Locoregional Therapies for HCC

A look throughout the BCLC stages

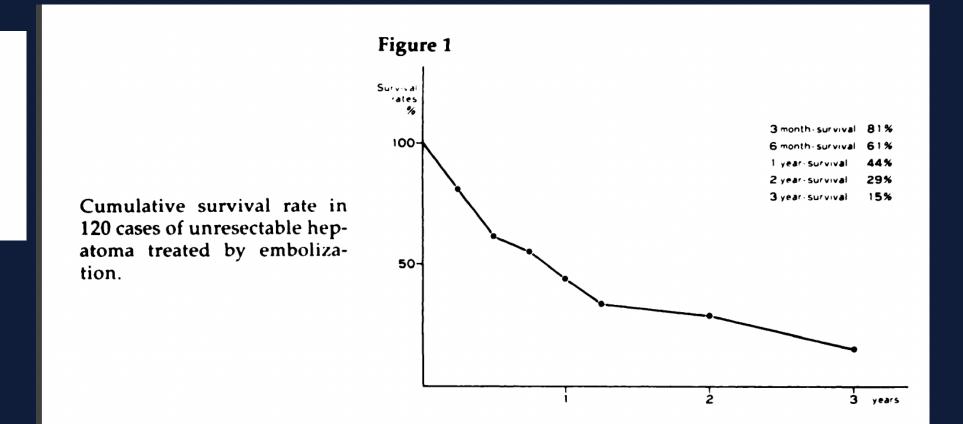
Zach Berman MD Interventional Radiology Assistant Clinical Professor, UC San Diego Health

A Brief History Lesson (1977)

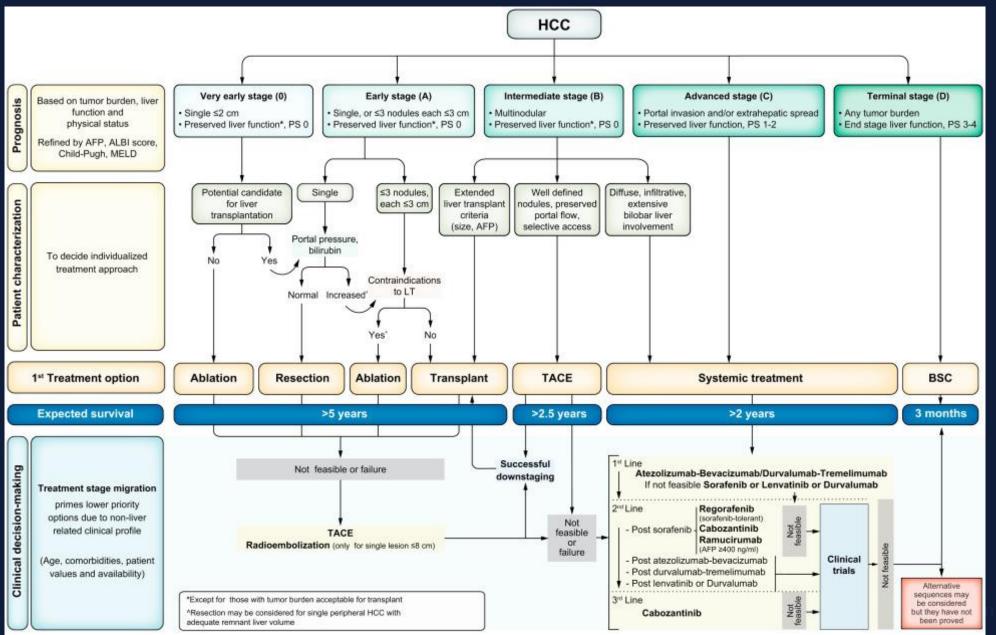
INTERVENTIONAL RADIOLOGY

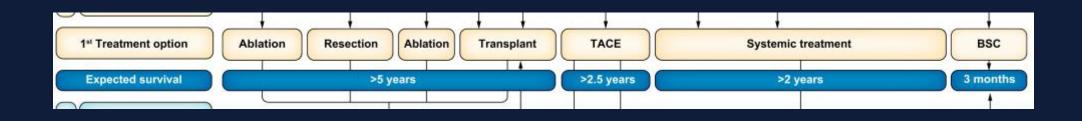
Hepatic Artery Embolization in 120 Patients with Unresectable Hepatoma¹

> Ryusaku Yamada, M.D. Morio Sato, M.D. Mamoru Kawabata, M.D. Haruki Nakatsuka, M.D. Kenji Nakamura, M.D. Sumio Takashima, M.D.

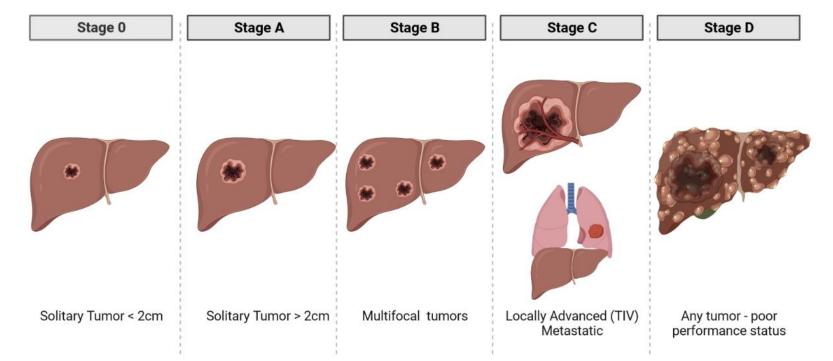


2022 BCLC Guidelines

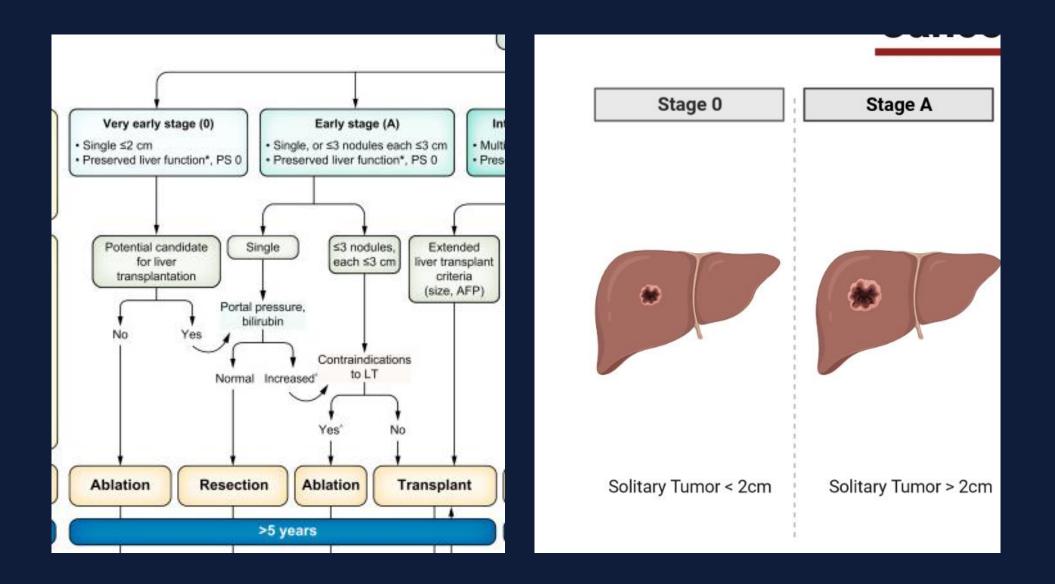




Barcelona Clinic Liver Cancer (BCLC) Stages



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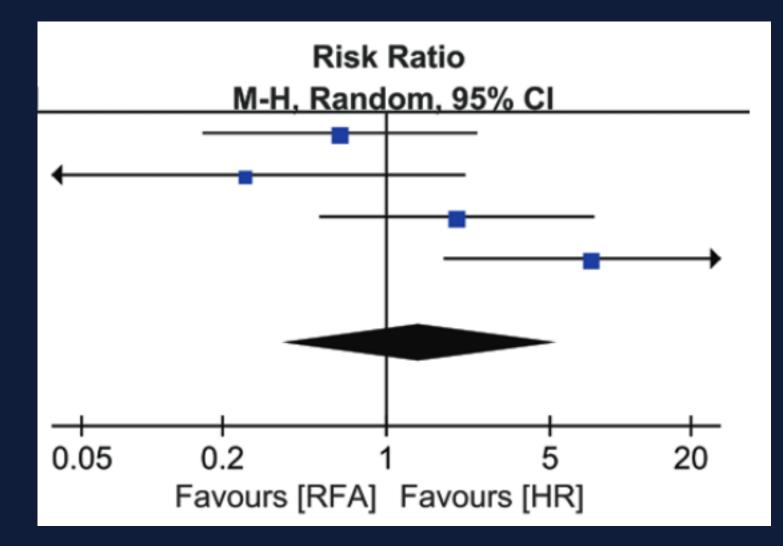


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Why is ablation in the guidelines?

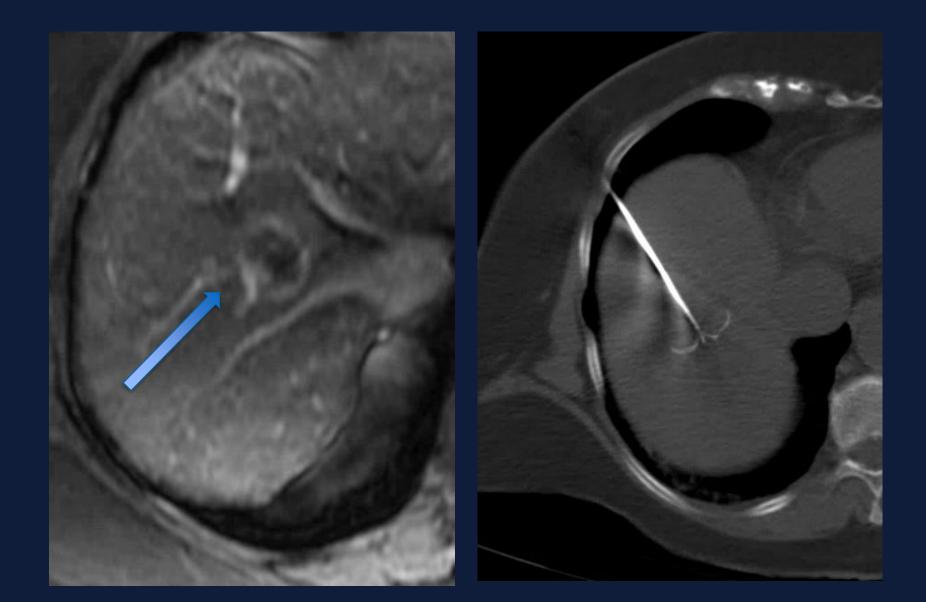
Table 3 Randomized controlled trials comparing RFA and surgical resection for the treatment of early stage HCC									
Study	Number of patients		1-year OS (%)		3-year OS (%)		5-year OS (%)		P value*
	RFA	Resection	RFA	Resection	RFA	Resection	RFA	Resection	-
Chen et al. (2006)64	90	90	96	93	71	73	NR	NR	NS
Huang et al. (2010) ⁶⁵	115	115	87	98	70	92	55	76	0.001
Feng et al. (2012) ⁶⁶	84	84	93	96	67	75	NR	NR	NS

Ablation (RFA) vs Surgery



Xu et al. Radiofrequency Ablation versus Hepatic Resection for Small Hepatocellular Carcinoma: Systematic Review of Randomized Controlled Trials with Meta-Analysis and Trial Sequential Analysis. Radiology 2017

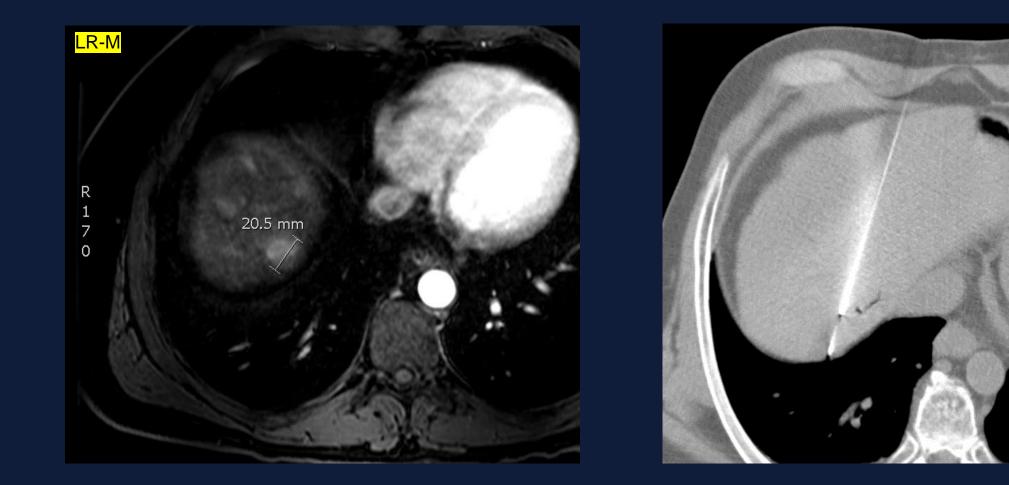
Radiofrequency Ablation



Radiofrequency Ablation

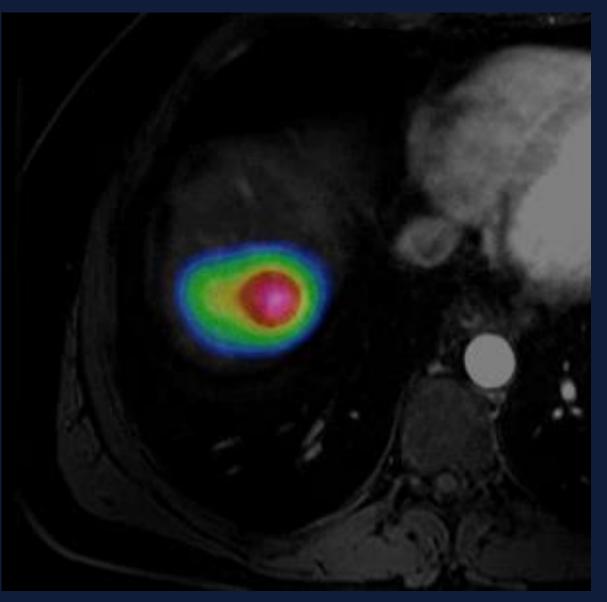


What if you can't ablate?



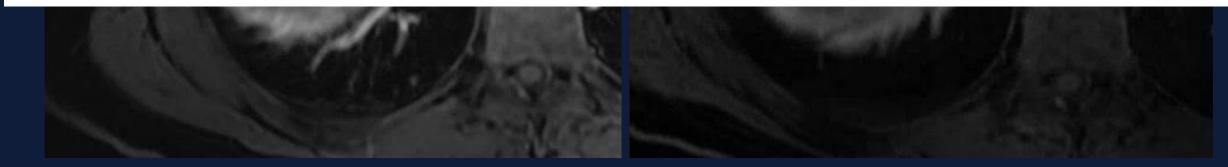
Boosted Segemental Radioembolization





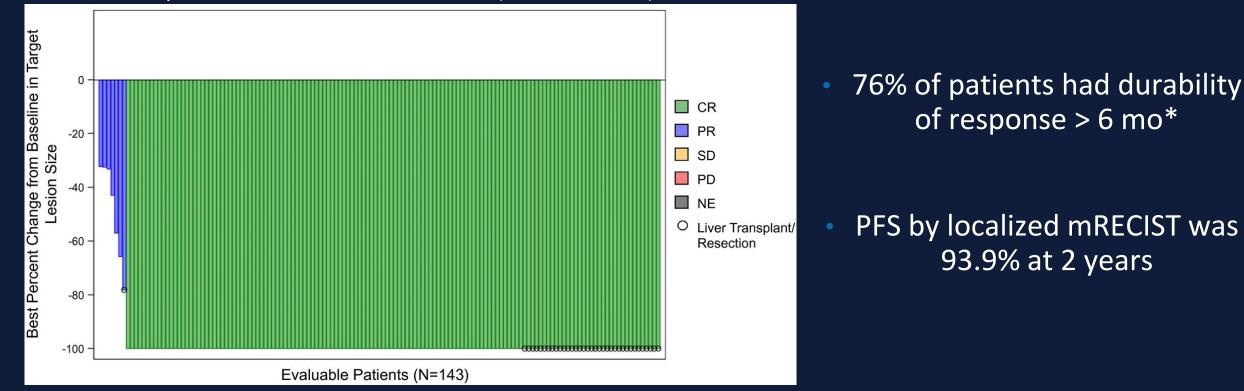


-No residual hepatocellular carcinoma, post-treatment changes, ypT0. There is a 3.0 cm nodule in the 6/7 segment corresponding to observation 2 on the 6/4/2021 MRI and sections show diffusely necrotic tissue and associated ablation beads.



LEGACY Study

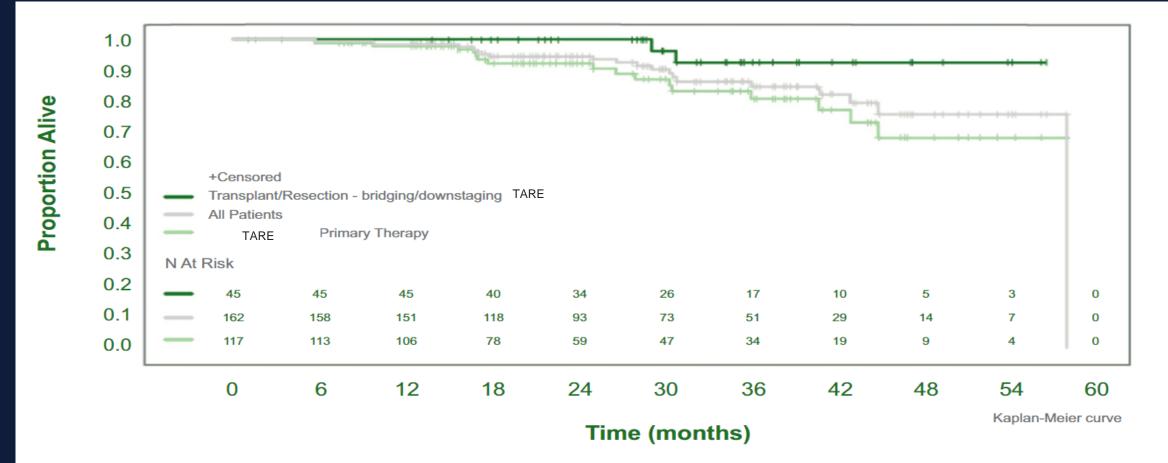
162 patients - Tumors 1 – 8 cm in size (median 2.6 cm)



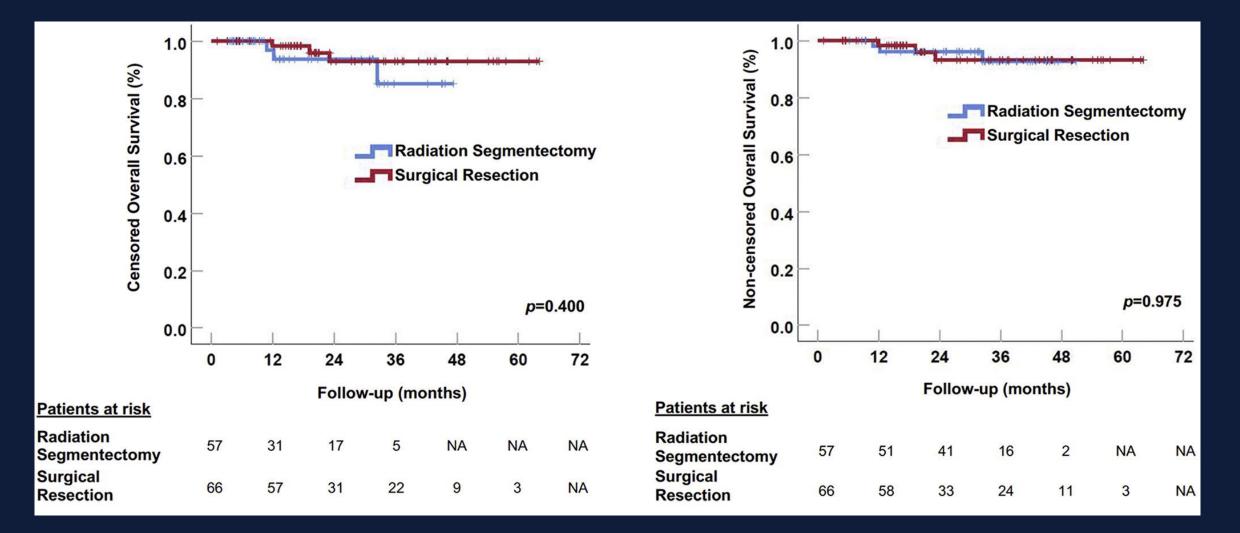
Salem R et al. Hepatology 2021 Mar 19 doi. 0.1002/hep.31819



Overall Survival 87% at 3 years, 93% in transplanted patients



TARE vs Surgical Resection



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De La Garza, et al. Journal of Vascular and Interventional Radiology 2022 33775-785

Tissue is the issue

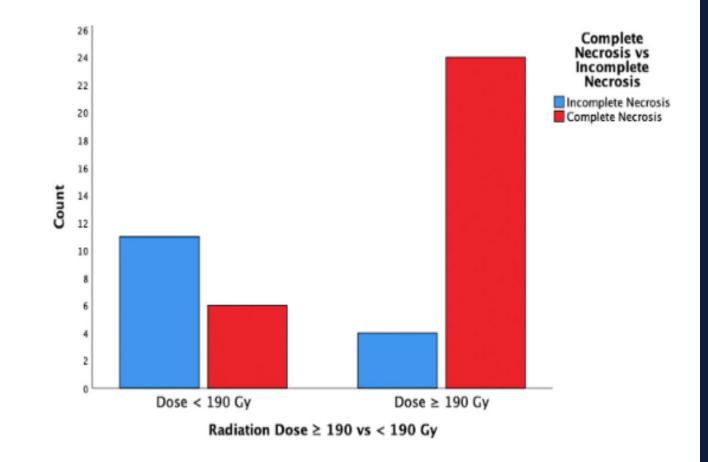
Legacy: 100% of patients with > 400 Gy had CPN (UCSD 74% overall, 93% > 400 Gy)

In context CPN rates:

- Ablation – 55-100%

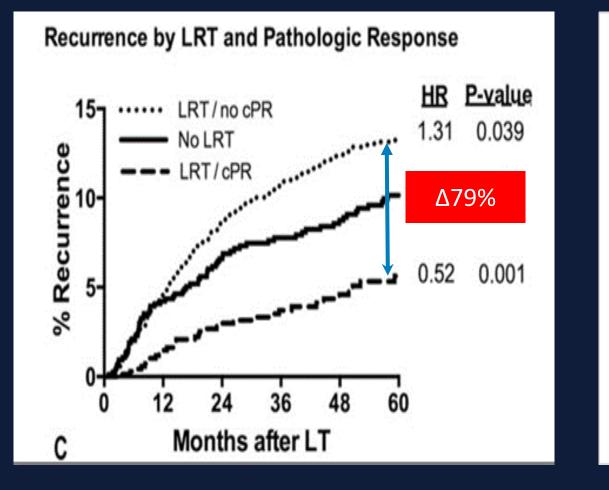
SBRT – 13-50%

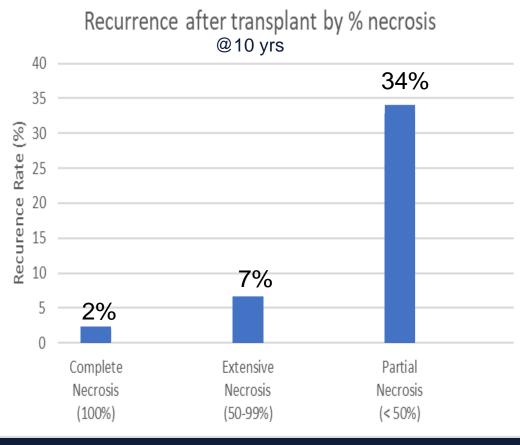
- TACE – 20- 57%



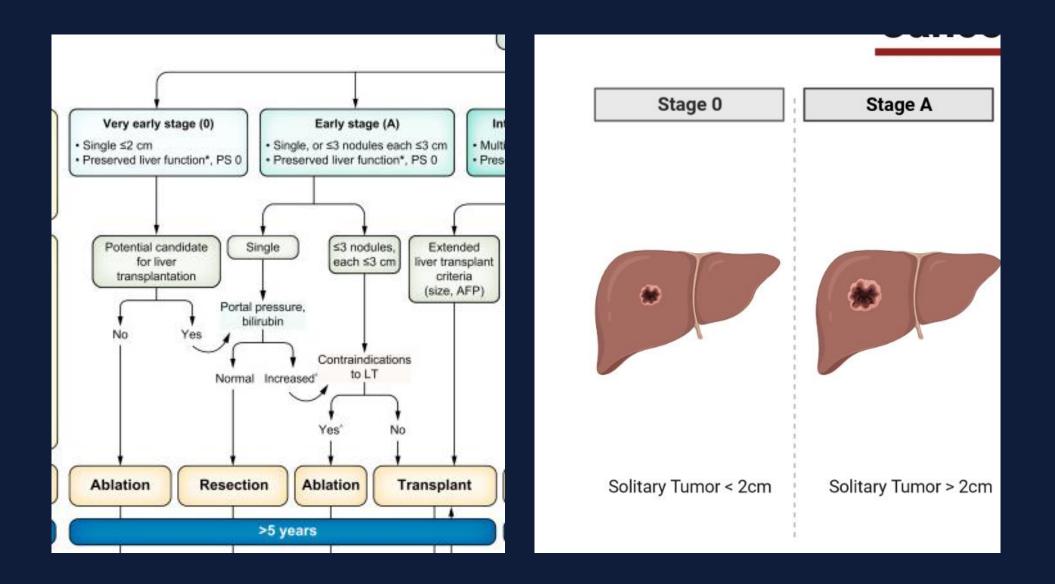
Correlation of Y90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. Gabr A et al. Eur J Nucl Med Mol Imaging. 2021 Individualized Ablation of Hepatocellular Carcinoma: Tailored Approaches across the Phenotype Spectrum. Devcic et al. Semin Intervent Radiol 2019;36:287–297 Complete Pathologic Response to Pretransplant Locoregional Therapy for Hepatocellular Carcinoma Defines Cancer Cure After Liver Transplantation. Vatche et al. Annals of Surgery 2015.

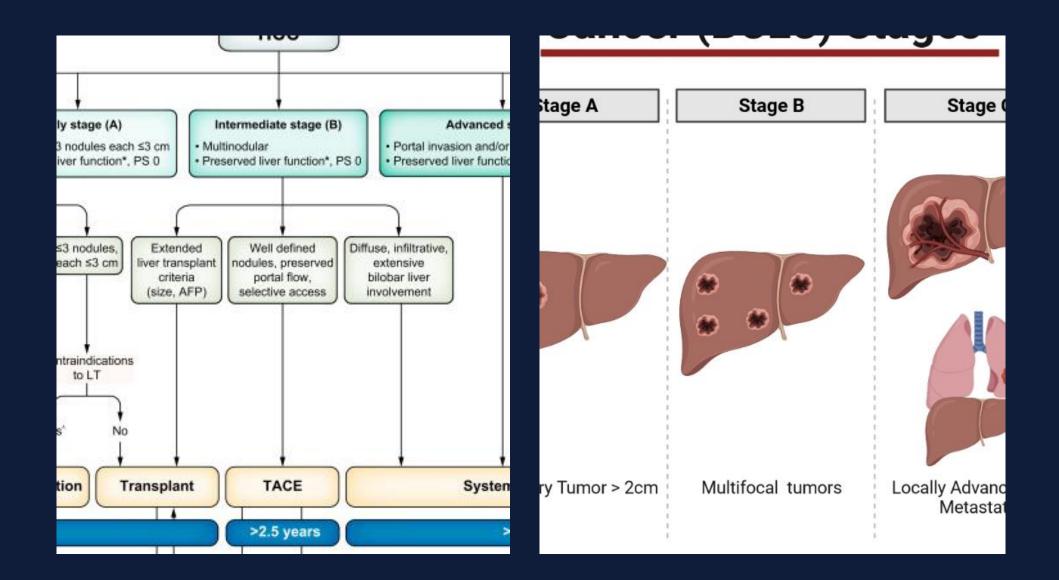
Why is CPN important if they're going to transplant?



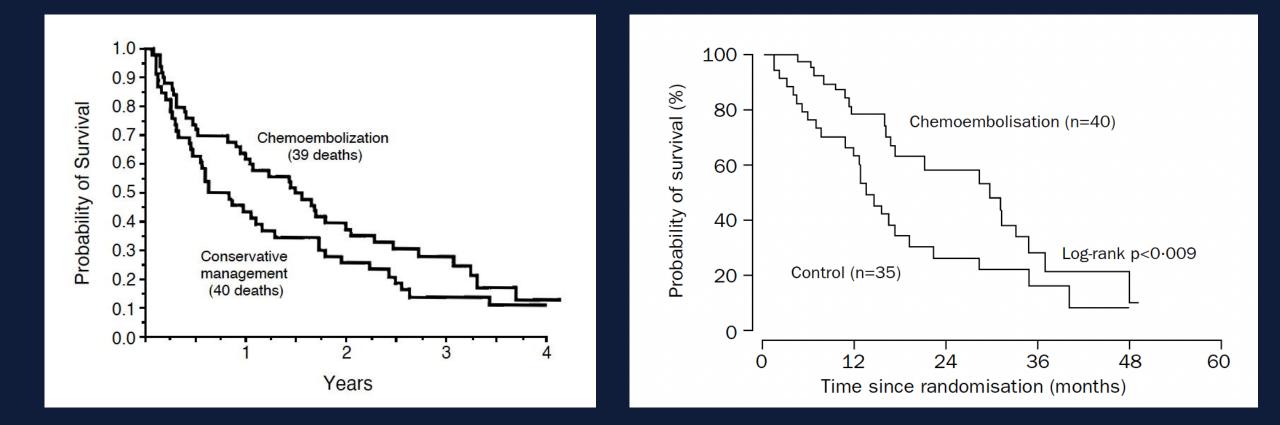


Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. 2017 Gabr A, Kulik L, Mouli S, et al. Liver transplantation following yttrium-90 radioembolization: 15-year experience in 207-patient cohort. Hepatology 2021; 73:998–1010



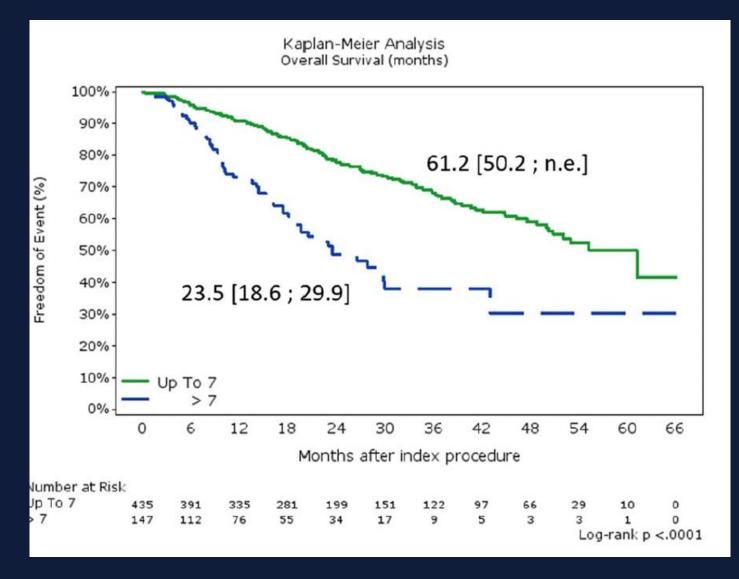


Initial Trials ~2000



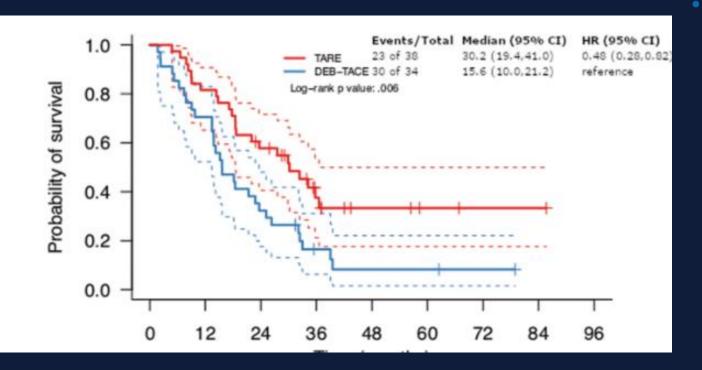
Llovet JM, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359(9319):1734-1739. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med.* 1995;332(19):1256-1261.

Contemporary TACE



Veloso Gomes F, et al. Transarterial Chemoembolization with Anthracyclines-Loaded Polyethylene Glycol Drug Eluting Microspheres for the Treatment of Hepatocellular Carcinoma: A Pooled Multicentric Analysis of Survival in 580 Patients. Cardiovasc Intervent Radiol. 2023;46(4):436-446.

TRACE Trial



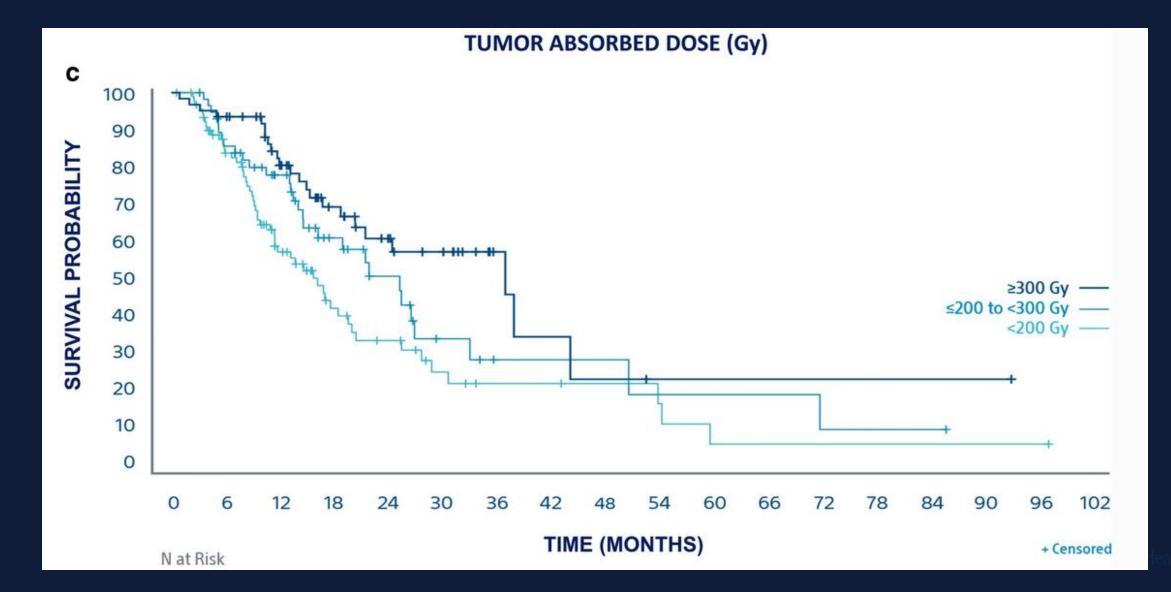
Prospective phase II randomized controlled trial

Median OS was 30.2 months after
TARE versus 15.6 months after TACE (HR 0.48)

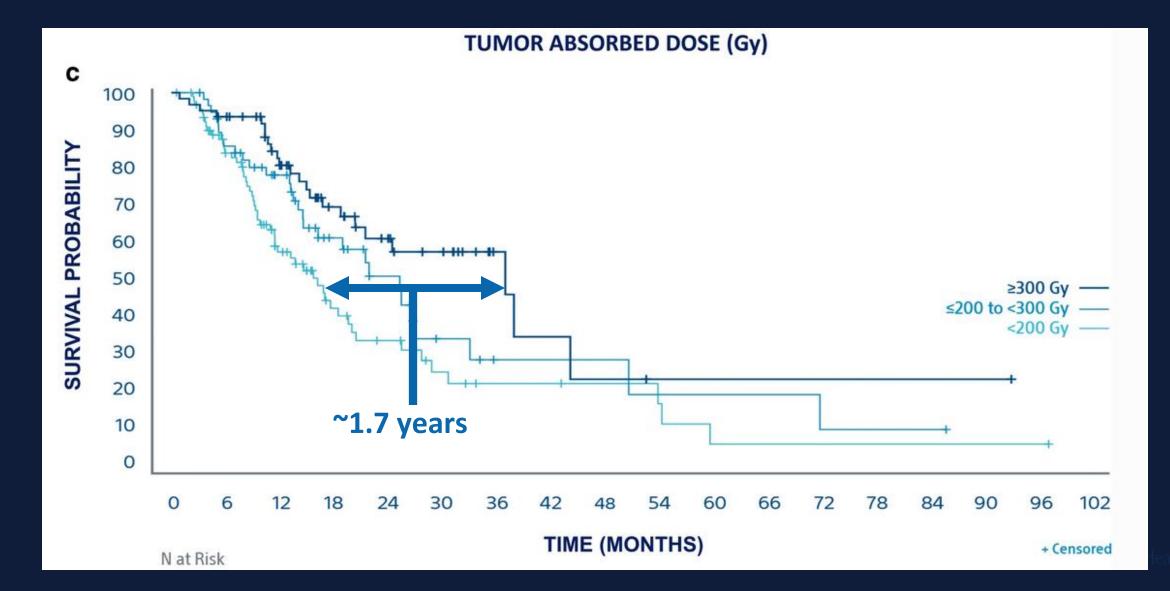
- TTP was 17.1 months in the TARE arm (n = 38) versus 9.5 months in the TACE arm (n = 34)
- Terminated at first safety analysis for efficacy

Dhondt E, Lambert B, Hermie L, et al. ⁹⁰Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. *Radiology*. 2022;303(3):699-710.

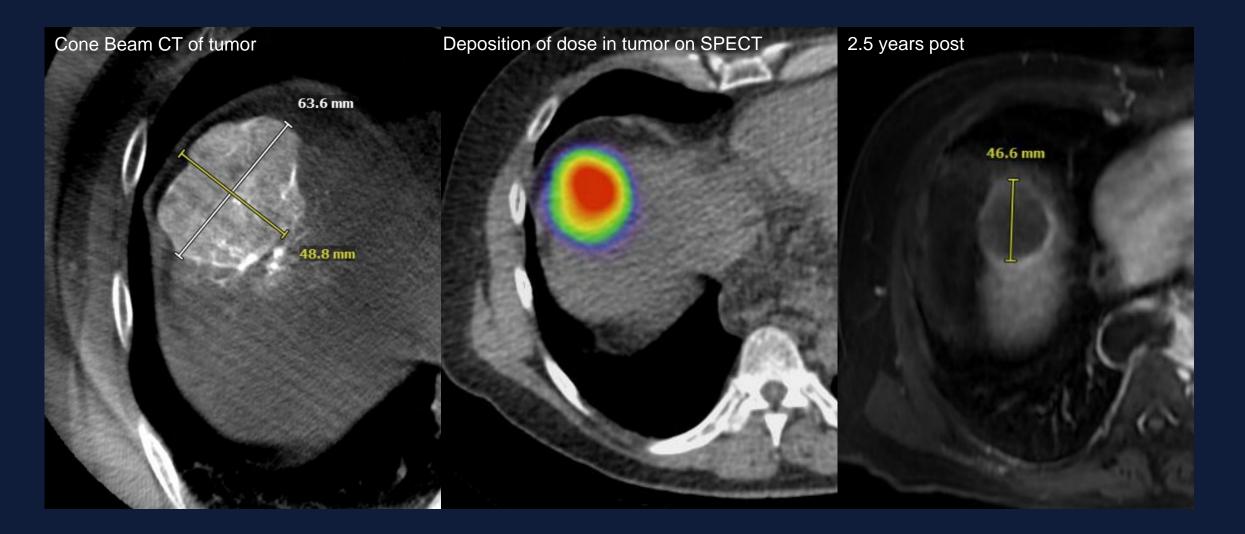
Overall Survival by Dose Thresholds

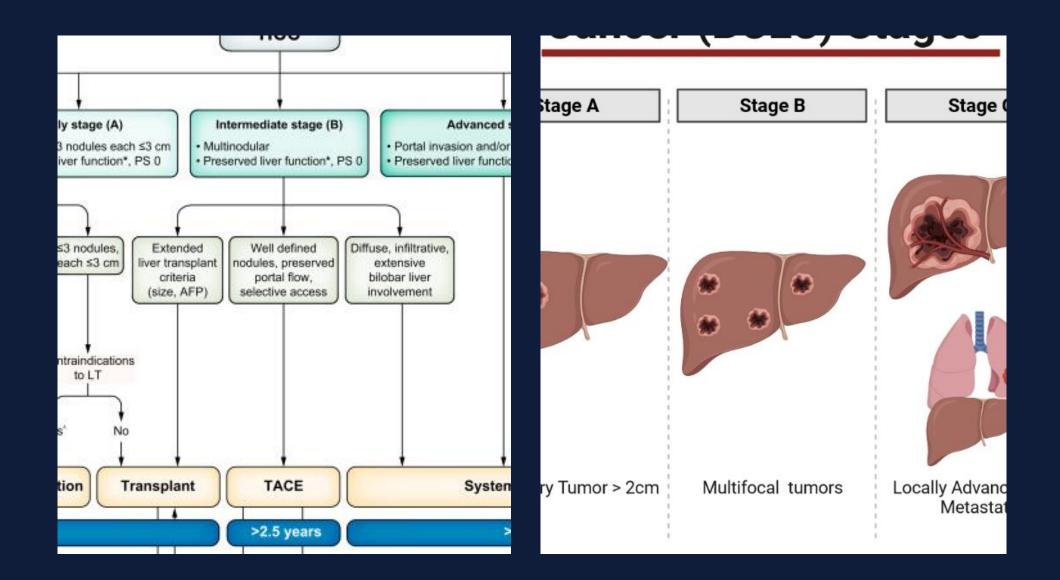


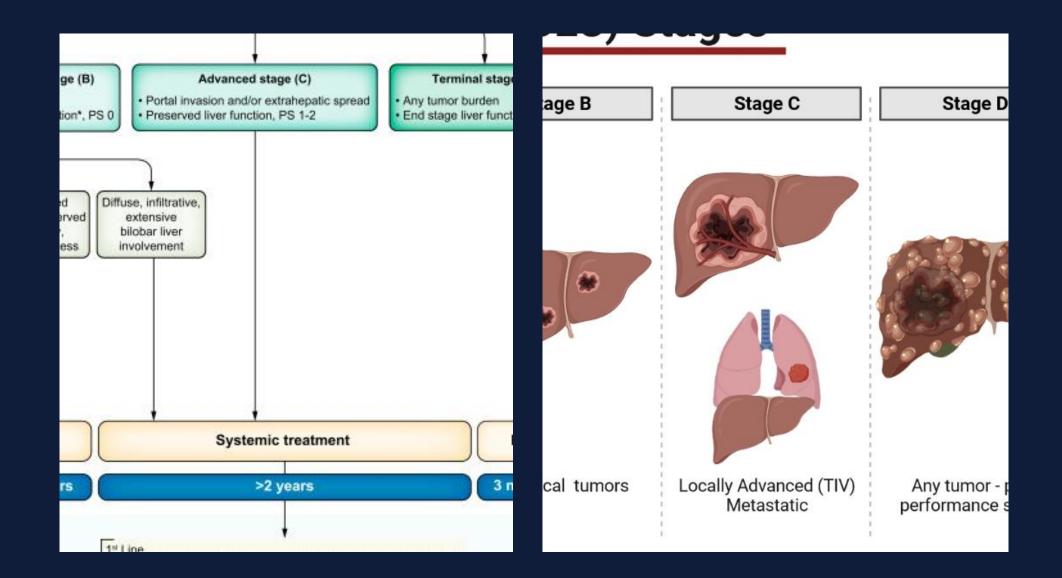
Overall Survival by Dose Thresholds



Modern Boosted Dose Example

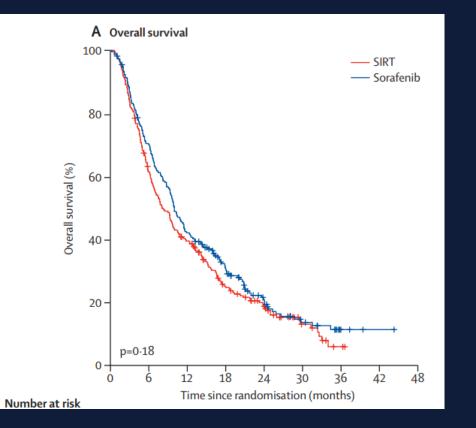




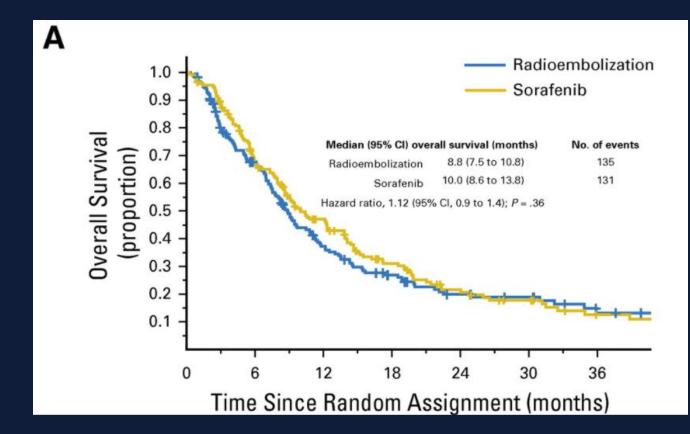


Where were we?

- SARAH Trial (Lancet Onc 2017)
 - Resin Y90 vs Sorafenib (median OS ~9 mo)



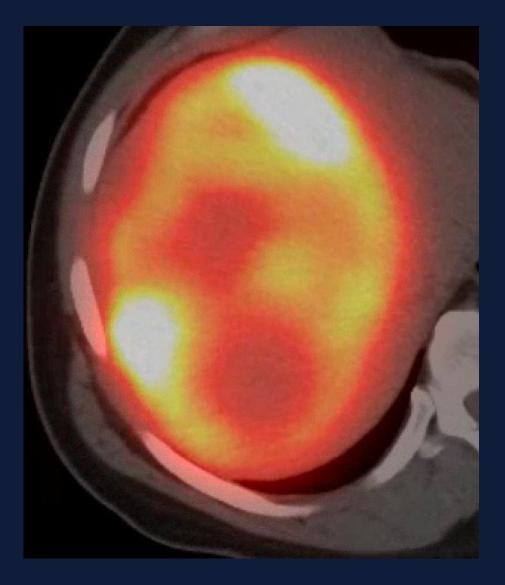
- SIRveNIB Trial (JCO 2017)
 - Resin Y90 vs Sorafenib (median OS ~9 mo)



Where are we today?

- DOSISPHERE 01 (Lancet Onc 2021)
 - Randomized, Multicenter
 - Standard vs **Personalized** (TD > 205 Gy)
 - N=60, Unresectable HCC
 - Median tumor size > 10 cm
 - 64% with TIV

Halted at first safety analysis due to efficacy (powered for 220 pts)

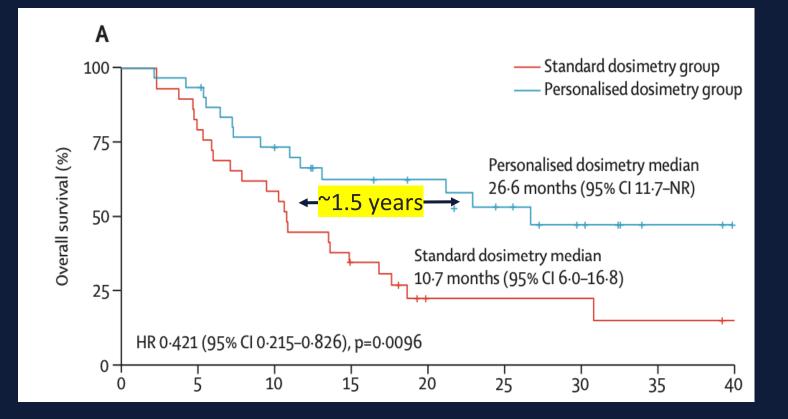


Garin E, et al DOSISPHERE-01 Study Group. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021 Jan;6(1):17-29.

Dosisphere - 01

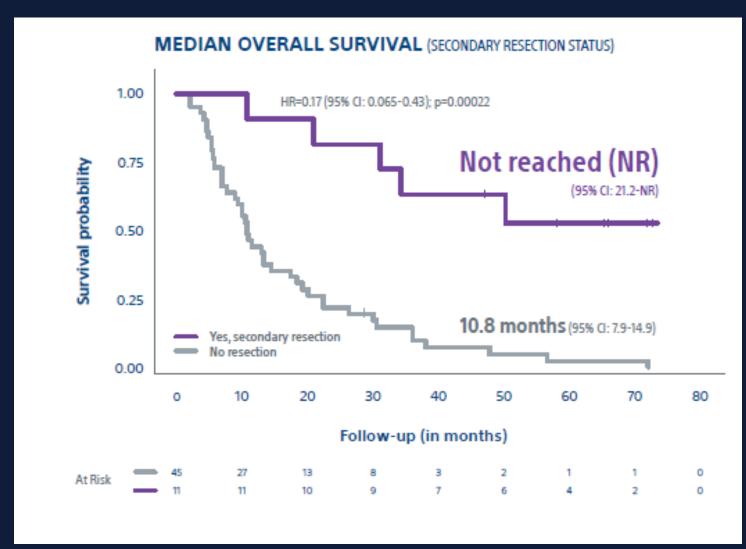
36% of **all** personalized patients downstaged to resection

44% of PVT in personalized arm downstaged to resection



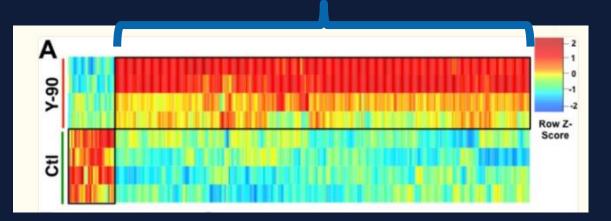
Garin E, et al DOSISPHERE-01 Study Group. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. Lancet Gastroenterol Hepatol. 2021 Jan;6(1):17-29.

Why resection is important



LRT or Systemic Therapy \rightarrow Probably both...

Immune Related Gene Expression



TNF- α level increased on CD8+ and CD4+ T cells, and the proportion of APCs increased.

Increase in CD8+ T cells and CD8+ T cells expressing homing receptors (CCR5 and CXCR6) TARE has potential to shift <u>tumors from a less</u> <u>favorable immune subclass</u> <u>to one that can synergize</u> <u>effectively with</u> <u>immunotherapy.</u>

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Chew V, Lee YH, Pan L, et al. Immune activation underlies a sustained clinical response to yttrium-90 radioembolisation in hepatocellular carcinoma. Gut 2019; 68:335–346

Combination therapy, the future?

NCT Number	Title	Interventions	Characteristics	Enrollment	Location
NCT03575806	Combine TACE and Autologous Tcm Immunotherapy Versus TACE Alone for HCC With MVI After Radical Resection	TACE plus autologous Tcm immunotherapy	Phase II nonrandomized	52	China
NCT04174781	Neoadjuvant Therapy for HCC	Sintilimab	Phase II	61	China
NCT04273100	PD-1 Monoclonal Antibody, Lenvatinib and TACE in the Treatment of HCC	PD-1 mAb combined with TACE and lenvatinib	Phase II	56	China
NCT03914352	A Novel Immunotherapy PD-1 Antibody to Suppress Recurrence of HCC Combined with PVTT After Hepatic Resection	PD-1 antibody with TACE	NA	40	China
NCT04653389	Perioperative Therapy for HCC	Sintilimab Injection TACE	Phase II	30	China
NCT03753659	IMMULAB - Immunotherapy With Pembrolizumab in Combination With Local Ablation in HCC	Radiotherapy Pembrolizumab Procedure: RFA, MWA, Brachytherapy, TACE	Phase II	30	Germany
NCT03817736	Sequential TACE and Stereotactic RadioTherapy With ImmunoTherapy for Downstaging Hepatocellular Carcinoma for Hepatectomy	TACE SBRT	Phase II	33	Hong Kong
NCT04988945	START-FIT TACE and SBRT Followed by Double Immunotherapy for Downstaging HCC	Immune Checkpoint Inhibitor TACE SBRT Durvalumab	Phase II	33	Hong Kong
NCT04522544	Durvalumab and Tremelimumab in Combination With Either Y-90 SIRT or TACE for Intermediate Stage HCC With Pick-the-winner Design	Tremelimumab	Phase II	84	Germany
NCT02638857	Immunotherapy Usig	TACE TACE, dendritic cell, mitomycin C, epirubicin, multiple antigen T cell	Phase I/II	60	China
NCT03638141	CTLA-4 /PD-L1 Blockade Following Transarterial Chemoembolization (DEB- TACE) in Patients With Intermediate Stage of HCC Using Durvalumab and Tremelimumab	Durvalumab Tremelimumab TACE	Phase II	30	USA
NCT04981665	A study to Evaluate TACE Sequential Tielizumab as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection		Phase II	50	China
NCT04518852	TACE, Sorafenib and PD-1 Monoclonal Antibody in the Treatment of HCC	TACE combined with sorafenib and PD- 1 mAb	Phase II	60	China
NCT04521153	Camrelizumab Combined With Apatinib Mesylate for Perioperative Treatment of Resectable Hepatocellular Carcinoma	Camrelizumab with apatinib Mesylate TACE	NA	290	China
NCT04220944	Combined Locoregional Treatment With Immunotherapy for Unresectable HCC.	Surgery Sintilimab MWA, TACE	Phase I	45	China
NCT04796025	TACE Combined With Sintilimab Plus Bevacizumab Biosimilar in Hepatocellular Carcinoma (BCLC-C Stage): a Prospective Single-arm Phase II Clinical Study T-Double	Sintilimab; Bevacizumab Biosimilar	Phase II	34	China
NCT05033522	ALIVE	AlloStim [®] immunotherapy FOLFOX regimen Best Supportive Care	Phase II/III	150	Malaysia/ Thailand
NCT04229355	DEB-TACE Plus Lenvatinib or Sorafenib or PD-1 Inhibitor for Unresectable Hepatocellular Carcinoma	DEB-TACE plus Sorafenib DEB-TACE plus Lenvatinib DEB-TACE plus PD-1 inhibitor	Phase III	90	China
NCT01828762	Autologous Immune Cell Therapy in Primary Hepatocellular Carcinoma Patients Following Resection and TACE Therapy	DEB-TACE plus PD-T inhibitor DC-TC +GM-CSF	NA	8	China
	DC-TC- subcutaneous injections of autologous dendritic cells incubated with irradiated autologous tumor stem cells				
NCT04268888	Nivolumab in Combination With TACE/TAE for Patients With Intermediate Stage HCC TACE-3	Drug: nivolumab and TACE/TAE	Phase II/III	522	UnitedKingdom
NCT02487017	DC-CIK Combined With TACE in the Treatment of Hepatocellular Carcinoma	TACE with DC-CIK	Phase II	60	China

	nco).				
NCT Number	Title	Interventions	Characteristics	Enrollment	Location
	Camrelizumab in Patients With Unresectable Hepatocellular Carcinoma A Basic-clinical Translational Research in HBV-Specific Antigen Peptides and HepG2 Cell Lysate Co- activated Dendritic Cells Combined With TACE in HBV-related HCC Treatment	Camrelizumab ADCC and TACE	NA Phase I/II	1000 70	NA China
NCT03937830	Combined Treatment of Durvalumab, Bevacizumab, Tremelimumab and TACE in Subjects With HCC or Biliary Tract Carcinoma	Durvalumab, doxorubicin- eluting beads TACE bevacizumab Tremelimumab	Phase II	22	USA
NCT01853618	Tremelimumab With Chemoembolization or Ablation for Liver Cancer	Tremelimumab, RFA TACE Cryoablation	Phase I/II	61	USA
NCT03592706	Autologous Immune Killer Cells to Treat Liver Cancer Patients as an Adjunct Therapy	Immune killer cells TACE	Phase II/III	60	Taiwan
NCT02856815	Safety and Efficacy of 'Immuncell-LC' in TACE Therapy	Immuncell-LC	Phase II	78	Republic of Korea
NCT04803994	The ABC-HCC Trial: Atezolizumab Plus Bevacizumab vs. TACE in Intermediate-stage HCC	Atezolizumab Bevacizumab TACE	Phase III	434	Germany, Spain
NCT04712643	A Study of TACE Combined With Atezolizumab Plus Bevacizumab or TACE Alone in Patients With Untreated HCC	Atezolizumab Bevacizumab TACE	Phase III	342	China
NCT04229355	DEB-TACE Plus Lenvatinib or Sorafenib or PD-1 Inhibitor for Unresectable Hepatocellular Carcinoma	DEB-TACE plus sorafenib DEB-TACE plus lenvatinib DEB-TACE plus PD-1 inhibitor	Phase III	90	China
NCT03778957	A Global Study to Evaluate TACE in Combination With Durvalumab and Bevacizumab Therapy in Patients With Locoregional HCC EMERALD-1	Durvalumab Bevacizumab TACE	Phase III	710	USA
NCT04909866	The Efficacy and Safety of TACE, Lenvatinib and Camrelizumab in the Treatment of BCLC Stage B/ C HCC: a Single- arm, Single-center, Open-label Study	TACE +lenvatininb +camrelizumab	Phase II/III	40	China
NCT04011033	Study of Adoptive Transfer of iNKT Cells Combined With TACE to Treat Advanced HCC	iNKT cells Cyclophosphamide Human recombinant Interleukin-2 TACE	Phase II/III	144	China
NCT04246177	Safety and Efficacy of Lenvatinib With Pembrolizumab in Combination With TACE in Participants With Incurable/ Non-metastatic HCC	Lenvatinib Pembrolizumab TACE	Phase III	950	USA
NCT04340193	A Study of Nivolumab and Ipilimumab in Combination With TACE in Participants With Intermediate Stage Liver Cancer CheckMate 74W	Nivolumab ipilimumab	Phase III	765	USA

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Brown ZJ, Hewitt DB, Pawlik TM. Combination therapies plus transarterial chemoembolization in hepatocellular carcinoma: a snapshot of clinical trial progress. Expert Opin Investig Drugs. 2022 Apr;31(4):379-391



- Ablative modalities for early-stage HCC has similar survival as surgical resection. Though improved with liver transplantation.
- For intermediate stage disease radioembolization (TARE) has improved survival over chemoembolization (TACE).
- For advanced tumors, personalized dosimetry has the potential to vastly increase survival over historical dosimetry. Possible synergies with immunotherapy.



Thanks for the invitation!

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