Hepatology Snapshot:

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Interventional treatment of hepatocellular carcinoma

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Patient selection factors

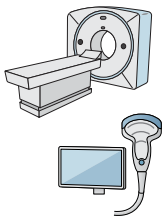
Multidisciplinary team

- Hepatologist
- Nurse
- Surgeon
- Radiotherapist
- Interventional radiologist
- Oncologist
- Radiologist
- Pathologist

Host

- Patient status (ECOG-PS, history)
- Liver function (ALBI, Child-Pugh)
- Advanced chronic liver disease (Fibrosis, cirrhosis, steatosis)
- Portal hypertension
- Anthropometry (Sarcopenia, obesity)

Imaging



- Angiography (ConeBeam-CT)
- MRI
- CT-scan
- Ultrasound

Tumor

- Tumor(s) size and number (AFP score, ...)
- Tumor location (Central/peripheral, unilobar/bilobar)
- Tumor conspicuity (US, CT, MR, angiography)
- Extrahepatic disease (EHD)
- Tumor in vein (TIV)

Interventional radiological treatments for HCC

Overall survival (OS)

Local Percutaneous ablation

RFA, MWA, CRYO, IRE

Single probe

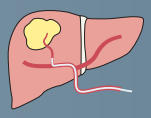
Multi probe

	RFA	MWA	CRYO	IRE
Local efficacy	+++	+++	++	++
"Heat sink effect"	+++	++	++	+
Compatible with Pacer	+	++	+++	-
Hemorrhagic risk	+	+	++	++
Advantages	• Large experience • Multipolar for >3 cm	• Fast • Less passive heating	Ablation zone visibility (per-treatment)	Less damage to neighboring organs
Evidence	+++ (RCTs)	++ (large series)	+	+
Cost	+	++	+++	+++

Loco-regional Intra-arterial therapies

Chemoembolization — TAE, cTACE, DEB-TACE

Radioembolization — ^{90}Yttrium (glass/resin)



- Thermal ablation of HCC ≤3 cm provides equivalent OS to surgical resection
- TACE in selected BCLC B populaltion provides >2 years OS
- Superselective TACE improves outcomes (efficacy/toxicity) and is recommended in most guidelines
- Radioembolization (a.k.a. SIRT) may be considered as curative in BCLC A patients
- Radioembolization demonstrates compelling downstaging to resection data in large lesions (10 cm) with TIV
- Combination of immunotherapies with thermal ablation and intra-arterial therapies is under research

Early

Percutaneous ablation (<3 cm)

RFA *vs.* surgery		
Chen 2006	N = 180	4-year OS: 67.9 *vs.* 64%, *p* = n.s.
Huang 2010	N = 230	5-year OS: 54 *vs.* 75%, *p* = 0.001 5-year RFS: 28 *vs.* 51%, *p* = 0.017
Feng 2012	N = 168	3-year OS: 67.2 *vs.* 74.8%, *p* = 0.342
Ng 2017	N = 218	Recurrence: 81.7 *vs.* 71.3%, *p* = 0.09
Izumi 2019	N = 293	3-year RFS: 47.7 *vs.* 49.8%, *p* = 0.79
Xia 2019	N = 240	mOS: 37.5 *vs.* 47.1 mo, *p* = 0.17
Takayama 2021	N = 301	Med RFS: 3 *vs.* 3.5 yr, *p* = 0.58

TACE + ablation or multiprobe (>3 cm)

RFA + TACE vs RFA and Multipolar RFA		
Morimoto 2010	N = 37	3-year OS: 93 *vs.* 80%, *p* = 0.37 3-year RFS: 94 *vs.* 61%, *p* = 0.012
Zhang 2021	N = 189	Med OS: 62 *vs.* 48 mo, *p* = 0.001 Med RFS: 46 *vs.* 25 mo, *p* = 0.007
Seror 2016	N = 108	3- and 5-year OS: 96 and 94%

Intermediate

TA(C)E

cTACE *vs.* BSC		2-year OS	Med OS
Lo 2002	N = 80	31%	14.0 mo
Llovet 2002	N = 112	63%	28.7 mo
cTACE		2-year OS	Med OS
Okusaka 2009	N = 161	48%	21.2 mo
Yu 2014	N = 98	N.A.	20.1 mo
Ikeda 2018	N = 128	N.A.	36.5 mo
DEB-TACE		2-year OS	Med OS
de Baere 2020 (PARIS)	N = 98	66%	N.E.

TA(C)E ± TKI

TACE *vs.* TACE + TKI (Sorafenib or Brivanib)		
Lencioni 2016 (SPACE)	N = 397	mTTP: 5.5 *vs.* 5.6 mo, *p* = 0.072
Meyer 2017 (TACE 2)	N = 313	mPFS: 7.7 *vs.* 7.8 mo, *p* = 0.85
Kudo 2018 (ORIENTAL)	N = 889	mOS: 31.1 *vs.* 32.3 mo, *p* = 0.435
Kudo 2020 (TACTICS)	N = 176	mPFS: 13.5 *vs.* 25.2 mo, *p* = 0.006
Kudo 2014 (BRISK)	N = 502	mOS: 26.4 *vs.* 26.1 mo, *p* = 0.53

Advanced

SIRT

SIRT *vs.* Sorafenib (Med OS)		
Vilgrain 2017 (SARAH)	N = 459	8 *vs.* 9.9 mo, *p* = 0.18
Chow 2018 (SIRVENIB)	N = 360	8.8 *vs.* 10 mo, *p* = 0.36
Sorafenib ± SIRT (Med OS)		
Ricke 2019 (SORAMIC)	N = 424	12.1 *vs.* 11.4 mo, *p* = 0.95

Today

Level of evidence

- Positive trial
- Negative trial
- Single IR arm

Tomorrow

SIRT or selective TACE

Intra-arterial therapy for early HCC: SIRT and TACE (selective *vs.* lobar)		
Salem 2021 (LEGACY)	N = 162 HCC <8 cm	Med OS: 57.9 mo 2-year OS: 94.8%
Golfieri 2011	N = 67 HCC <5 cm	Mean necrosis: 75.1 *vs.* 52.8%, *p* = 0.002 Complete necrosis: 53.8 *vs.* 29.8%, *p* = 0.013

SIRT or TACE or HAI

SIRT *vs.* TACE (RCT)		
Salem 2016 (PREMIERE)	N = 45	Med OS: 18.6 *vs.* 17.7 mo, *p* = 0.99 Med TTP: >26 *vs.* 6.8 mo, *p* = 0.0012
HAIC *vs.* TACE (RCT)		
Li 2021	N = 315	Med OS: 23.1 *vs.* 16.1 mo, *p* <0.001 Med PFS: 9.6 *vs.* 5.4 mo, *p* <0.001

SIRT for large HCC or MVI

SIRT with standard *vs.* personalized dosimetry arm		
Garin 2021 (DOSISPHERE)	N = 45	Med OS: *p* = 0.0096 SDA: 10.7 mo; PDA: 26.6 mo
HAIC vs Sorafenib (RCT)		
Lyu 2022	N = 262	Med OS: *p* <0.001 HAIC: 13.9 mo; TACE: 8.2 mo

Research

Ablation + IO

Ongoing Phase 2 trials: Ablation + Immunotherapy		
IMMULAB	Pembrolizumab + RFA or MWA + adjuvant Pembrolizumab	ORR, OS
ABLATE-02	Atezolizumab + RFA + adjuvant Atezolizumab/Bevacizumab	RFS, OS
NIVOLEP	Nivolumab + IRE in curative intent + adjuvant Nivolumab	LRFS, OS
IMbrave 050	Ablation or resection + adjuvant Atezolizumab/Bevacisumab	RFS, OS

TACE or SIRT + IO

Ongoing trials: TACE + Immunotherapy	
EMERALD-1	± Durvalumab ± Bevacizumab
LEAP-012	± Pembrolizumab + Lenvatinib
ML 42612	± Atezolizumab + Bevacizumab
TACE-3	± Nivolumab

Ongoing trials: SIRT + Immunotherapy	
ROWAN	SIRT ± Durvalumab/Tremelimumab
HOLMBRAVE	SIRT ± Atezolizumab/Bevacizumab
HIPANIV (Ongoing Phase 1)	
Intra-arterial Ipilimumab infusion + Nivolumab IV	

Keywords: Image guidance; Percutaneous ablation; Intra-arterial therapies; Chemoembolization; TACE; Radioembolization; SIRT; Hepatic arterial infusion of chemotherapy; Hepatocarcinoma; Evidence based; Combination therapies
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Local therapies are standard of care for most hepatocellular carcinoma (HCC),[1] and image-guided interventions play a predominant role.[2] A multidisciplinary approach, technological breakthroughs[3] and better patient selection, supported by clinical evidence, are the key factors allowing for this continuous development.

Improvement in patient selection and treatment allocation implies some granularity in classification of the tumor and patient characteristics that are not yet fully expressed in guidelines. Hence the concept of "therapeutic hierarchy" relies on a multidisciplinary approach and expertise and can be applied for various therapeutic approaches and tumor stages.[4] For example, while ablation is recommended in small size tumors and clear diameter thresholds are expressed, tumor location and tumor conspicuity on imaging are not included in any guideline. Possibility of selective vascular access, such as superselective transarterial chemoembolization (TACE) and selective internal radiation therapy (SIRT), provide very high complete response rates when treating small tumors.[5] The same applies to unilobar *vs.* bilobar tumors. Furthermore, although intra-arterial therapies are mainstream for intermediate HCC, SIRT is also offered to patients with advanced disease, specifically for tumors invading the portal vein branches.[6]

Evidence-based medicine drives treatment algorithms; thus, interventional treatments are part of all the HCC management guidelines. For early-stage HCC, according to BCLC classification, randomized controlled trials have proven the non-inferiority of ablation *vs.* resection for selected patients and intra-arterial therapies (notably SIRT) have entered the guidelines in this setting.[5] The combination of ablation and immunotherapies in the neoadjuvant or adjuvant settings are under evaluation, with the aim of reducing the risk of recurrence and relapse.

For patients with intermediate-stage HCC who are not candidates for liver transplantation or liver resection, intra-arterial therapies are the gold standard. No significant differences have been shown with various delivery platforms used for TACE. SIRT, on the other hand, and now hepatic arterial infusion of chemotherapy (HAIC) are challenging TACE as the first-line option, with promising results both regarding efficacy and safety.[7,8] The combination of kinase inhibitors with intra-arterial therapies has not proven to add any benefit but has defined an updated benchmark of what can be expected nowadays with TACE as a standalone treatment. Modern systemic approaches with immune-checkpoint inhibitors together with TACE or SIRT arouse enthusiasm and are also under evaluation in large clinical trials.[9]

Patients with advanced HCC are typically not eligible for interventional therapies, and all controlled randomized phase III trials, except the FOHAIC-1 trial using HAIC,[10] have failed to show an OS advantage of intra-arterial therapies. But some patients, mainly those classified as advanced because of performance status or limited portal vein invasion, can be excellent candidates for HAI or SIRT, especially when using personalized dosimetry.[11] More data are needed for SIRT in order to enter the guidelines in this setting, but, on a per patient basis, multidisciplinary discussion can offer it as a valuable option. Once again, the combination of immunomodulating agents with or without antiangiogenic drugs and interventional treatments need to be explored, on the back of their reciprocal potentiating effects.

Image-guided local immunotherapy[12] is of particular interest for patients with both early and advanced stage HCC, and results from studies testing percutaneous and intra-arterial administration routes are awaited. This approach might find a place in the interventional radiology armamentarium in the near future.

Finally, interventional treatments for HCC are not only well established but also have great potential and their role should increase and be strengthened in the future.

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Conflict of interest

Riad Salem: Eisai, Genentech, Astra Zeneca, Sirtex, Boston Sci, Bard, QED Therapeutics. Lambros Tselikas: BMS, Boston Scientific, GE Healthcare, Quantum Surgical. Thierry de Baere: Terumo, Boston Scientific, Guerbet, GE Healthcare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors contributed to design, writing, editing of this snapshot.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.03.037.

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