European Radiology (2021) 31:2227–2230
https://doi.org/10.1007/s00330-020-07356-w

EDITORIAL

Interventional radiology for liver diseases

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Received: 26 July 2020 / Accepted: 25 September 2020 / Published online: 3 October 2020

Over the past thirty years interventional radiology of the liver has evolved tremendously. Established as portal vein decompression and tumor treatment, IR technology advanced continuously. Covered ePTFE stents significantly increased TIPS patency and ascites control [1, 2]. ePTFE-covered stents were tested in percutaneous palliation of biliary malignancies to prevent tumor ingrowth and increase patency. Randomized controlled trials (RCT) endorsed covered stents in extrahepatic bile duct malignancies [3]. For intrahepatic biliary malignancies, ePTFE-covered stents worked but failed to fulfill their promise: sludge formation on the inner coating impedes longer patency times [4]. Long-term patency of stents becomes a major issue, as progress in medical treatment offers longer live expectancy for patients with, i.e., portal hypertension, Budd-Chiari disease, biliary strictures, or malignancies. Research projects on drug-eluting stents and radioactive or resorbable stents are ongoing [5, 6]. Although metallic stents have been put aside in benign biliary strictures in favor of repeat balloon dilatation, preliminary results with a biodegradable stent are promising [7, 8].

Conventional chemoembolization (cTACE) and radiofrequency ablation (RFA) were embedded in the Barcelona Classification of Liver Cancer (BCLC), remaining unchallenged as level I treatments for intermediate and early HCC for almost twenty years [9–13]. However, cTACE suffers from drug and dose variation as well as technical permutations. The drug-eluting beads (DEB-TACE, Boston Scientific) installed standardization of chemoembolization, proving efficacy but not yet superiority over cTACE [14–16]. Because of a lower post-embolization toxicity, DEB-TACE research was continued with emerging of eluting microspheres manufactured from polyvinyl alcohol (CalliSpheres, Jiangsu Hengrui), expanding trisacryl/gelatin (HepaSphere or QuadraSphere, Merit Medical), polyethylene glycol (LifePearl, Terumo), and hydrogel with polyzene coating (Tandem, Varian). All DEB-TACE beads are non-resorbable agents, permanently blocking tumor supply at different levels according to bead sizes (from 500 to 40 μ) [17–20]. As tumor response did not quite differ, the question remains whether the eluting chemotherapeutic or the embolic particulate dominates the anti-tumor effect. Interestingly, degradable starch microspheres combined with a chemotherapeutic are finding their way into clinical practice, even in advanced HCC [21]. Biodegradable microspheres are captivating with a range of "biogel" materials now under investigation [22]. First in queue for clinical testing are combined degradable and drug-eluting beads (BioPearl, Terumo), which might provide more insight into the anti-tumoral mode of action.

Innovations in bead delivery such as radiopaque beads (DC Bead LUMI), beads in combination with Lipiodol or steerable microcatheters (swingNINA®, Merit), anti-reflux mechanism (Surefire, TriSalus Life Science; SeQure, Guerbet), or underpressure inducing balloon microcatheter (Occlusafe, Terumo) increase safety but impact on tumor response is still investigational [23–26]. Intriguing for the future are composite microbeads, made of magnetic nanoparticles and polymeric matrix microspheres that may induce tumor ablation effects upon application of alternating magnetic field [27].

Despite the huge experience with Y90 in HCC, modern transarterial radioembolization (TARE) still struggles to enter the BCLC classification [28]. The FDA only approved TARE as neoadjuvant for surgery or liver transplantation or in advanced stage with PVT [28]. Further promotion is not yet under discussion because powerful RCTs comparing Y90 with cTACE or its equivalent DEB-TACE are lacking [29–31]. The TRACE trial was halted at interim analysis because of significant improved time to tumor progression and overall survival (OS) with TARE (versus DEB-TACE). The trial missed its public premiere at SIR congress 2020, canceled by the COVID-19 pandemic [32]. Salem et al purposefully give a shot across the bows reporting their hospital HCC board

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had decided to adapt TARE as first-line locoregional treatment of liver-limited HCC [33].

Why is it so onerous to conduct a large RCT in locoregional HCC treatment? Patient accrual within one BCLC class is well-known slowly. Raising funds for a multicentric RCT to investigate expensive commercial particles for locoregional HCC treatment is a desperate job. But when to compare with a systemic tyrosine kinase inhibitor and to prove superiority of TARE, then company funding is attainable. Unfortunately, three large RCTs comparing TARE versus sorafenib [34, 35] and TARE plus sorafenib versus sorafenib alone [36] failed the endpoint of OS superiority of TARE. Combining these RCTs, a company-sponsored meta-analysis sublimed a non-inferiority of TARE for advanced HCC to sorafenib in terms of OS combined with a better safety profile [37]. Will this conclusion be enough to change the FDA's mind? Or will we have to wait until novel tyrosine inhibitors and immune check point inhibitors enter the competition, eventually opposing the latest TARE variant, Holmium-166 [38, 39]?

For colorectal liver metastasis (mCRC), TARE was a great hope to grant patients a "chemo-holiday" and eventually improve outcome. However, there is no evidence that chemotherapy with resin Y90 TARE improves OS or quality of life [40, 41]. Whether the glass Y90, with less particles but higher activity per bead, will turn the tables for TARE in second line for mCRC will be revealed soon [42].

Established IR solutions are challenged by innovations in endoscopy (i.e., percutaneous versus echo-endo biliary stenting), surgery (i.e., portal vein embolization versus ALLPS), or even systemic treatments [43]. Competition, research, and collaboration should keep IR in the front line for delivery of future pharmacology such as radio- and nanoparticles or modified virus or other immunotherapy. Portal and hepatic vein research, whether for implantation of I125 seeds in tumorous occlusion, as entry for auto-transplantation of islet cell, as part of percutaneous hepatic perfusion (chemosaturation) or to increase safety of hepatectomy should receive full attention [44–47]. Extending angiography by cone beam or hybrid angio-CT systems with image fusion, combined with high frequency jet ventilation should keep IR in pole position for efficient and safe tumor ablation [48–51]. Cost-effectiveness studies combining quality of life and/or treatment outcome should increase acceptance of IR, even if "willingness to pay" is heavily dependent on one country's health policy [52–54]. Finally, IR should contemplate not only on trial protocols comparing locoregional treatments but also disclose and publish existing data to avoid futile research and underreporting [55].

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Luc Defreyne.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was not required for this study because it is an Editorial comment.

Ethical approval Institutional Review Board approval was not required because it is an Editorial comment.

Methodology
• Editorial comment

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