





## SIRT in 2025

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**Abstract** Selective internal radiation therapy represents an endovascular treatment option for patients with primary liver malignancies, in different clinical stages. Potential applications of this treatment are in early-stage hepatocellular carcinoma, as a curative option, or in combination with systemic treatments in intermediate and advanced-stages. This review, based on existing literature and ongoing trials, will focus on the future of this treatment in patients with hepatocellular carcinoma, in combination with systemic treatments, or with the use of new devices and technological developments; it will also describe new potential future indications and structural and organizational perspectives.

**Keywords** SIRT · Locoregional treatment · HCC · TARE · Yttrium-90 · TKI · Chemotherapy · Immunotherapy

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## Introduction

Selective internal radiation therapy (SIRT) is a locoregional treatment for primary and secondary liver neoplasms which applies high radiation energy selectively targeting tumor tissue, sparing the surrounding parenchyma. SIRT is mostly performed using glass or resin microparticles loaded with Yttrium-90 (90Y), and its role is well known in intermediate and advanced HCC, particularly in patients with portal vein thrombosis [1]; however, according to the recent update of Barcelona Clinic Liver Cancer Criteria, SIRT may be administrated also in BCLC stage 0 patients as an alternative to percutaneous ablation, with a curative intent, especially in elderly patients with contraindications for surgery or in patients with nodules difficult to treat with other techniques [2]; moreover in BCLC stage A patients in case of a solitary tumor or as a second choice if ablation or resection could not be performed or as a bridge treatment before surgery [3]. In the last few years SIRT has demonstrated a safety and efficacy profile comparable with transarterial chemoembolization or even superior in terms of time to progression of the disease in advanced tumors [2, 4]. In addition, radiation lobectomy can be considered to induce liver tissue hypertrophy before surgery, and also to control tumor progression as a bridge to liver transplantation [4]. In advanced HCC, SIRT will be combined with systemic treatment such as tyrosine kinase inhibitors, immunotherapies, or both [2].

This review will focus on available data and ongoing trials on the future applications as well as structural and organizational perspectives of SIRT, exploring new potential combined treatment options as well as new devices, technological developments, that will allow potential new indications.

## Combination of TARE with TKI Medication

Radiation therapy (RT) is efficient in an oxygenated environment, as the production of reactive oxygen species causes cell death; conversely, hypoxic conditions determine radiation-resistance. RT (particularly fractionated RT) enhances the production of Hypoxia Inducible Factor (HIF), Vascular Endothelial Growth Factor (VEGF), Platelet-derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and other proinflammatory cytokines, inducing vessels proliferation. Tumor cells escape from hypoxia producing VEGF and other cytokines, activating neoangiogenesis; however, these vessels are aberrant, leading to the maintenance of the hypoxic environment. Antiangiogenic drugs restore the radiosensitivity of tumors by remodeling vessels and causing a transient vascular normalization that provides oxygen delivery to tumor cells, whereas in the long-term the reduction of blood vessels leads to hypo-oxygenation. High radiation doses damage tumor vessels and induce endothelial cells apoptosis; antiangiogenic drugs counteracting VEGF corroborate RT efficacy [33–36]. As HCC is highly vascularized, antiangiogenic drugs such as the tyrosine kinase inhibitors (TKIs) Sorafenib and Lenvatinib are used for the first-line treatment of advanced, unresectable HCC. Regorafenib and Cabozantinib are TKIs used as second line options after progression to Sorafenib, similarly to the anti-VEGF receptor-2 monoclonal antibody Ramucirumab [37–41]. SIRT has been compared with Sorafenib in patients with advanced HCC or with locally advanced HCC after transarterial chemoembolization (TACE) failure [2, 37, 42]. The SARAH study was the first multicenter prospective phase-III trial comparing the efficacy of SIRT with Sorafenib. Patients treated with SIRT showed a better safety profile and quality of life, and higher tumor response rates (19% versus 12%,  $p = 0.0421$ ), even in patients with portal vein invasion [43]. Analyzing the tumor recurrence rate, the SIRT group showed fewer events than the Sorafenib group and better tolerability profile, suggesting the choice of SIRT in patients with intrahepatic disease, tumor burden  $\leq 25\%$  and compensated liver function [44]. Despite these relevant results, the study did not meet the primary endpoint criteria, as OS was not different between the SIRT and Sorafenib groups. An ancillary study demonstrated a significant difference in OS in patients who received a TD  $\geq 100$  Gy (14.1 months) than those who received  $< 100$  Gy (6.7 months) ( $p = 0.001$ ), with 74% of disease control in the first ones; no differences in adverse events were described [45]. A prospective multicenter trial in the Asian population obtained the same results of the SARAH trial, demonstrating better local tumor control, safety and tolerability profile versus systemic therapy and

tumor response rate of 16.5% in the RE group versus 1.7% in the TKI group ( $p < 0.001$ ) in patients with BCLC B/C HCC, but without significant benefits on OS and progression-free survival (PFS) [46].

Considering the SIRT local tumor control and the modulation on inflammation and neoangiogenesis of anti-VEGF therapies that may overcome radiation resistance, several studies evaluated the combination of SIRT and TKIs in patients with advanced HCC [33–36].

The SORAMIC study was prospectively designed to evaluate if the combination of SIRT plus Sorafenib would improve OS versus Sorafenib monotherapy in patients with advanced HCC [47]. The results were similar to previous studies: OS was 14 months for SIRT versus 11 months for Sorafenib; the subgroups evaluation showed better OS in patients  $\leq 65$  years, in non-cirrhotic or compensated non-alcoholic cirrhotic patients, and in patients with more than seven nodules. Previous TACE was associated with better survival in the Sorafenib arm [47, 48]. The SORAMIC trial also evaluated the alteration of liver enhancement after gadoteric acid administration during hepatobiliary phase of magnetic resonance imaging (MRI) compared to the spleen enhancement; the Liver-to-Spleen ratio (LSR) directly correlates with reduced liver function: a low LSR was described in the presence of higher levels of AST, bilirubin, ascites and varices [49]. Extrahepatic disease spread did not significantly impact on survival between the two groups ( $p = 0.6483$ ), nor the progression during the study (19% of cases); conversely, lung metastases reduced patients' survival in both groups ( $p = 0.0060$ ). Therefore, except for lung metastases, presence of extrahepatic metastases in patients with a high HCC liver burden should not affect the possibility to perform locoregional treatments to control the intrahepatic disease, as the main cause of death in these patients is intrahepatic progression and liver failure [50, 51]. A meta-analysis of three studies revealed the non-inferiority of SIRT compared to Sorafenib for the treatment of advanced HCC [43, 46, 47]. SIRT led to a better OS in patients with chronic hepatitis B or in non-cirrhotic HCC patients. Furthermore, a higher percentage of partial responses (PR) was observed in the SIRT arm, while patients in the Sorafenib group frequently showed disease stability (DS) [52]. However, these studies did not address the delivered TD, which could have affected the final results [53, 54].

A phase-II study determined safety and efficacy of Sorafenib followed by SIRT in patients with advanced or metastatic HCC and Child–Pugh A, naive to locoregional treatments or who were unsuccessfully treated: 35.7% of patients presented PR, 47% DS, whereas none achieved complete response (CR). Median PFS was 10.3 months; OS was 13.2 months [55].

## Combination of TARE with Immunotherapy

Immune checkpoint inhibitors (ICIs) represent the new frontier in cancer therapy [56–61]. They are antibodies targeting proteins called “immune checkpoints”, such as programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein-4 (CTLA-4), which are present on T-cells, B-cells and antigen presenting cells (APCs), involved in maintenance of self-tolerance. Cancer cells implement evasion mechanisms of immune checkpoints hyperexpression to escape immune response. Blocking immune checkpoints enhances immune response and promotes anticancer defense. ICIs are used as first- or second-line therapy, often in combination with TKIs or other antiangiogenic drugs [62].

RT boosts inflammation, leading to a systemic response that may result in anti-tumor effects in sites distant from the irradiated area, the so-called “abscopal effect”, linked to “immune cell death” [63]. Stress derived by RT enhances damage-associated molecular patterns (DAMPs) expression and recruiting of immune cells. RT damage on endoplasmic reticulum and cellular or nuclear membranes, causes the activation of calreticulin and its exposition on the cell membrane, leading to dendritic cells (DCs) activation, phagocytosis of tumor cells and antigen presentation to cytotoxic lymphocytes [64, 65]. Dying tumor cells also release antigens, as DNA, that stimulate immunological response [64].

Therefore, combination of RT and ICIs is expected to obtain promising results. ICIs need appropriate antigen presentation to be effective, a process enhanced by RT. On the other hand, RT also causes upregulation of immune checkpoints, generating radiation-resistance; thus, ICIs can restore the cytotoxic T-cell and APCs activities, and may implement the abscopal effect, overcoming the radiation-resistance [66–68]. SIRT determines a significant shift in the characteristics of tumor infiltrating lymphocytes (TIL), increasing CD56 + natural killer (NK), CD4 + and CD8 + T cells [69]. Conversely, before SIRT, TIL were mostly regulatory T-cells that downregulated the immune response against tumors. Tumor necrosis factor (TNF)-alpha was elevated in SIRT responders, and a sustained response was found when TIL expressed higher levels of PD-1 before and after SIRT [70].

Indeed, as described by previous studies, following radioembolization it is reported an increased production of inflammatory cytokines, such as interleukin (IL) 1, IL-6 and IL-8, TNF $\alpha$ , and the release of several inducible factor as hypoxia inducible factor 1 $\alpha$ , VEGF, matrix metalloproteinases (MMPs), and mammalian target of rapamycin (mTOR). The combination of SIRT with immune checkpoint inhibitors has demonstrated to enhance the systemic

inflammatory response by reverting the suppressive phenotype derived by the upregulation of tumor induced immune checkpoints on peripheral and intratumoral immune cells and stimulating them to produce TNF  $\alpha$  and granzyme B that lead to a sustained systemic inflammation and an increased anti-tumor response [13, 71, 72].

Given their synergistic immunomodulatory effects, association of SIRT and immunotherapy has been tested in several clinical trials [69].

In a retrospective study, patients with advanced or intermediate-stage HCC and good liver function (Child–Pugh A–B7) were treated with Nivolumab or Nivolumab plus Ipilimumab after SIRT: two patients experienced delayed grade 3/4 hepatobiliary toxicity [71]. Another retrospective study evaluated patients with BCLC B/C HCC, prevalently Child–Pugh A, who underwent SIRT or TACE after Nivolumab: two patients discontinued treatment due to immune-related adverse events (irAEs) (pneumonitis and transaminitis), five grade 3/4 hepatobiliary toxicity occurred within 3 months after locoregional therapy, with no grade 3/4 adverse events attributable to Nivolumab. 1-month overall objective response rate (ORR) was 45% [72].

A prospective phase-I clinical trial evaluated the combination of Nivolumab plus SIRT in patients with advanced HCC not eligible for surgical treatments. Nivolumab was started after SIRT at the dose of 80 mg (group 1) or 240 mg (group 2); primary endpoint was defining the maximum tolerated dose of Nivolumab when combined with SIRT. Group 2 dose was well-tolerated; the most relevant irAE in both groups was grade 1–2 transaminases elevation. Overall disease control (ODC) rate was 82%; 9 out of 11 patients showed stable disease [73]. A phase-II clinical trial enrolled patients with advanced HCC and Child–Pugh A cirrhosis not eligible for surgery, who underwent SIRT followed by Nivolumab administration, obtaining 30.6% ORR (1 CR, 10 PR); five patients presented serious treatment-related adverse events (Steven–Johnson syndrome, hepatitis E infection, fever, liver abscesses, ascites) [74].

Several ongoing studies are evaluating the safety and efficacy of SIRT plus ICIs. A phase-I study [NCT03812562] is evaluating the combination of Nivolumab plus SIRT after surgical resection; primary endpoint is recurrence rate. NCT03099564 is evaluating the combination of Pembrolizumab plus SIRT in patients with HCC not eligible for surgical resection or liver transplantation; primary endpoint is 6-months PFS.

Combination of Durvalumab, an anti PD-L1 antibody, and Tremelimumab, an anti CTLA-4 antibody, was superior to Sorafenib in terms of OS either in combination or as Durvalumab monotherapy [61, 75]. A phase-Ib trial [NCT04605731] will evaluate the safety of Durvalumab

plus Tremelimumab or Durvalumab alone after SIRT in patients with unresectable locally advanced BCLC B/C HCC with Child–Pugh A and tumor burden < 50% in terms of ORR according to RECIST, mRECIST and immune mRECIST criteria. A multicenter randomized phase-II trial [NCT05063565] will evaluate the efficacy of SIRT plus combination of Durvalumab and Tremelimumab versus SIRT alone in terms of ORR and response duration in naive HCC patients not eligible for (or who refused) curative treatments. A phase-II randomized trial [NCT04522544] will investigate safety and efficacy of Durvalumab plus Tremelimumab after TACE or SIRT in patients with multifocal HCC or with a single nodule not eligible for curative treatments, or with hepatic veins or portal vein involvement. Another phase-I/II trial [NCT0412499] will investigate if combination of Durvalumab plus SIRT can improve time to progression (TTP) in locally advanced unresectable HCC. A multicenter randomized phase-II trial [NCT04541173] is evaluating patients with Child–Pugh A and BCLC B HCC not eligible for surgical treatments that will receive SIRT alone or followed by Atezolizumab plus Bevacizumab; primary endpoint is 1-year PFS.

### Potential New Isotopes

Currently, the most used radiopharmaceutical product for transarterial radioembolization (TARE) consists of  $^{90}\text{Y}$  microspheres available in two formulations: the glass-based TheraSphere (BTG, Ontario, Canada) and resin-based SIR-Spheres® (SIRTex, North Sydney, Australia) microspheres [76]. Unfortunately, there are some limits concerning  $^{90}\text{Y}$  utilization: microspheres production is a high-cost multi-step process, since  $^{90}\text{Y}$  derives from strontium-90 ( $^{90}\text{Sr}$ ), which is a fission product of uranium in nuclear reactors; this process needs high specialized personnel and brings a heavy radioactive environmental burden [77]. In addition,  $^{90}\text{Y}$  is a pure therapeutic beta-energy emitter, which makes the evaluation of radiation dosimetry and post-TARE microspheres distribution in tissues difficult to be detected, because of intrinsic properties of beta rays, not suitable for diagnostic imaging. For these reasons, in the last few decades new microspheres labeled with  $^{166}\text{Ho}$  have been developed [26].  $^{166}\text{Ho}$  TARE seems to be a feasible option for HCC treatment, with a good safety and toxicity profile, as well as for patients with unresectable and chemo-resistant liver metastases [78, 79]. Compared with  $^{90}\text{Y}$ ,  $^{166}\text{Ho}$  has the advantage of possessing a  $\gamma$  emission (81 keV) suitable for SPECT imaging. Moreover, holmium is highly paramagnetic, thus enabling MRI imaging and quantification. Van Roekel et al. found that patient survival was significantly

longer in case of a mean-tumor absorbed dose greater than 90 Gy in case of  $^{166}\text{Ho}$  TARE [80].

Another interesting isotope which is gaining interest among interventional radiologists is Samarium-153 ( $^{153}\text{Sm}$ ) [81].  $^{153}\text{Sm}$  is a radionuclide derived from purification and neutron activation of  $^{152}\text{Sm}$ . It has a half-life of 46.3 h and emits beta rays of 0.81 MeV (20%), 0.71 MeV (30%), and 0.64 MeV (50%), with maximum penetration in soft tissue up to 4.0 mm; moreover,  $^{153}\text{Sm}$  releases gamma particles of 103 keV that may be utilized for scintigraphy imaging and single-photon emission computed tomography (SPECT) and it has a thermal neutron activation cross section of 210 barns [82]. Neutron activation has a lower cost of production compared to nuclear fission and may be more available worldwide. During neutron activation, the  $^{152}\text{Sm}$  atoms absorb one neutron from the thermal neutron flux to become  $^{153}\text{Sm}$ , with consequent release of energy in the form of gamma radiation. Neutron irradiation may last at maximum of 6 h; longer processes cause radionuclide impurities production. In one study, the radioactive microspheres with size of 20–40  $\mu\text{m}$  were produced and bound to Amberlite cation exchange resin but they resulted inappropriate and irregular for shape and presented a high rate of fragmentation during the neutron activation process [83]. In another study,  $^{152}\text{Sm}$  chloride hexahydrate and  $^{152}\text{Sm}$  carbonate have been used to obtain 35  $\mu\text{m}$  diameter resin microspheres; they resulted able to preserve their shape and integrity during the neutron activation process showing a better efficiency (97–99%) than  $^{153}\text{Sm}$ -labeled microspheres (85–97%) [84]. The same research group in recent years formulated a new type of poly-L-lactic acid microspheres (PLLA) incorporated with  $^{152}\text{Sm}$  acetylacetonate [85]. In another study,  $^{153}\text{Sm}$  oxide-loaded polystyrene microspheres were developed, and they had a remarkable retention efficiency in both saline solution and blood plasma with a medium duration of 550 h [86]. Since no ionizing radiation is needed for the production, these microspheres may be synthesized in a standard chemistry laboratory and then they may be sent in a specialized center to be activated and obtain radioactive  $^{153}\text{Sm}$  oxide-loaded polystyrene microspheres. Previously to  $^{153}\text{Sm}$ , others neutron activated radionuclides such as Holmium and Rhenium were tested as possible alternatives to  $^{90}\text{Y}$ , but they were excluded because of their short half-lives and the need of elevated neutron flux reactors compared to  $^{153}\text{Sm}$  [86, 87].  $^{153}\text{Sm}$  is a promising “theranostic” (therapeutic and diagnostic) agent, suitable for a combinatory diagnostic and therapeutical approach, but further studies are needed to better delineate its cytotoxicity and its efficiency in comparison to  $^{90}\text{Y}$  microspheres.

## Potential New Indications: Outside the Liver

Interest in applications of TARE outside of the liver is emerging and small initial studies have been performed primarily in animal models to assess the effects of TARE on other organs, such as brain.

The standard of care for Glioblastoma multiforme (GBM), a malignant brain tumor, is surgical resection followed by adjuvant chemotherapy [88]. GBM local recurrence, even with treatment, is common due to tumoral cell infiltration [89]. Radiation therapy is an important tool for newly diagnosed GBM and is commonly performed using external beam radiation therapy (EBRT), which provides little neurotoxicity [90, 91]. Other options are brachytherapy and stereotactic radiosurgery. TARE, which is commonly used for the treatment of liver cancer, delivers much more radiation dose in hypervascular tumors compared to EBRT, and reduces nontarget radiation dose [92]. Using TARE for intra-axial brain tumors could be problematic due to the potential ischemic changes induced by microspheres in the normal brain tissue. The potential effectiveness of TARE for the treatment of GBM could be based on the balance of ischemic effects, delivered radiation dose within the tumor, and delivered radiation dose to healthy brain tissue. A recent paper evaluated the safety, feasibility, and efficacy of 90Y TARE for the treatment of spontaneous brain cancers in a canine model [93]. In this study, three healthy research dogs and five patient dogs affected by spontaneous intra-axial brain masses underwent cerebral 90Y TARE using glass microspheres (TheraSphere). Post-treatment PET-CT and neurological examinations by veterinary neurologists were performed. Research dogs were euthanized after 1 month and the brains were extracted and analyzed (micro-dosimetry and histopathologic analyses); on the other hand, patient dogs underwent post-treatment MRI at 1-, 3-, and 6-months with a long-term follow-up. 1 month after treatment, research dog pathologic analysis revealed no evidence of atrophy and rare foci of chronic infarcts. Absorbed doses to masses in patient dogs ranged from 45.4, to 64.1 Gy and the dose to healthy brain tissue was from 15.4 to 33.3 Gy. Among both groups (patient and research dogs), six developed acute transient neurologic deficits after the treatment. At 1 month follow-up, patient dogs showed a 24–94% reduction in tumor volume, achieving a partial response in 3 of them at 6 months follow-up. This preliminary study in dogs underlines the feasibility and safety of 90Y TARE as a potential treatment for brain cancer.

In 2001 van Es et al. published a study in which 22 rabbits with VX2 squamous cell carcinomas implanted into the auricles were treated with TARE using radioactive or inactive holmium-labeled poly-(L-lactic acid) (HoPLA)

microspheres, achieving a complete response in 79% and 86% following embolization with radioactive and inactive microspheres, respectively [94]. More than 95% of the microspheres were retained within the tumor. TARE with 166HoPLA microspheres could be a promising treatment for unresectable head-and-neck cancer but further studies on humans are needed.

Another potential new indication would be related to prostate diseases, in case of malignancy or also benign hyperplasia. In detail, as reported in the paper of Mouli et al. performed in a canine model, prostate 90Y TARE seems to be safe and feasible, leading to focal dose-dependent changes in the gland, such as atrophy and focal necrosis, without inducing unwanted extra-prostatic effects [95].

## Structural and Organizational Perspectives

Office-based interventional oncology (IO) offers great benefits compared with hospital-based IO, as a more comfortable environment and greater convenience for patients. The outpatient setting allows for patient-focused services, faster check-in, less paperwork, and efficient postprocedural management/discharge, with greater patient satisfaction [96]. Physician benefits include better work-life balance, more manageable hours, no call or weekend obligations.

The increasing burden of IO procedures, pressure to reduce costs, and patients' wishes – particularly due to pandemic conditions – has stimulated the development of ambulatory care for many procedures historically performed in the hospital, such as liver-directed therapies.

SIRT is characterized by potential adverse events ranging from acute (post-embolization syndrome, pain, vomiting, nausea, fever, leucocytosis, cholecystitis, pancreatitis) to delayed ones (gastro-duodenal inflammation, ulceration, bleeding, pneumonia); however, the most frequent ones are represented by constitutional symptoms, usually lasting for 1 week, not requiring hospitalization, treated with medications [97–106].

RE procedures can be safely and effectively performed on an outpatient basis; Aberle et al. retrospectively evaluated 212 patients treated with SIRT for primary and secondary malignancies, with only a 3.3% of adverse events requiring hospitalization and a very low radiation exposure [107, 108]. These advantages could be improved with the use of transradial approach, characterized by a less post-procedural discomfort at the access site, and reduced limitations in patient's basic activities, leading to faster discharge [109, 110].

Careful selection of patients is mandatory, based on medical (comorbidities and risk factors) and sociological

(compliance, social and family situation, access to medical care, available home aid) criteria.

The possibility to perform a single-day SIRT reduced the disadvantages of RE (typically requiring at least two visits) compared to other locoregional therapies: RE can be safely performed with pre-treatment diagnostic angiography, dosimetry evaluation, and therapeutic SIRT in the same day [111–116].

Dosimetry measurements can deliver personalized and optimized dose to the tumor in TARE treatments, with both increase in treatment safety and efficacy.  $^{99m}\text{Tc}$ -MAA SPECT represents the current standard for “scout” dosimetry; however, research in this field is constantly evolving and refining, with alternative particles tested in clinical studies: in particular, the use of the same particle in both scout and treatment procedure could grant better accuracy in dose delivery than MAA [117, 118]. Safety and effectiveness of  $^{166}\text{Ho}$  use as a “scout” dose, have been evaluated by various studies, concluding that  $^{166}\text{Ho}$  can be used as an alternative to  $^{99m}\text{Tc}$ -MAA, with a greater predictive value in evaluating lung shunt presence, more reliable pre-treatment imaging and better agreement between scout and treatment volumes [119, 120].

Bakker et al. demonstrated how Holmium-166 ( $^{166}\text{Ho}$ ) microspheres used for RE can be accurately detected at postprocedural CT scan, being an alternative to SPECT evaluation, leading to faster patient discharge [121, 122].

Performing an outpatient single-day procedure, SIRT could become even more competitive with other locoregional therapies, beneficial for patients with travel hardships, difficult vascular access, contrast medium allergies, resulting in cost savings and fewer complications, becoming an attractive care model and an opportunity to mitigate infection risk and logistical challenges associated with COVID-19 pandemic [115].

## Conclusions

Radioembolization is a minimally invasive procedure with an established role in the management of primary and secondary hepatic tumors, providing personalized treatment approaches with palliative and curative indications. Recent advancements and new techniques led to its application across the Barcelona Clinic Liver Cancer staging paradigm, as a curative treatment or as a bridge or down-stage to liver transplantation. Great improvement in liver cancer treatment will also be granted by combined application of radioembolization and systemic or immunotherapy, with the possibility to be performed in an outpatient single-day setting. Appropriate patient selection, comprehensive work-up and multidisciplinary tumor board evaluation remain the main preprocedural criteria to offer an

effective and safe treatment, improving clinical outcome and patient survival. Innovative devices, new techniques as well as technological developments will also allow to expand its clinical indications beyond the liver.

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## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Consent for Publication** Consent for publication was obtained for every individual person’s data included in the study.

**Informed Consent** For this type of study informed consent is not required.

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