorafenib could be explained by the wide range of patients included. Furthermore, TARE showed a better tumour response although this did not translate to a better OS. TARE also showed lower toxicity in both trials.
Despite these findings, the benefits of TARE for patients with advanced HCC found in large cohort studies should not be disregarded**.**

A meta-analysis comparing TARE and sorafenib in patients with HCC and PVT recently concluded that TARE is safer and more effective in patients with PVT and is also associated with higher OS. Furthermore, TARE delayed tumour progression with better tolerance [34].

Moreover, the SORAMIC phase II trial studied whether the addition of TARE to sorafenib in advanced HCC patients improved survival. However, it failed to demonstrated better OS when TARE was added to sorafenib vs sorafenib alone [35].

The STOP-HCC Phase 3 trial is currently underway across North America, Europe and Asia. Its primary endpoint is overall survival for sorafenib vs transarterial embolization in unresectable HCC. It is thought that it will help to establish the role of TARE in unresectable HCC [36].

In conclusion, although the trials performed up to now comparing TARE and sorafenib have failed to demonstrate the superiority of TARE over sorafenib in terms of OS, TARE achieved more favourable TTP. Moreover, other studies have reported longer survival for TARE when compared with sorafenib even in the presence of PVT. Further investigation is therefore required to determine which patients with advanced HCC would benefit from TARE instead of sorafenib.

TARE for downstaging and bridging approaches

Yttrium 90 radioembolization has been suggested as an option to control tumour burden while patients are awaiting liver transplantation; this is known as "bridging". This is different to downstaging, which involves tumour reduction so that patients meet the Milan criteria.

Unfortunately, only a minority of patients with HCC are suitable for liver transplantation**.** Successful downstaging to within Milan criteria allows a curative option to be offered to HCC patients. However, an optimal downstaging protocol has not been defined. It has been suggested that transarterial radioembolization could bring patients within the Milan criteria. In addition, a downstaging approach would allow reduction in the tumour burden to be identified during aggressive HCC.

The success rate of the use of RE for downstaging so that curative therapy may be used ranges from 22 to 78.9%, the lowest rates being reported in patients with tumours and ipsilateral portal vein invasion [37].

In a systematic review including 13 studies and 950 patients, Neehar reported no significant differences in the success rate of downstaging or the recurrence rate between TACE and TARE. The highest success rates of downstaging were reported in multimodal approaches. Post-transplantation recurrence was higher in the downstaging group than in those that presented within Milan criteria [38].

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 [39].

The role of RE in downstaging is promising according to Dendy et al., who reported two patients with infiltrative HCC with PVT with disease advanced beyond the criteria for transplantation, who underwent TARE and achieved a complete response after single high-dose lobar radioembolization during a 2-year follow-up and as a result underwent orthotopic liver transplantation [40].

Surgical resection or liver transplantation are curative options for stage A HCC patients. Liver transplantation is usually the best option for patients presenting underlying cirrhosis.

TARE/SIRT using yttrium-90 microspheres for bridging to transplantation has been investigated in patients with BCLC-A.

The median time to liver transplantation is around 1 year depending on region and blood type. Disease progression occurs in 10-23% of patients waiting for transplantation. Therefore, a bridging therapy needs to be established in order to improve overall survival in patients with HCC.

Local therapies such as TACE and TARE have been advocated to control tumour 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 effectiveness of cTACE versus Y90 radioembolization for unresectable HCC. It included 43 patients with BCLC stage A/B, Child-Pugh A/B and no systemic therapy. The primary outcome was time-to-progression (TTP). It demonstrated longer TTP for Y90 when compared with TACE (more than 26 vs 6.8 months) although this did not mean better overall survival (18.6 vs 17.7 months), probably because this local control was not enough to improve survival in patients with cirrhosis. However, this better local control could be translated to a lower dropout rate from the transplant waiting list. The rate of transplantation was higher in the TARE group (87% vs 70%) [40]. Similarly, other studies have highlighted the role of TARE in bridging [41,42]

Recurrence is a major concern after liver transplantation. Bridging therapy has not been shown to have a beneficial effect after liver transplantstion. 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 [43]. Further investigations are required to determine bridging and downstaging strategies including TARE.

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, radioembolization 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 [37,44].

Subsequent studies reported a hypertrophy grade 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 [45,46].

Furthermore, radiation can 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 [37,47].

The benefits of radiation segmentectomy have been described in several studies. 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 26.9 months (overall survival 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 being the most common side effect (52%). Biochemical toxicity ranged from 2-6% [47].

Similarly, 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 mRECIST complete response, partial response and stable disease rates were 47%, 39% and 12% respectively. 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 and with a Child-Pugh A score had longer survival [48].

To summarize, TARE may be used for curative and ablative purposes when administrated as segmentectomy for early HCC not suitable for curative techniques. However, more studies are required in this field.

LIVER METASTASES FROM COLORECTAL CANCER

Introduction

Colorectal cancer constitutes the second most common cancer in Europe. Approximately 20% of colorectal cancers present metastatic disease at diagnosis. The most common metastatic sites include liver, lung, lymph nodes and peritoneum [49]. However, only 10-20% are candidates for surgery [50].

In recent years, the prognosis of patients with colorectal cancer (CRC) liver metastases has improved thanks to the appropriate selection of patients for surgery, a more effective systematic chemotherapy approach and the advance in ablative techniques. Up to now, surgery remains the gold standard treatment for these patients. When surgery is possible, the five-year survival rate after resection ranges from 24-58% with a mortality rate of less than 5% [51].

Systemic chemotherapy is the first-line treatment for patients with unresectable CRC liver metastases. First-line chemotherapy regimens include FOLFOX and FOLFIRI, with a median survival of 16-20 months. The addition of biological agents could improve progression-free survival and OS [52,53].

However, other local therapies such as radiofrequency ablation, TACE or TARE have also been proposed for unresectable liver metastases from CRC with acceptable results. The phase II CLOCC trial demonstrated that radiofrequency ablation combined with systematic chemotherapy improved progression-free survival rate at 3 years in unresectable CRC liver metastases. Moreover, the combination of RF ablation plus chemotherapy achieved a 30-month overall survival rate of more than 38% [54].

TACE has also been advocated for unresectable CRC liver metastases with acceptable results. A phase III trial found that OS was significantively longer in the TACE group vs FOLFIRI (22 vs 15 months). Furthermore, progression-free survival was more favourable with TACE when compared with the FOLFIRI group (7 months vs 4 months, statistically significant) [55]. Similarly, TARE has been described as a local therapy for CRC liver metastases with acceptable results, achieving an improvement in time to liver progression when compared with FU in patients with unresectable CRC liver metastases.

In the early 1990s, Gray reported the benefit of Y-90 TARE in 29 patients with unresectable CRC liver metastases. CT tumour size decrease was more than 50% in 48% of patients and the decrease CEA compared with pre-treatment levels was 70% [56,57].
However, the use of TARE in this scenario is not defined and further investigation is required in order to achieve consensus.

The USE of TARE IN CRC liver metastases:

<u>**TARE as first-line treatment**</u>

Up to now, the possible benefit of combining TARE with chemotherapy versus chemotherapy alone has been reported in many studies, although evidence is not enough to establish a consensus.

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 months vs 3.6 months, p<0.005, respectively). Similarly, median survival was higher in the combined treatment group (29.4 months vs 12.8 months, p=0.02). No difference in the quality of life was observed between the two groups [58].

The randomized SIRFLOX trial studied the role of selective internal radiation therapy (SIRT) with Y90 combined with FOLFOX6 chemotherapy as a first-line treatment in patients with unresectable liver-dominant metastatic CRC (mCRC) with or without extrahepatic disease. It demonstrated that although the addition of SIRT to FOLFOX did not improve PFS (progression-free survival ((10.7 vs 10.2 months), it significantly delayed liver disease progression (20.5 vs 12.6 months). Moreover, SIRT did not have an adverse impact on the delivery of chemotherapy [59].

The benefit of SIRT in combination with chemotherapy in achieving tumour size reduction for resection has recently been reported. The SIRFLOX trial included 472 patients. In the SIRT plus FOLFOX (with or without bevacizumab) group, more patients had resectable disease compared with chemotherapy alone (38.1% vs 28.9%, p<0.001).

The impact of SIRT plus FOLFOX on quality of life has also been studied. ==Although the addition of SIRT to FOLFOX reduces significantly HRQOL quality of life for up to 3 months following SIRT==, this difference lacks clinical importance [61].

The FOXFIRE and FOXFIRE-Global trials were designed in the same manner as the SIRFLOX trial. They found the combination of SIRT with chemotherapy to have no benefit versus chemotherapy alone in terms of overall survival or progression-free survival [59].

Gibs et al. reported on the effect of location of the primary tumour on survival. They analysed the data from two randomized trials (SIRFLOX and FOXFIRE) with a total of 739 patients and concluded that when SIRT was added to chemotherapy a significant improvement in OS was observed for right-sided primary tumours but not for left-sided primary tumours (HR, 0.67; 95% CI, 0.48-0.92) [62].

It has been reported that patients with CRC liver metastases and a right-sided primary tumour have a poor prognosis. SIRT therefore seems to be a promising choice in these patients [63].

In conclusion, although the addition of SIRT to chemotherapy may achieve delayed liver disease progression, this has not been shown to result in a significant gain in either OS or PFS. SIRT could be beneficial in selected patients such as those with right-sided primary tumours. However, further investigation is required to determine the role of SIRT in combination with chemotherapy.

TARE for disease refractory to QT

Most CRC liver metastases are not suitable for surgery and treatment is more palliative than curative. The objective of the chemotherapy is therefore to increase progression-free survival times, prolong life, improve quality of life and shrink tumours [64].

TARE has been proposed as an alternative for patients with unresectable CRC liver metastases in which standard chemotherapy regimens have failed. In a multicentre 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. OS was significatively different in patients responding to TARE vs non-responders (79.2 vs 20.2% at 1 year and 40.3% and 0% at 2 years respectively). Moreover, two patients (4%) were sufficiently downstaged to be candidates for potentially curative resection. In addition, procedure-related toxicity was low (4%). However, more interesting was the fact that a response to chemotherapy was noticed after TARE in 3 patients. This could open a new line of investigation [65].

Similarly, other authors have reported the benefit of TARE for patients who had shown no response to systemic chemotherapy, with minimal toxicity [66].

In 2015, in a study that included 53 patients in whom systematic chemotherapy had failed, 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 stable disease at 4 to 8 and 12 to 16 weeks (80% and 61% respectively). These data were consistent with the previous studies [67].

The safety of radioembolization in this scenario, as well as the acceptable results, were supported by subsequent studies [68].

The MORE study included 606 patients and reported a median OS after radioembolization of 13.2 months in patients treated with RE as a monotherapy in the second line (after 1 line of chemotherapy failed). When RE was a third-line treatment, OS was 9.1 months and as a fourth-line treatment, 8.1 months. The study concluded that radioembolization provided favourable survival even in patients who received 3 or more previous lines of chemotherapy [69].

Other investigators supported the use of chemotherapy in combination with radioembolization (SIR-Spheres) vs radioembolization because of its more favourable benefits in terms of the liver disease control rate and prolonged liver disease PFS when compared with radioembolization alone. Concurrent chemotherapy could improve tumour responses to radioembolization in patients whose disease is refractory to chemotherapy.

The EPOCH phase 3 randomized clinical trial is studying the role of SIRT with Y90 combined with second-line therapy in patients in whose disease has failed in the first line. It is thought that this will establish the role of TARE combined with oxaliplatin or irinotecan chemotherapy regimens [70].

In summary, systematic chemotherapy continues to be the gold standard for patients with unresectable CRC liver metastases. However, some studies have pointed to the benefit of TARE for patients with disease refractory to chemotherapy. In this situation, radioembolization seems to be a promising choice; however the selection of patients is challenging.
The ESMO currently advises the use of radioembolization for patients with unresectable CRC liver metastases in which other chemotherapeutic options have failed.

TARE for oligometastatic disease

Oligometastatic diseases is characterized by the existence of metastases at up to 2 or 3 sites and 5 lesions, although occasionally more than 5 lesions. They predominantly occur at the internal organs but lymphonodal disease is also possible.

According to ESMO guidelines, treatment of these patients should entail the option that could possibly achieve complete ablation of all tumour lesions. This ranges from surgery to local ablative therapies and, in many cases, systematic chemotherapy as the initial therapy [71,72].

TARE could be a good option for patients showing liver-dominant disease in whom systematic chemotherapy has failed in order that the segmental or lobar delivery reaches many lesions. The main advantages of TARE vs TACE in this scenario are the ability of TARE to achieve hypertrophy of the FLR and its safety in the presence of PVT [73].

However, further research is required in order to reach a consensus on which local ablative option to use and which patients would benefit.

BILIARY TUMORS

Intrahepatic cholangiocarcinoma (ICC) is an uncommon primary liver cancer. The only possible curative treatment is surgery. However, the vast majority of cases are diagnosed when the disease is at advanced stage and surgical resection with clear margins is not possible. For advanced and unresectable cases, chemotherapy based on gemcitabine and cisplatin is the first line of treatment [74]. The median OS for unresectable ICC patients is less than 8 months [75].

In recent years, TARE has been proposed as an option for patients with unresectable ICC in whom systematic treatment has failed. However, the role of TARE in this scenario needs to be defined.

In a systematic review of 12 studies and 298 patients with unresectable ICC that had mostly received some type of treatment prior to radioembolization, Al-Adra reported an overall median survival of 15.5 months after TARE. Partial response was observed in 28% and stable disease in 54% patients at 3 months. Furthermore, in 7 patients the disease could be downstaged and they were able to undergo surgical resection [76].

In this paper, the OS reported after TARE is slightly superior to the OS reported for systemic chemotherapy (cisplatin-gemcitabine) (11.7 months) and after TACE (13.4 months) [74,75].

In terms of tolerability, fatigue was reported in 33% cases. The second most common undesirable effect was abdominal pain (28%) [76].

Other authors have also reported the ability of TARE to bring patients within resectability criteria [77,78].

This may support the use of TARE as a first-line treatment in patients with borderline resectable ICC, but this option needs further investigation.
The safety and efficacy of TARE in unresectable ICC has been reported in subsequent studies. Yanhua et al. recently found a median OS of 14.0 months for TARE in a pooled analysis of 16 studies. Although no complete response was reported, partial response and stable disease were 11.5% and 61.5% respectively. In terms of toxicity, fatigue and abdominal pain were the most common side effects but they were mild with little clinical impact. Moreover, the different types of microsphere were studied and no significant differences were found between the two groups (resin and glass matrix) [79].

However, the results vary across the various studies. In a prospective observational study performed in 10 sites that included 61 patients with unresectable and chemotherapy-refractory ICC, White reported a median OS of 8.7 months, which was lower than the OS reported by other authors [80].

Some authors have found similar outcomes for TARE when compared with TACE in patients with unresectable ICC. Olaguoke reviewed 40 patients treated in a single institution and found a similar response rate and disease control rate between TARE and TACE groups [81].

It is crucial to identify prognostic factors that help to select the patients that may benefit from TARE. Köhler reported that the worst results after TARE were observed in patients who had previously undergone surgical resection (OS of 4 months). Moreover, previous systematic chemotherapy was associated with lower survival. Furthermore, survival after TARE was related to the extent of disease, bilobar disease showing a decreased survival rate when compared with unilobar disease. However, tumour volume did not turn out to be a prognostic factor for survival [82].

More studies are therefore required to establish the role of TARE in unresectable and chemotherapy-refractory ICC. In the same way, scores and tools that help to select which patients will benefit are mandatory to improve results. Trials comparing systematic chemotherapy, TARE and TACE are required.

Moreover, the combination of chemotherapy and TARE for unresectable ICC has been proposed as a safe alternative with acceptable results. A phase Ib trial studied the gemcitabine-TARE combination in 8 patients with unresectable hepatic metastases from pancreatic cancer and unresectable ICC. It reported an overall disease control rate of 100% for ICC. However, this was a small clinical trial with only 8 patients [83].

In addition, TARE has also been proposed as a first-line treatment when administrated in combination with chemotherapy. The MISPHEC phase 2 clinical trial showed the benefit of combination chemotherapy (cisplatin and gemcitabine) and Y-90 radioembolization for unresectable ICCs that had not received any treatment in a previous line. It included 41 patients. OS

rates of 75% at 12 months and 45% at 24 months were reported. More promising was the effect on downstaging: 22% were downstaged to surgical resection. The response rate was 39% at 3 months [84].

To summarize, the literature supports the use of TARE, with favourable results in combination with chemotherapy and acceptable side effects. However, further studies are required to determine which patients would benefit from this approach.

CONFLICT OF INTERESTS

All the authors declare no conflict of interests.

LEGENDS

Figure 1 . Management of HCC. BCLC staging.

Figure 2. This shows different papers and the most relevant evidence on TARE strategies.

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