Selection of Locoregional Therapies in Hepatocellular Carcinoma

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Disclosures

- Employers – Medical College of Wisconsin, Dept. of Veterans Affairs

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Why this is Important

- Radiologists play a key role in the evaluation and treatment of patients with hepatocellular carcinoma (HCC).

Screening → Imaging-based diagnosis → Liver-directed therapies → Response Assessment

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Llovet et al., *Nat Rev Gastroenterol Hepatol.* 2021

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Overview

- Introduction to Hepatocellular Carcinoma
- Treatment Paradigm
- Options for Unresectable Disease
- Response Assessment

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HCC at a Glance

- Worldwide 4th most common cause of cancer-related death, 6th in number of incident cases
- In the US, rate of death from liver cancer increased by 43% between 2000 and 2016 (from 7.2 to 10.3 deaths per 100k)
- Risk factors: HCC arises from sustained hepatic inflammation and fibrosis – most commonly from cirrhosis
  - HBV, HCV
  - NAFLD
  - Alcohol

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Villanueva, *NEJM* 2019

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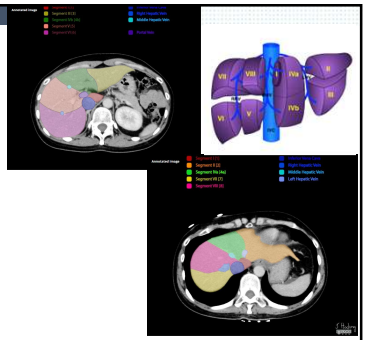
Anatomy

- Liver divided into 8 functional units (Couinaud classification)
- Dual blood supply:
  - Portal vein (75%): oxygen poor, nutrient rich
  - Hepatic arteries (25%): oxygen rich, nutrient poor
    - Also supply biliary system
- Venous drainage into 3 hepatic veins → IVC



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Images from Dr. Jeffrey Hocking, https://radiopaedia.org

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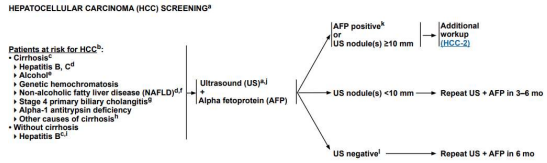
Screening

- From NCCN, Version 2.2023



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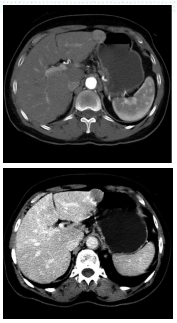
Imaging Findings - CT

- Benign lesions supplied by branches of portal system; malignant nodules supplied by arterial system.
- Multi-phase contrast-enhanced 3D imaging
  - Phases: early arterial, late arterial, portal venous or later
  - HCC is characterized by **arterial phase hyperenhancement** and **portal venous phase hypoenhancement ("washout")**
  - Other major considerations: size, growth > 10mm in 1 year, definite tumor within lumen of vein, enhancing "capsule"



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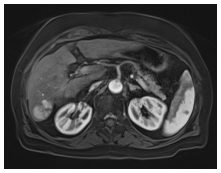
Imaging Findings - MRI

- T1 and T2 can be variable, especially in the setting of regenerative nodules due to cirrhosis
- T1 + gadolinium: Extracellular contrast
  - Arterial enhancement with rapid washout becoming hypointense to remainder of liver
  - Rim enhancement may persist ("capsule")
- T1 + Eovist/Primovist: Late hepatobiliary phase
  - Hepatobiliary phase 20 min post-injection is specific to hepatocytes and not taken up by metastases
  - Assessment of hepatobiliary phase in HCC not specific (may or may not enhance)



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Diagnosis

- Diagnosis of HCC can be established in patients without need of pathologic confirmation.

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5 Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

American College of Radiology, Liver Imaging Reporting & Data System

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Child-Turcotte-Pugh Score

- Also known as Child-Pugh score

Criteria	1 point	2 points	3 points
Total bilirubin (mg/dL)	<2	2-3	>3
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
Ascites	None	Mild / controlled	Moderate / Med refractory
Encephalopathy	None	Grade I-II	Grade III-IV

- Criticisms: ascites and encephalopathy are subjective and fluctuate with medication, albumin and ascites interdependent.
- One alternative: ALBI score / grade.

Knox, J JCO 2015

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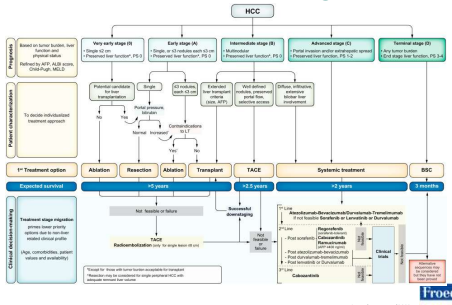
Barcelona Clinic Liver Cancer Algorithm



Reig et al., *J Hepatol* 2022

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What about non-surgical patients?

- There remains a patient population with unresectable disease or are awaiting transplant
- Many options available:
  - Percutaneous approach:
    - Thermal ablation (RFA, MWA, Cryotherapy)
  - Transarterial approach:
    - Chemoembolization
    - Radioembolization (Y90)
  - External beam radiation

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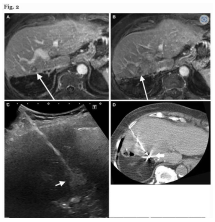
Ablative Techniques

- Image-guided ablation most performed with radiofrequency (RFA) microwave (MWA).
  - Cryotherapy, laser interstitial thermotherapy less common.
- Ultrasound-guided needle electrode placement
  - There also exist some single-institution series for MR-guided RFA and MWA
- Limited by size of 3-5cm, and anatomy
  - Anatomic barriers: intestine, diaphragm, central bile ducts, blood vessels > 3mm in diameter (heat sink)



Harsinh et al., *Abdom Radiol* 2018.

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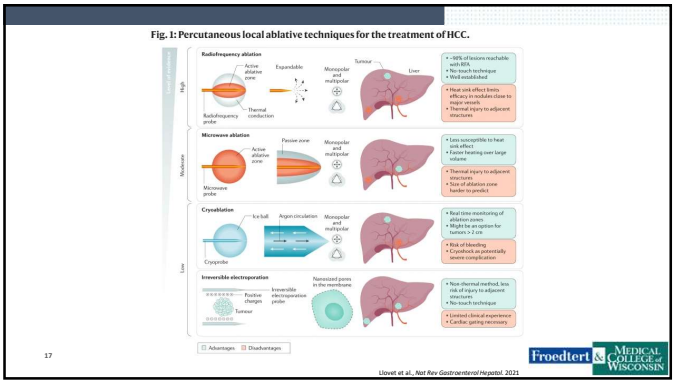

Llovet et al., *Nat Rev Gastroenterol Hepatol.* 2021

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Ablative Techniques

- There exists randomized phase III clinical data for RFA vs surgery (limited data for MWA as it was established later)
  - A meta-analysis of the four trials out of China and Hong Kong did not show any superiority of surgery over RFA
  - Japanese trial (SURF) did not show any recurrence free survival difference.
- AASLD and EASL guidelines have adopted RFA as front-line therapy for single tumors < 2cm
  - mRECIST response rates 70-90%, 5y recurrence rate 50-70%, median OS ~60m
  - Alternative for single tumor 3-4cm, 2-3 tumors < 3cm
- Side effects: bleeding, infection, biloma, pleural effusion, rare tumor seeding

Majumdar et al., *Cochrane Database Syst Rev.* 2017; Takayama et al., *Liver Cancer* 2021

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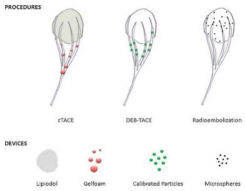
Catheter-directed Therapy

- Hepatic arterial blood supply of HCC allows for selective treatment of tumor.
  - Transarterial chemoembolization (TACE)
  - Drug-eluting beads (DEB-TACE)
  - Balloon-occluded TACE (B-TACE)
  - Embolic particles without drug ("bland embolization")
  - Y-90 Radioembolization (TARE)



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Sangro et al., *Semin Liver Dis* 2014; Hanzinh et al., *Abdom Radiol* 2018

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TACE: An Established Treatment

- Limited evidence directly comparing different embolization techniques, but TACE has RCTs demonstrating OS advantage compared with supportive care.
  - A 2003 meta-analysis of 7 trials demonstrating improved 2y survival compared with supportive care alone.
  - TACE established as global standard of care for patients with intermediate-stage HCC
  - Median OS ~30 months

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Llovet et al., *Lancet* 2002; Lo et al., *Hepatology* 2002; Llovet et al., *Hepatology* 2003; Lammer et al., *Cardiovasc. Intervent. Radiol* 2010

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Considerations for TACE

- Major contraindications for TACE in patients with intermediate-stage HCC
  - Decompensated cirrhosis
  - Extensive tumor involving both liver lobes
  - Renal insufficiency
  - AV fistula
  - Significant coagulopathy
  - Multiple organ failure
  - Distant metastasis
- Side effects: post-embolization syndrome
  - Pain
  - Nausea
  - Fever
  - Transaminitis
  - Ileus
- DEB-TACE with similar survival outcomes, but possible decreased side effects

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TACE is not Ablative…

- Much of the literature for TACE looks at imaging response rate and overall survival
- However, local progression rates in retrospective series range from 23% to 53%, even in the cases of early radiological CR (more to follow)
- Although phase III data is lacking, other modalities have shown improvement in tumor control:
  - Y90 radioembolization showed longer median time to progression in a randomized phase II trial (>26mo vs 6.8mo, Salem et al., *Gastroenterology* 2016)

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Y90 Radioembolization

- Due to small size of beads, does not cause tissue ischemia compared with the larger particles in TACE
  - Allows for use in setting of portal vein thrombosis
- Radiation doses recommended >190Gy (calculated based on injected activity, lung shunt fraction, and mass of infused liver)
  - Dose (Gy) = Activity (GBq) * (1- lung shunt fraction) * 50 (J/GBq) / mass of perfused liver (kg)
- Liver toxicity can be challenging, with decompensation 4-8 weeks after radioembolization (9.3% in one series, with severe toxicity in 3.1%)
- Rare complications of pneumonitis, cholecystitis, GI ulcerations
  - Maximum dose of 30Gy for a lung mass of 1kg

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Salem et al., *Eur J Nucl Med Mol Imaging* 2019; Gil-Alzugaray et al., *Hepatology* 2013; Kim et al., *Physica Medica* 2019

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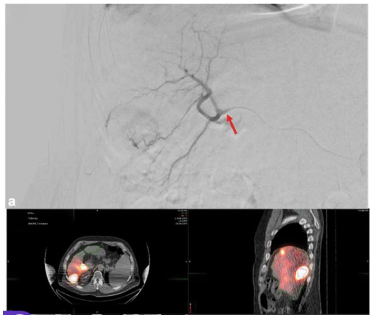

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Webster et al., *Semin Intervent Radiol*. 2021

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Varieties of Y90 Radioembolization

- Radiation Segmentectomy: Curative intent for small lesions not amenable to percutaneous ablation (Dose >190 Gy, frequently 250-300Gy)
  - LeGACY (2021) was a retrospective study of BCLC A patients which allowed tumors up to 8cm
    - 100% local control at median f/u 30 months
    - However, only 5% of patients had tumors from 5-8cm on this trial.
- Radiation Lobectomy: Lower non-ablative dose (80-120Gy)
- Palliative: sequential lobar infusions, typically on order of 120Gy

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Salem et al., *Gastroenterology* 2016; Salem et al., *Hepatology* 2021, Salem et al., *Eur J Nucl Med Mol Imaging* 2019

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Choice of Transarterial Therapy – A Summary

- BCLC-A: Catheter-based ablation/Resection preferred.
  - TACE is non-ablative, but there's some retrospective studies looking at ablative TARE in this setting
- BCLC-B: Level 1 evidence for TACE, but some phase 2 trials showing potential local control benefit for TARE so worth considering
  - When to use TACE over TARE: when percutaneous ablation planned, when TACE would be diagnostic, lung shunt, imminent transplant.
- BCLC-C: traditionally a systemic-only approach, although TACE and TARE being considered
  - TARE not superior to systemic therapy alone: SARAH (2017), SIRveNIB (2018)
  - Adding TACE to TKI did not have OS benefit: SPACE (2016), ORIENTAL (2018), SILIUS (2018), STAH (2019)
  - Adding TARE to TKI did not have OS benefit: SORAMIC (2019)

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Salem et al., *Gastroenterology* 2016; Padia et al., *J Vasc Interv Radiol* 2017

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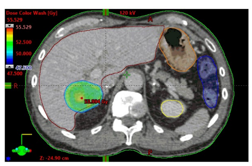
External Beam Radiotherapy – Late to the Party

- With TACE being well-established since the early 2000's and TARE adding on an ablative option in the late 2010's, this is already a crowded space.
- Several advances have led to external beam radiation therapy being used more:
  - More conformal radiation treatment planning
  - Better understanding of liver toxicity
  - Better patient immobilization / on-board imaging



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Varian Medical Affairs - Liver SBRT 50Gy (UK Consensus / RTOG 1112)

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External Beam Radiotherapy – Late to the Party

- However:
  - Like TARE, has been found to have superior LC compared with TACE in phase II trials.
  - In larger tumors > 3cm, has been found to have superior LC compared with RFA in retrospective series
  - SBRT has been combined with TKI to offer additional overall survival benefit (RTOG 1112), where TARE has not (SORAMIC).

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Local Control Data is Promising

Table 1. Select prospective and retrospective series showing outcome with stereotactic body radiotherapy.

Study	Patient number	Quality/type of study	Indication/ stage (BCLC)	Dose and fractionation	Follow up	Outcomes (LC/OS)	Toxicity (Grade 3 liver/GI)	Study conclusion	Level of Evidence*
Kim et al., 2021[30]	72	Phase III randomised trial- Proton vs RFA	0-C	66Gy/10Fr (Protons)	51.6m	2y LC: 92.8% 2y OS: 91.7%	none	Proton beam therapy was non-inferior to RFA and was tolerable.	II
Yoon et al., 2020[31]	50	Prospective Phase II trial	0 and A (small HCC)	45 Gy/3#	47.8 m	5y LC: 97.1% 5y OS: 77.6%	4%	SBRT showed good results for ablation of small HCC with minimal toxicity.	IV
Labrunie et al., 2020[32]	43	Prospective Phase II trial	A-C	45 Gy/3#	4 y	2y LC: 94% 2y OS: 69%	5%	LC and OS was promising in HCC treated with SBRT.	IV
Jang et al., 2020[33]	65	Prospective Phase II trial	0-C	60 Gy/3#	41m	2y LC:97% 2y OS: 84%	2%	SBRT for HCC was well tolerated.	IV
Park et al., 2020[34]	290	Prospective Phase II trial	0-A	30-60Gy/3#	38.2m	5y LC: 91.3% 5y OS: 44.9%	8.8%	SBRT is an ablative option for small HCC.	IV
Mathew et al., 2020[35]	297	Retrospective	0-D	27-60Gy/3-6#	19.9m	3y LC: 87% 3y OS: 39%	16%	SBRT provides good LC and OS in HCC when it is unsuitable or refractory to other locoregional treatment.	VI
Kim et al., 2019[36]	32	Prospective Phase I/II trial	A-B	36-60 Gy/4#	27m	2y LC: 87% 2y OS: 81.3%	None	SBRT is a safe treatment for HCC.	IV
Hara et al., 2019[37]	143	Retrospective	0-C	35-40Gy/5#	30.2m	3y LC: 95.6% 3y OS: 63.6%	8.2%	SBRT for HCC provides results comparable to RFA and acceptable alternative to RFA.	VI
Feng et al., 2018[38]	90	Prospective Phase II trial	A-C	23-60Gy/5#	37m	2y LC:95%	7%	Individualized adaptive RT was safe and provided good LC.	IV
Takeda et al., 2016[39]	90	Prospective Phase II trial	0-C	35-40 Gy/5#	41.7m	3y LC: 96.3% 3y OS: 66.7%	6%	SBRT achieved high LC with accepatable toxicity in solitary HCC.	IV
Lasley et al., 2015[40]	59	Prospective Phase I/II trial	A-C	48 Gy/3# in CPA 40 Gy/5# in CPB	33.3m	3y LC: 82-91% 3y OS: 26.1- 61.3%	20%	SBRT is a safe treatment for HCC.	IV
Scorsetti et al., 2015[41]	43	Prospective observational	A-C	48-75 Gy/3# to 36 Gy/6#	8m	2y LC: 64% 2y OS: 45%	16%	SBRT is safe with acceptable LC and toxicity.	IV
Bujold et al., 2013[42]	102	Prospective Phase I and II trials	A-C	24-56 Gy/6#	31.4m	1y LC: 87% Med OS: 17m	30%	Results provide strong rationale for studying SBRT as local treatment option in randomised phase III trials.	IV
Kang et al., 2012[27]	47	Prospective Phase II trial	A-C	42-60 Gy/3#	17m	2y LC: 94.6% 2y OS: 68.7%	6.4%	SBRT after incomplete TACE provides promising response and LC.	IV
Andolino et al., 2011[43]	60	Prospective observational	A-C	40-44 Gy/3-5#	27m	2y LC: 90% 2y OS: 67%	20%	SBRT is safe non-invasive option for HCC <6cm.	IV

GI, gastrointestinal; LC, local control; OS, overall survival.
* [44]

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Kimura et al., *Cancers (Basel)* 2022

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Potential Role for SBRT

- Consider SBRT over TACE after poor response to prior TACE, vascular involvement.
- Consider SBRT over RFA for larger tumors or those with limiting anatomic factors
  - However, limited data exists comparing SBRT and TARE
- Cost-Effectiveness?
  - Newer radiation technologies such as MRI guidance and proton therapies will cloud this picture

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Safavi et al., *Clin Transl Radiat Oncol* 2024

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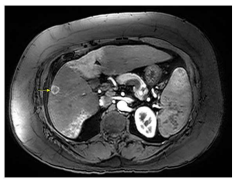
Tools to Evaluate Response

- RFA:
  - Coagulative necrosis in tumor → hypoenhancement on contrast CT and MRI
  - Peripheral enhancement suggestive of residual tumor



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Cox et al., *JGH Open* 2023; image from UpToDate

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Tools to Evaluate Response

- TACE:
  - Tumor growth or arterial enhancement suspicious for persistent disease
  - Lipiodol can be helpful with CTs initially but hinder later follow-up imaging.

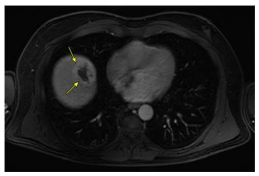

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Image from UpToDate

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Tools to Evaluate Response

- TARE:
  - Median time to develop tumor shrinkage around 120 days
  - Rim enhancement can persist over time
- SBRT:
  - Persistent arterial phase hyperenhancement for a year or more
  - Irradiated normal liver parenchyma may also show radiation-related changes.

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Are we speaking the same language?

- In 2000, the EORTC/NCI/NCIC put together the RECIST (Response Evaluation Criteria in Solid Tumors) to better define treatment response in clinical trials.
- However, in HCC, tumor size didn't necessarily always correspond to clinical benefit, and estimation of residual viable tumor by residual uptake during arterial phase on CT or MRI.
- mRECIST was developed in 2010:
  - Complete response: disappearance of all viable target lesions (arterial phase enhancement)
  - Partial response: >30% decrease in sum of diameters of viable target lesions
  - Progressive disease: Increase in >20% of sum of diameters of viable target lesions
  - Stable disease: Any cases that do not qualify for the above.

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Lencioni et al., Semin Liv Dis 2010

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Are we speaking the same language?

Imaging Response Assessment

Imaging Findings Within the First 12 Months of Hepatocellular Carcinoma Treated With Stereotactic Body Radiation Therapy

Mishal Mendiratta-Lala, MD,* Everett Gu, MD,* Dawn Owen, MD, PhD,† Kyle C. Cuneo, MD,† Latifa Bazzi, BSc,† Theodore S. Lawrence, MD, PhD,† Hero K. Hussain, MD,* and Matthew S. Davenport, MD*

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Received Apr 17, 2017, and in revised form Jul 15, 2017. Accepted for publication Aug 16, 2017.

In conclusion, despite the small sample size, this study is unique because all patients had pathologic evaluation confirming >90% necrosis or normalization of AFP values after SBRT. Standard response assessment criteria for treated HCC, such as EASL (7) and mRECIST (8), may not accurately characterize successful response within the first 12 months after SBRT.

- 10 patients, BCLC-A HCC
- Following SBRT, none increased in size, but 40% exhibited persistent arterial hyperenhancement
- This is different than what is expected after successful thermal ablation or TACE

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Mendiratta-Lala et al., *IJROBP* 2017

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Why this is Important

- Radiologists play a key role in the evaluation and treatment of patients with hepatocellular carcinoma (HCC).

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Llovet et al., *Nat Rev Gastroenterol Hepatol.* 2021

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Questions?

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