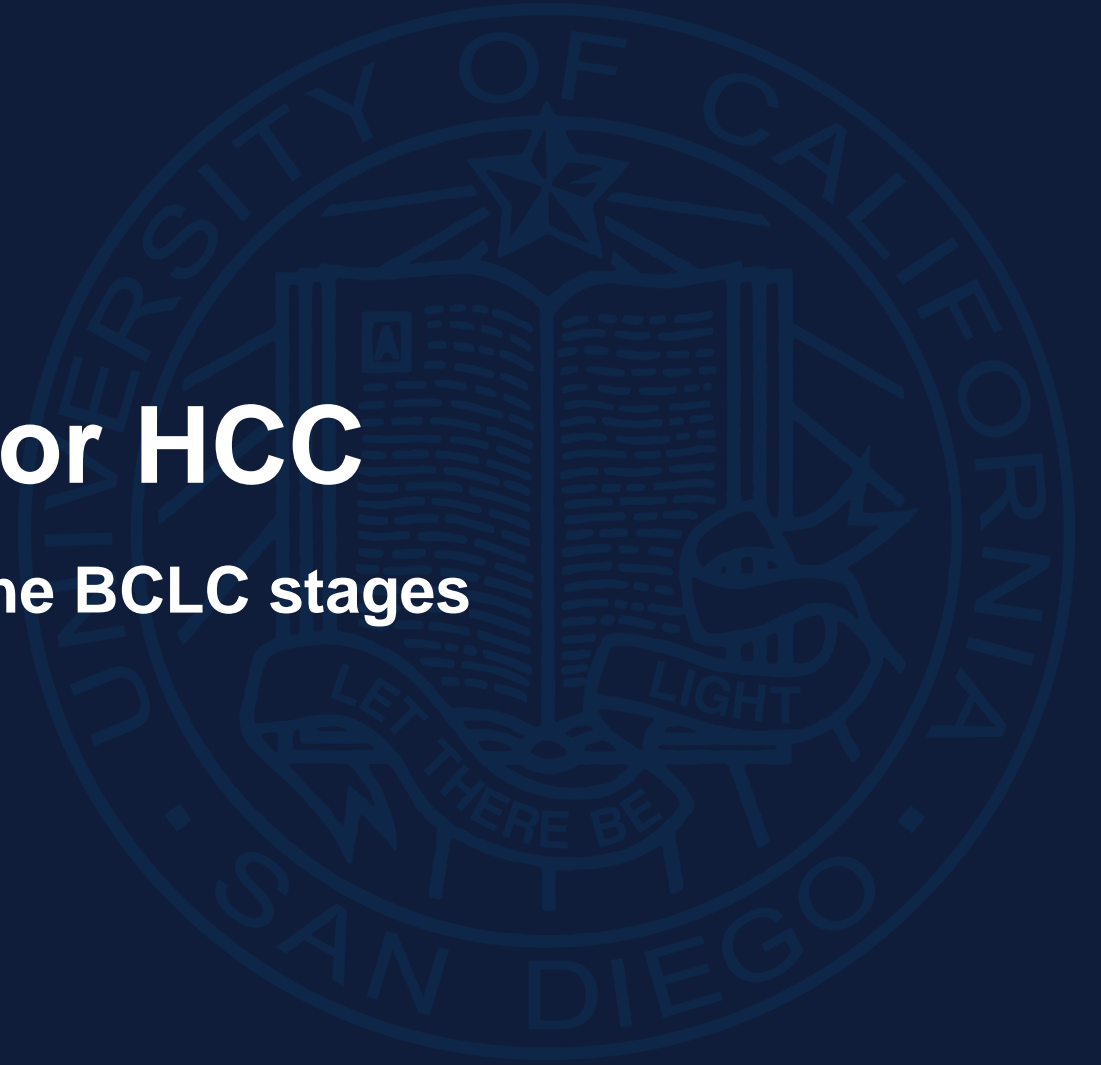


# Locoregional Therapies for HCC

A look throughout the BCLC stages

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



# A Brief History Lesson (1977)

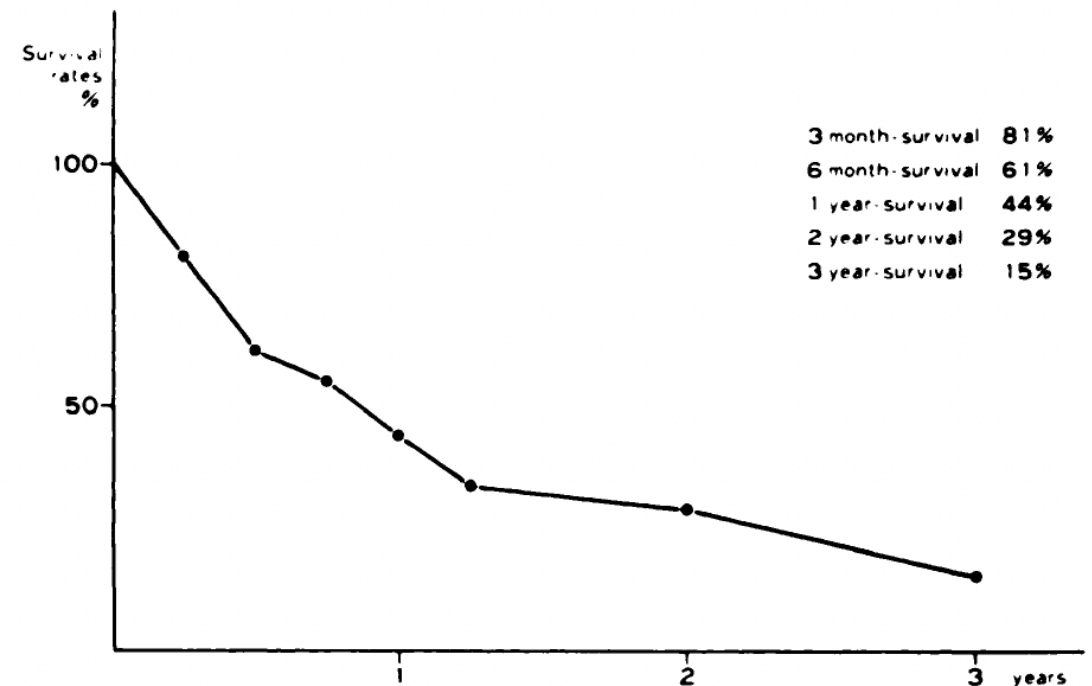
## INTERVENTIONAL RADIOLOGY

### Hepatic Artery Embolization in 120 Patients with Unresectable Hepatoma<sup>1</sup>

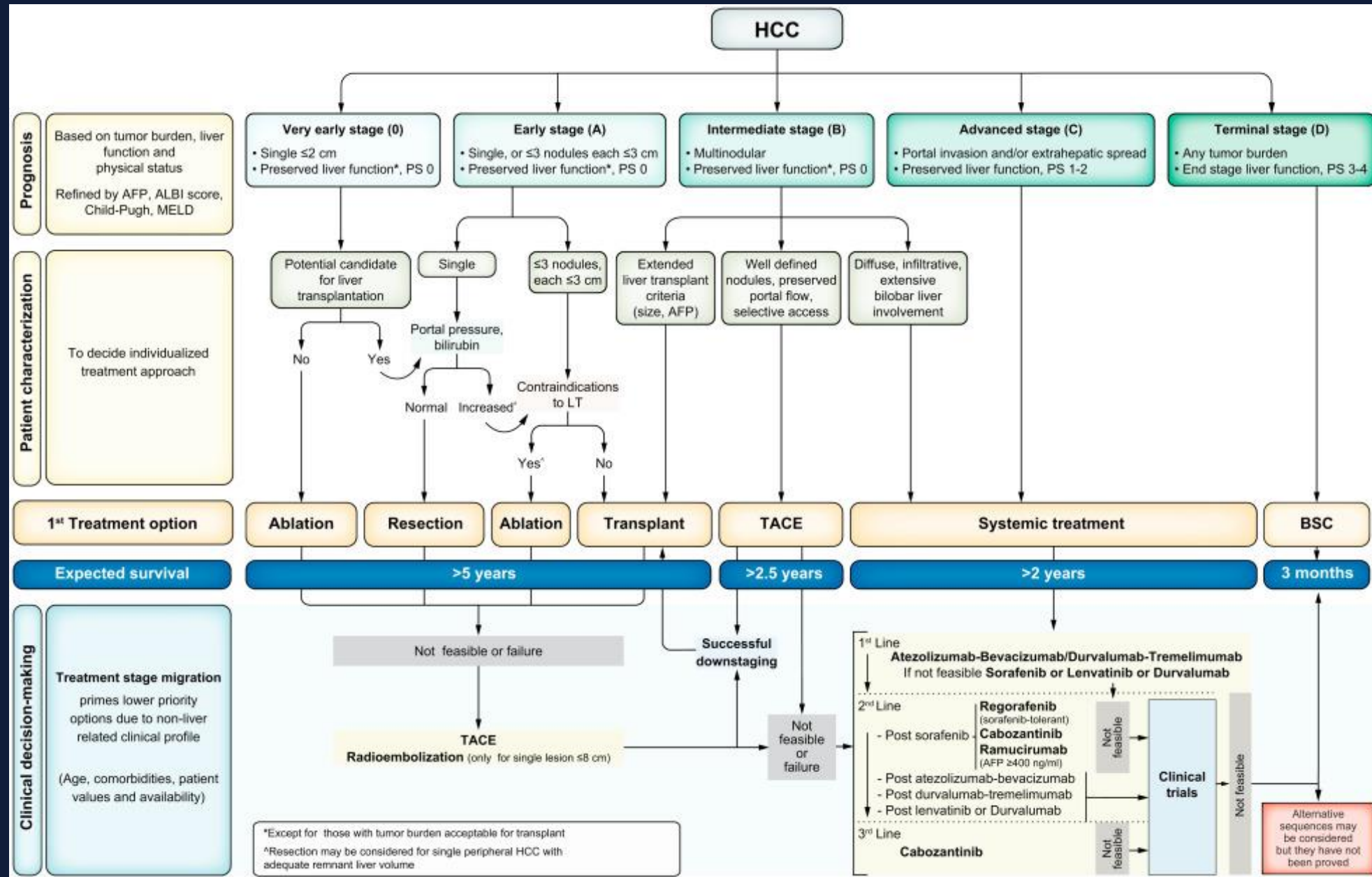
Ryusaku Yamada, M.D.  
Morio Sato, M.D.  
Mamoru Kawabata, M.D.  
Haruki Nakatsuka, M.D.  
Kenji Nakamura, M.D.  
Sumio Takashima, M.D.

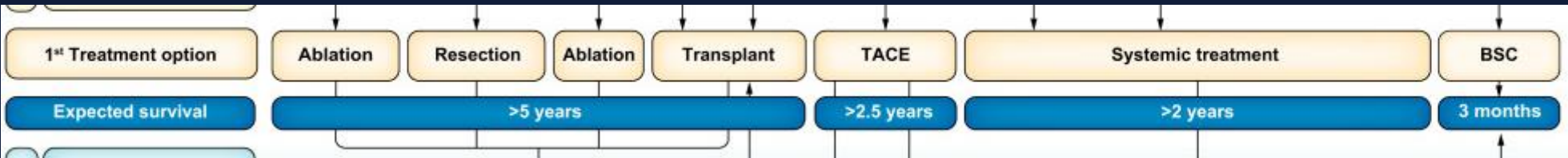
Cumulative survival rate in 120 cases of unresectable hepatoma treated by embolization.

**Figure 1**

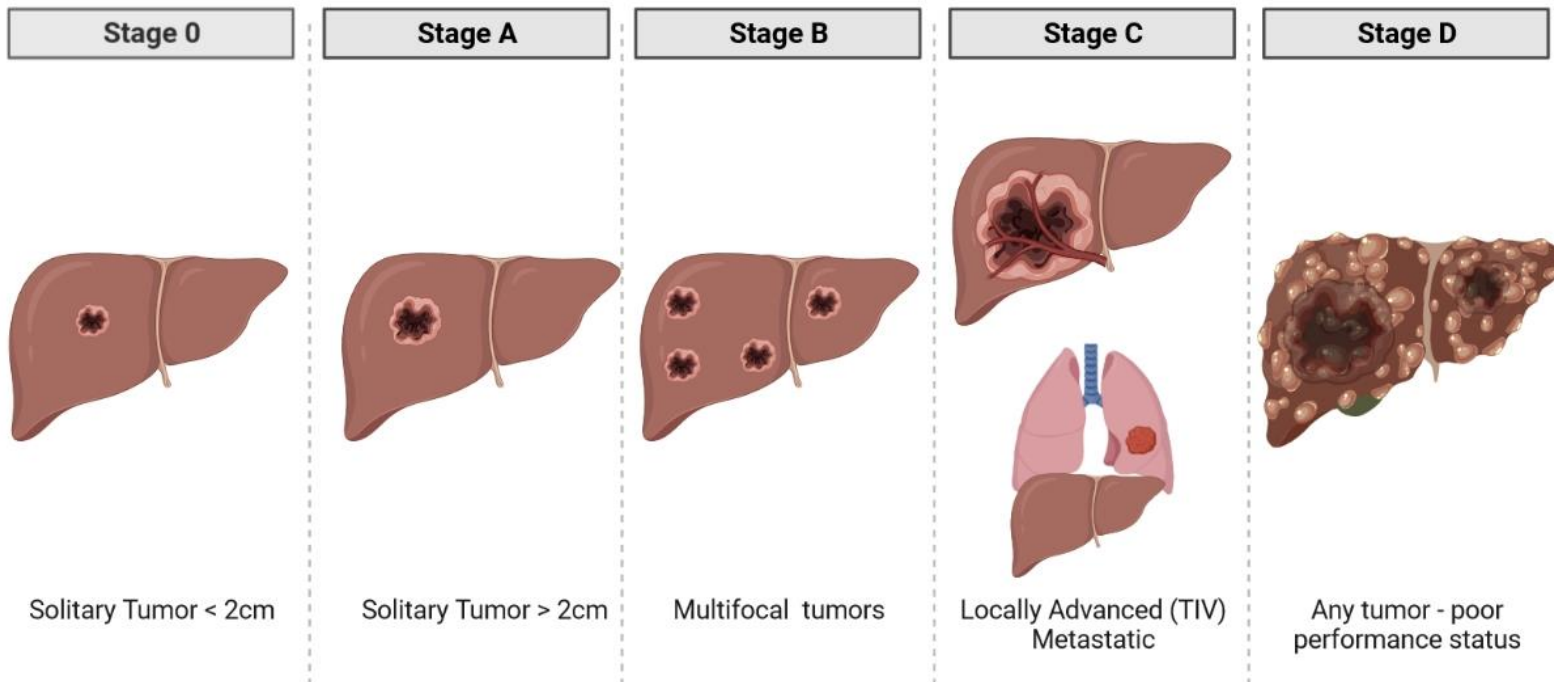


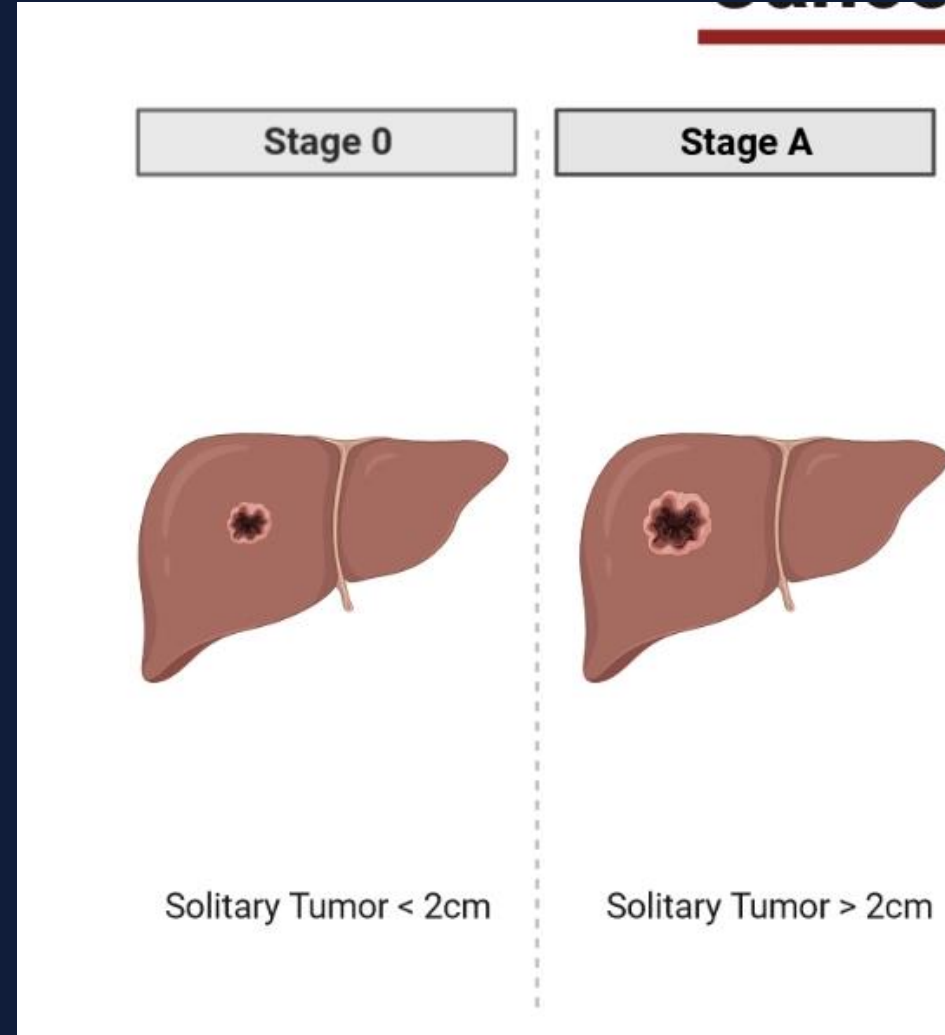
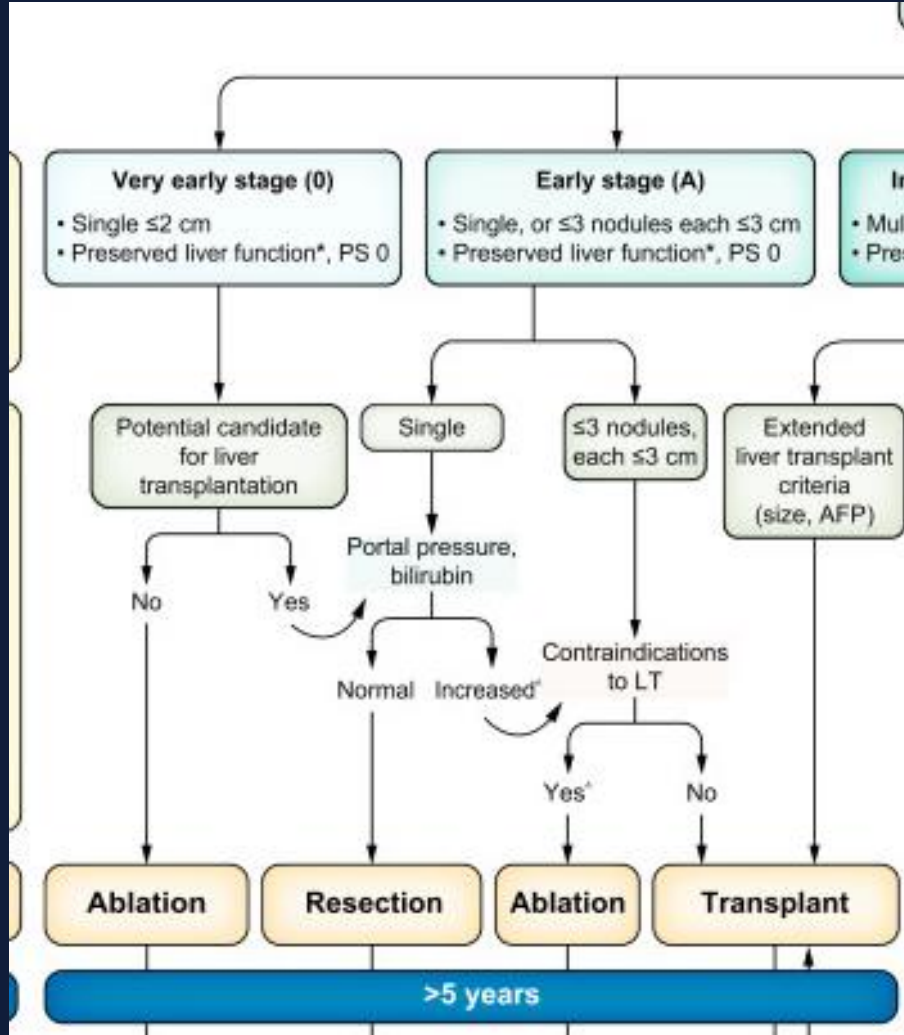
# 2022 BCLC Guidelines





## Barcelona Clinic Liver Cancer (BCLC) Stages



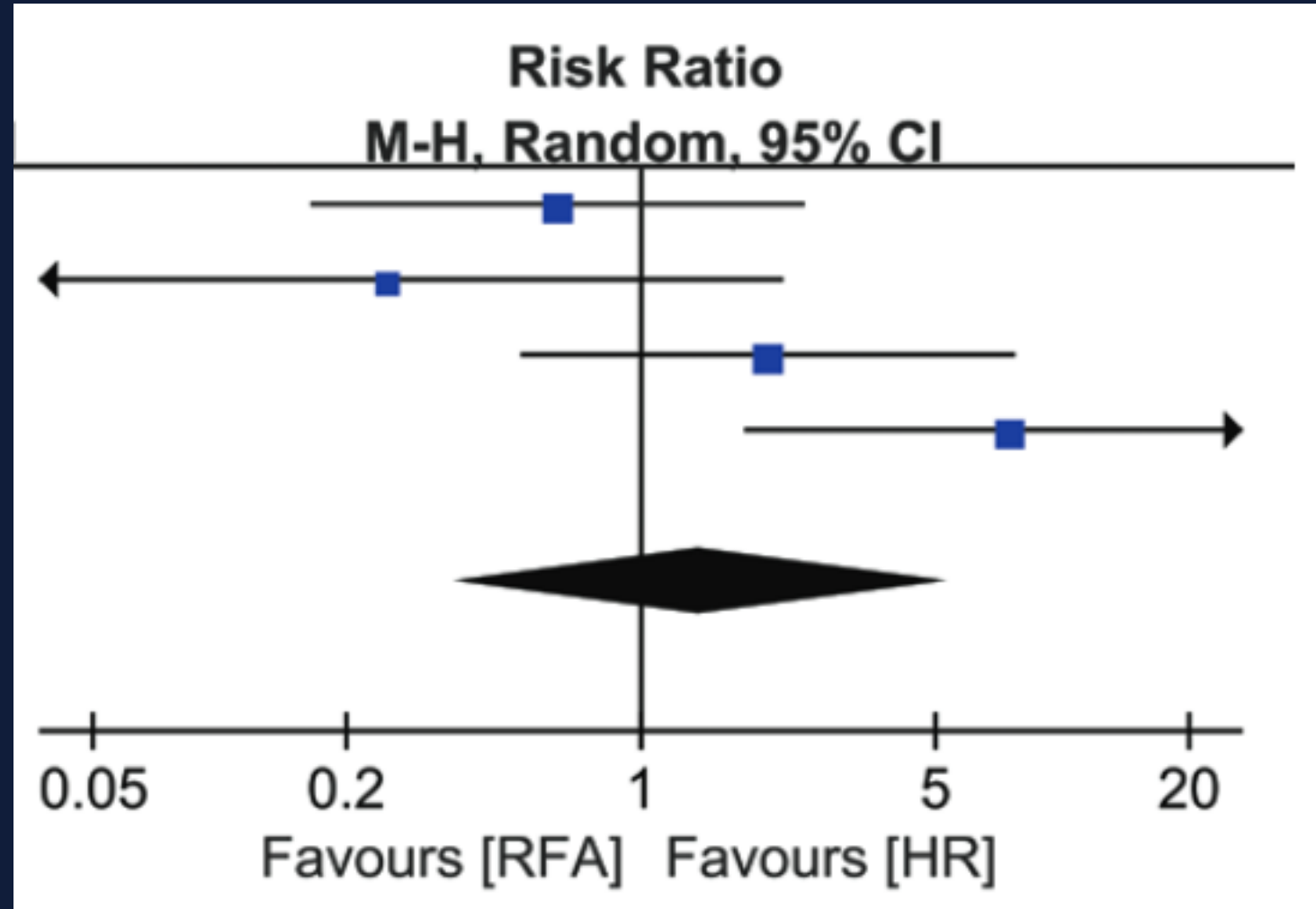


# Why is ablation in the guidelines?

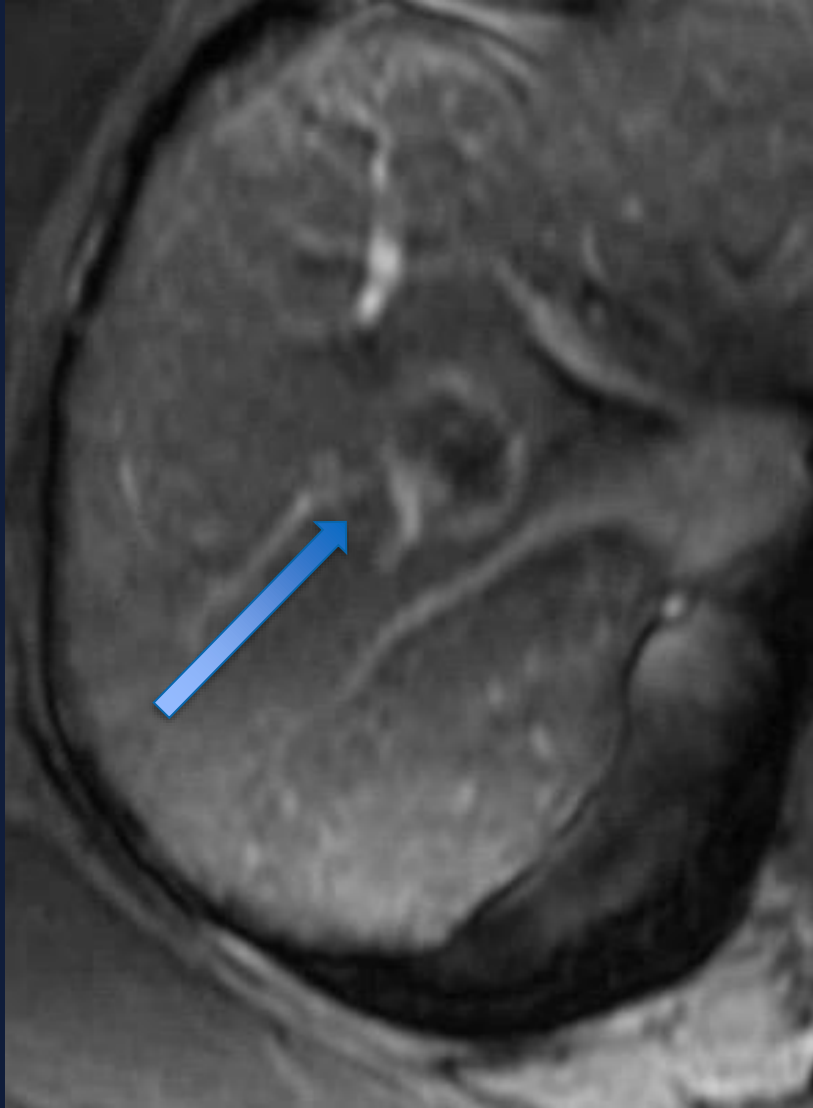
**Table 3** | Randomized controlled trials comparing RFA and surgical resection for the treatment of early stage HCC

Study	Number of patients		1-year OS (%)		3-year OS (%)		5-year OS (%)		P value*
	RFA	Resection	RFA	Resection	RFA	Resection	RFA	Resection	
Chen <i>et al.</i> (2006) <sup>64</sup>	90	90	96	93	71	73	NR	NR	NS
Huang <i>et al.</i> (2010) <sup>65</sup>	115	115	87	98	70	92	55	76	0.001
Feng <i>et al.</i> (2012) <sup>66</sup>	84	84	93	96	67	75	NR	NR	NS

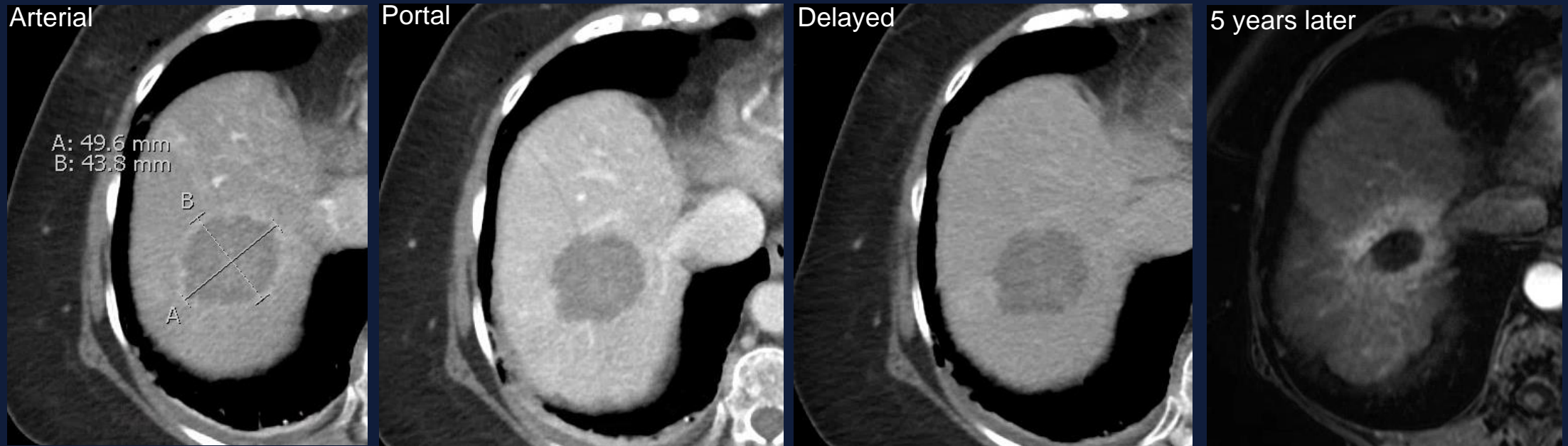
# Ablation (RFA) vs Surgery



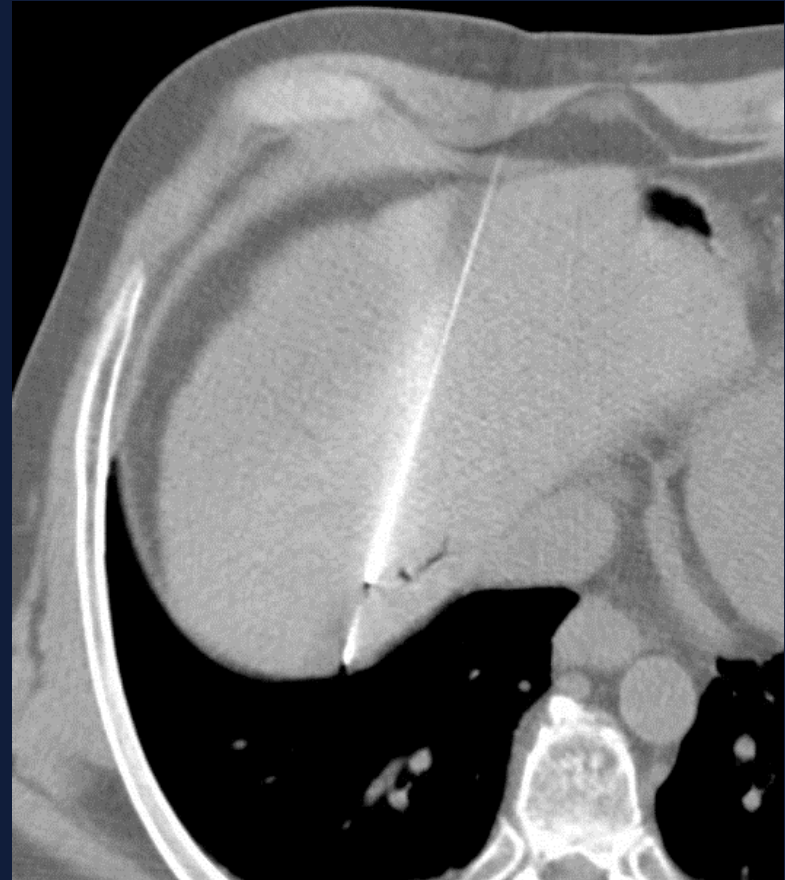
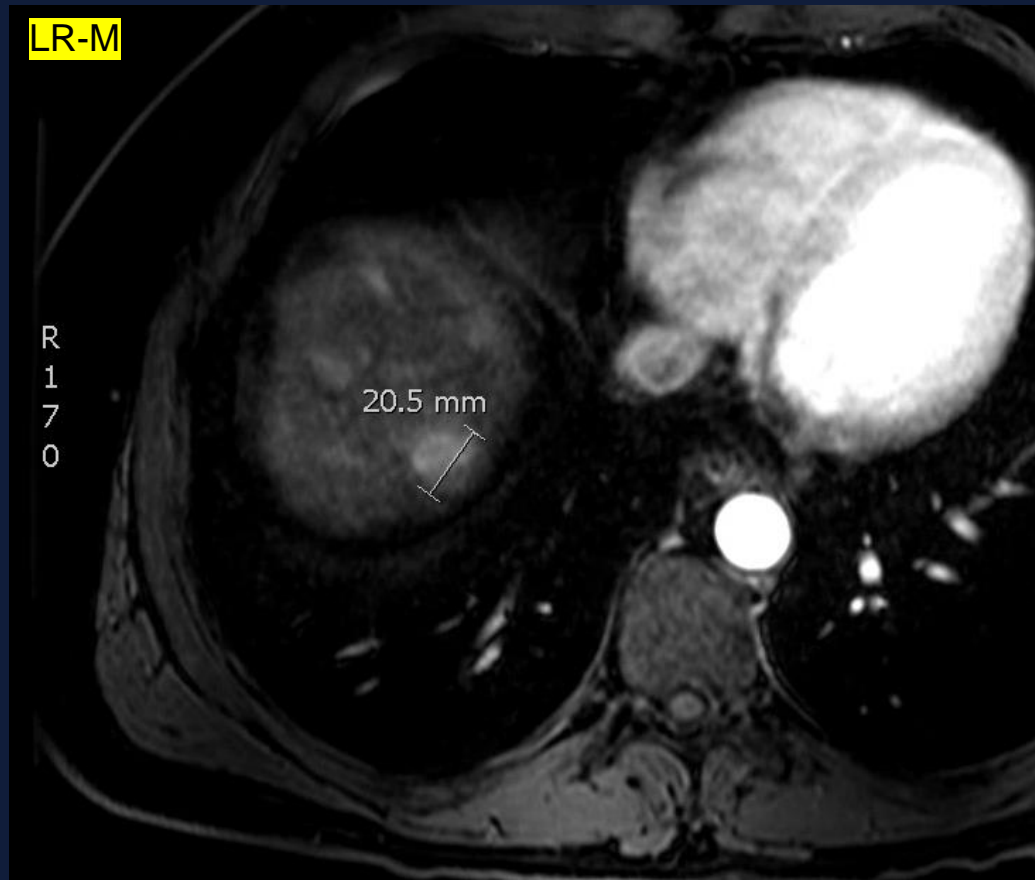
# Radiofrequency Ablation



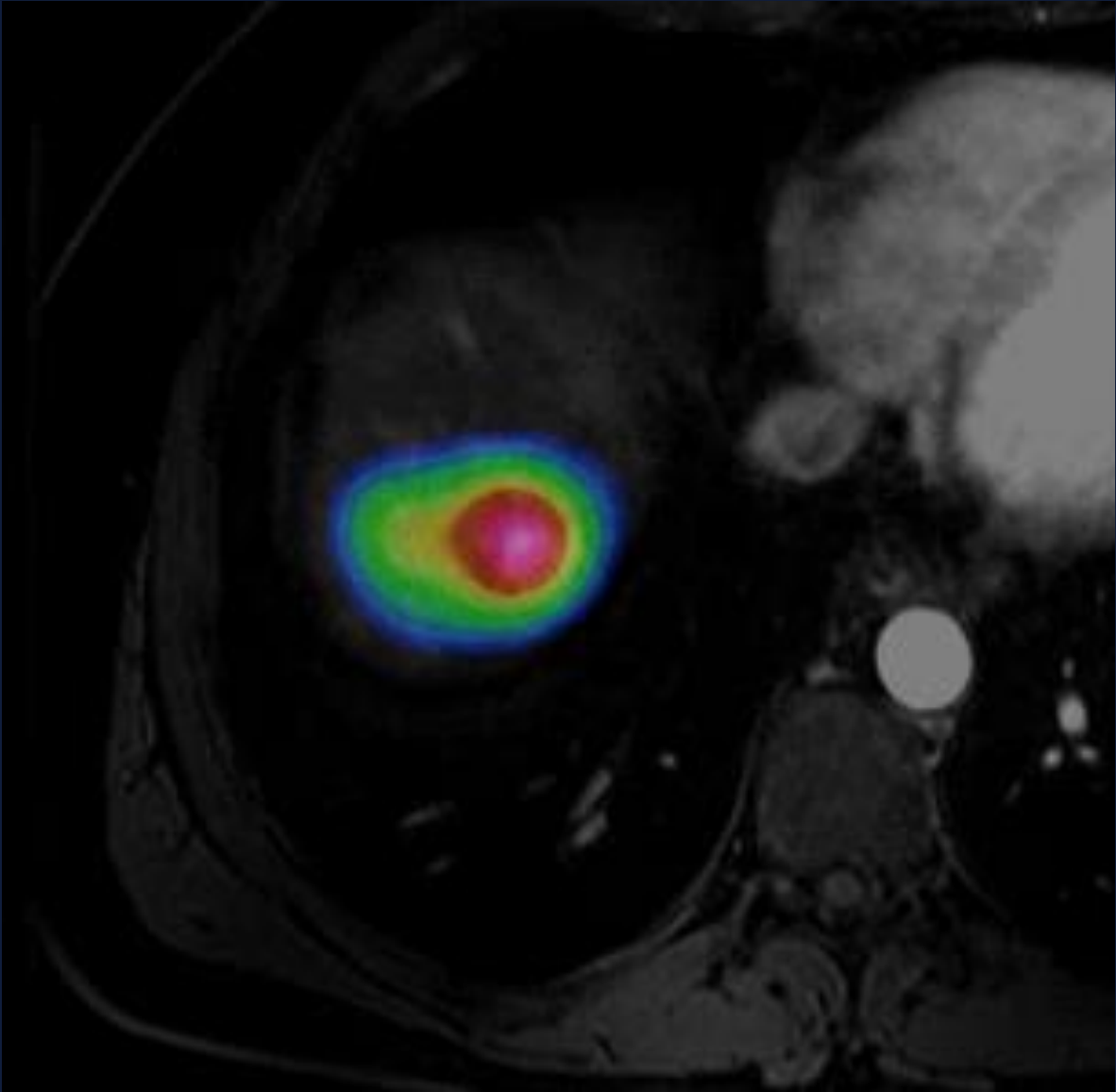
# Radiofrequency Ablation

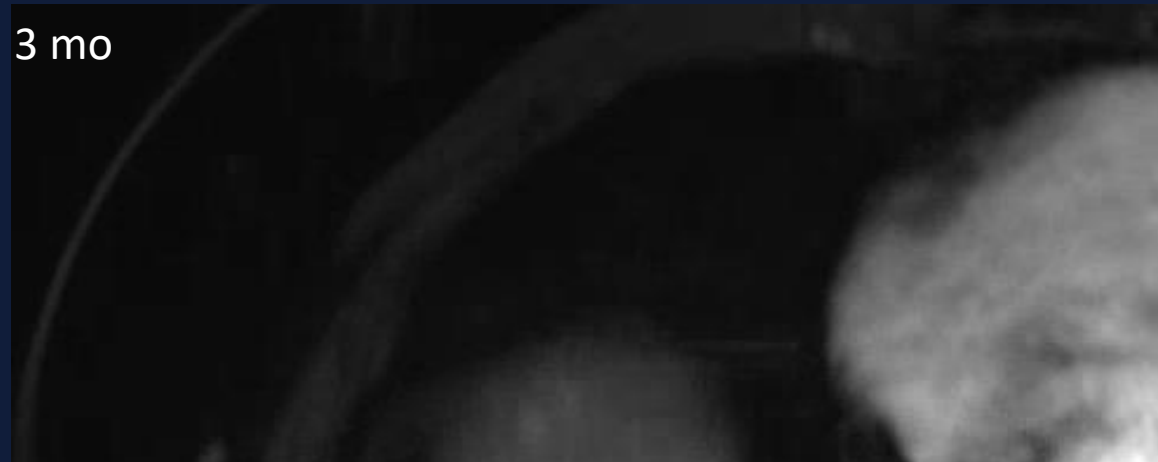


What if you can't ablate?



# Boosted Segmental Radioembolization

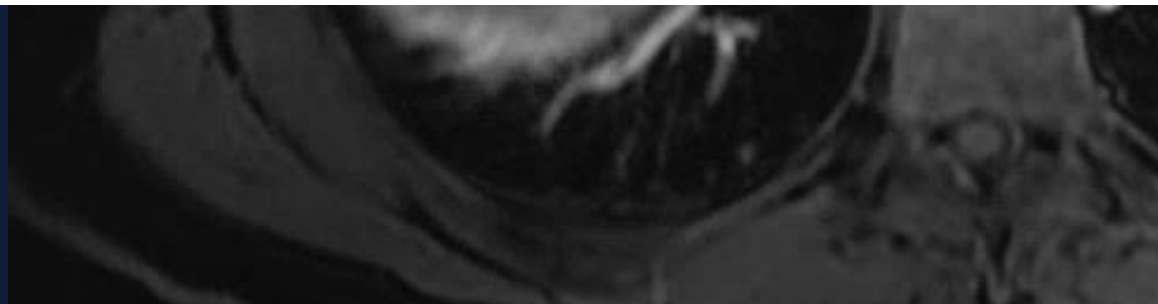




A: Liver, native, explant:

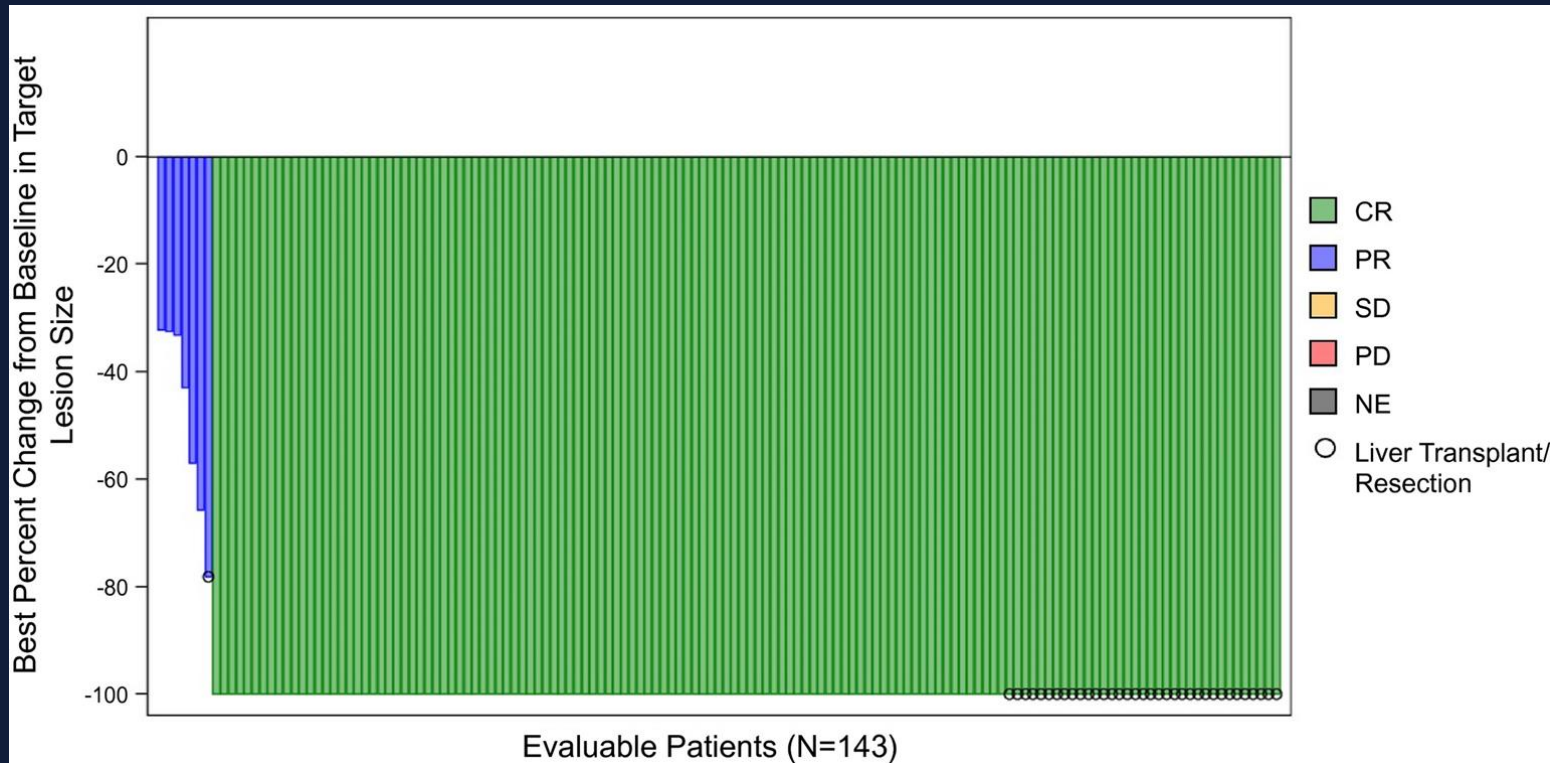
-No residual hepatocellular carcinoma, post-treatment changes, ypT0.

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

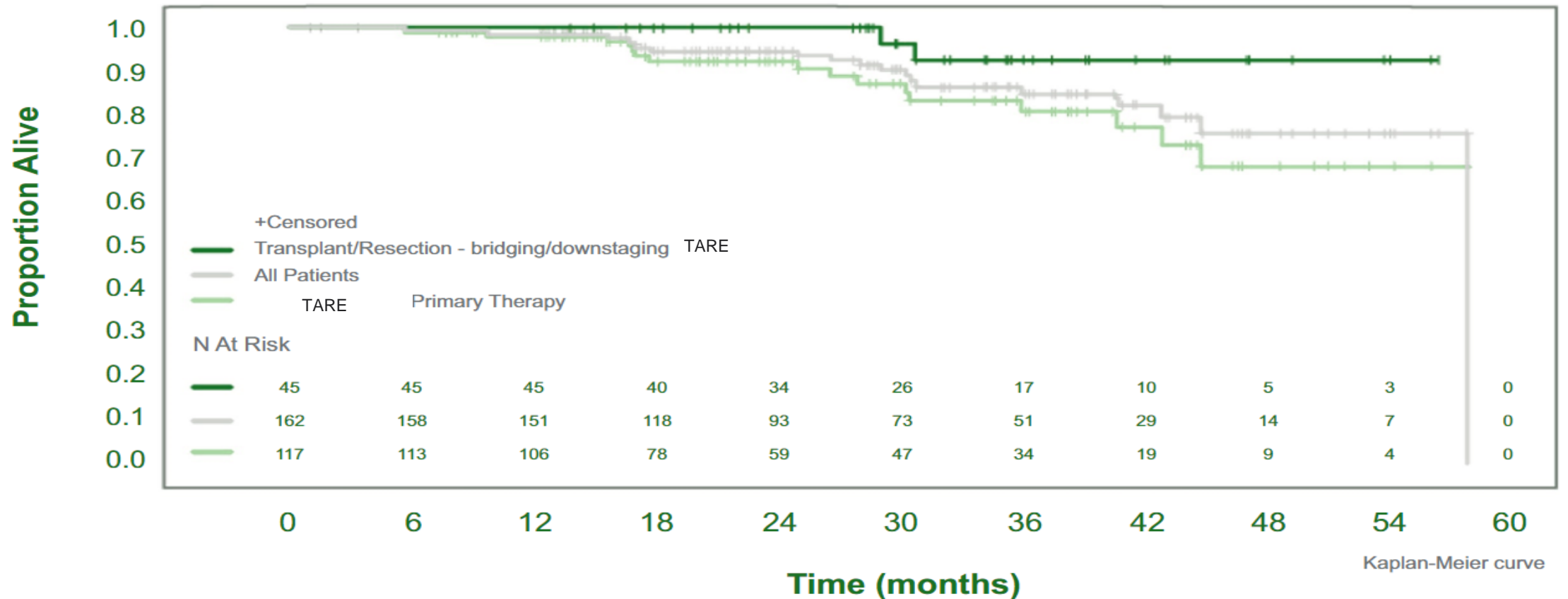
- 162 patients - Tumors 1 – 8 cm in size (median 2.6 cm)



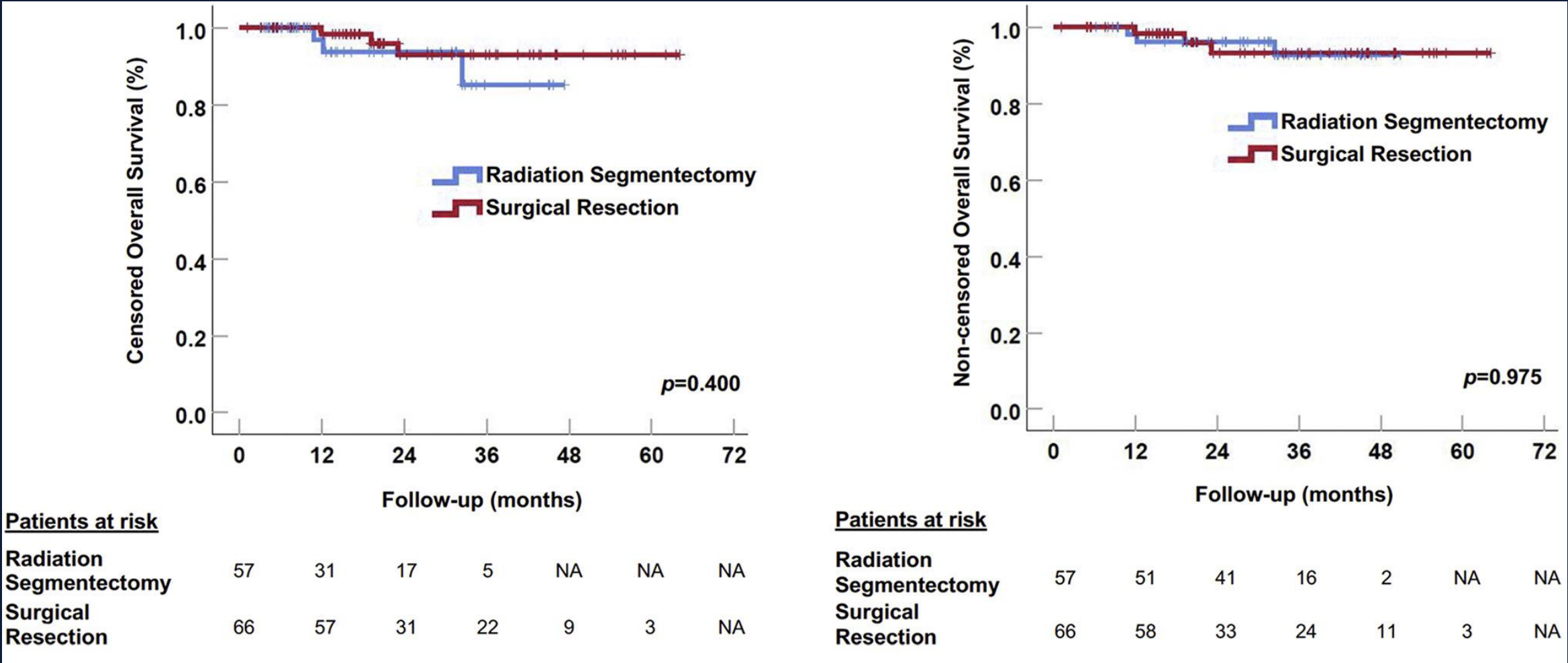
- 76% of patients had durability of response > 6 mo\*
- PFS by localized mRECIST was 93.9% at 2 years

# LEGACY Study

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



# TARE vs Surgical Resection

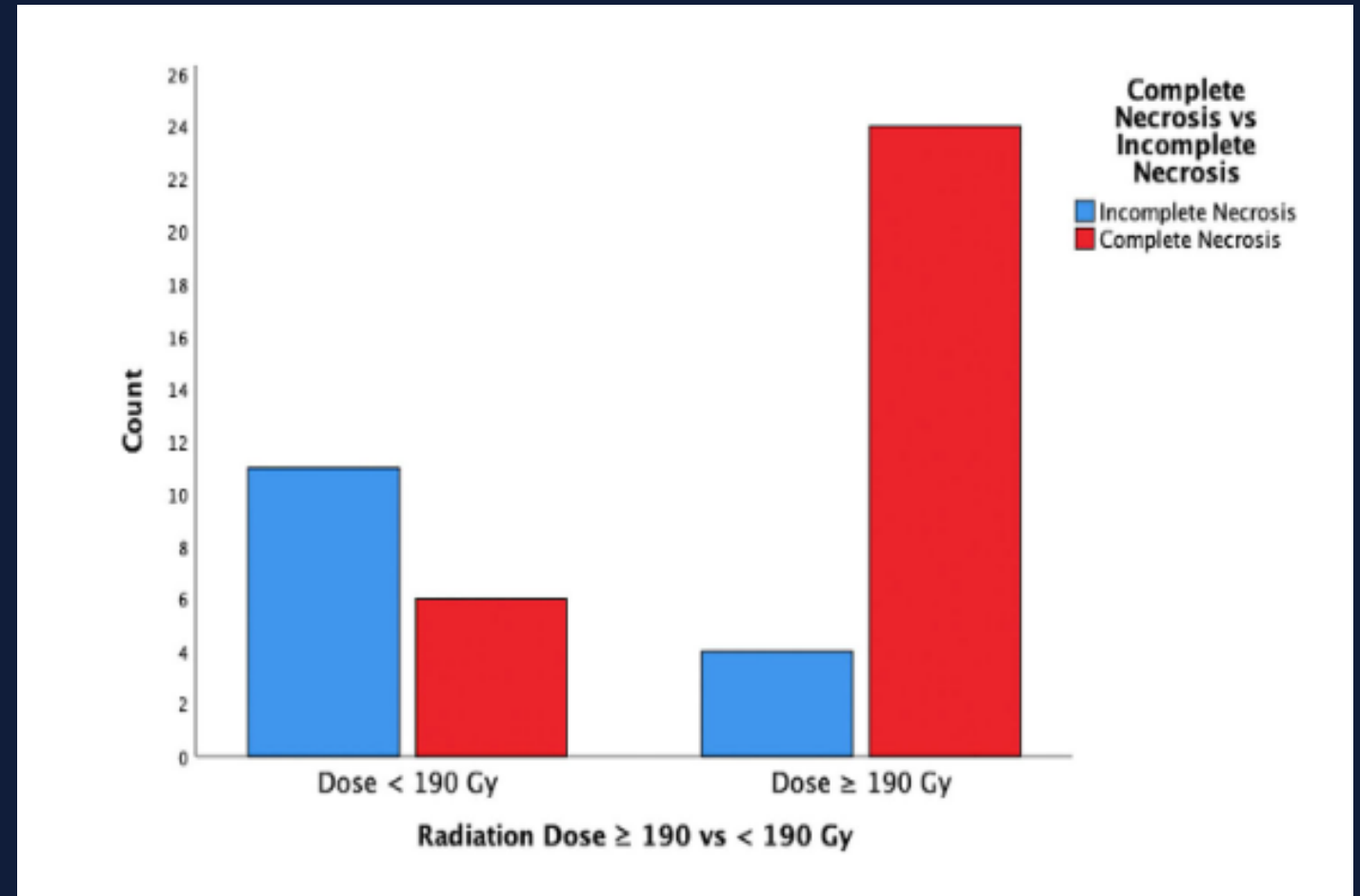


# Tissue is the issue

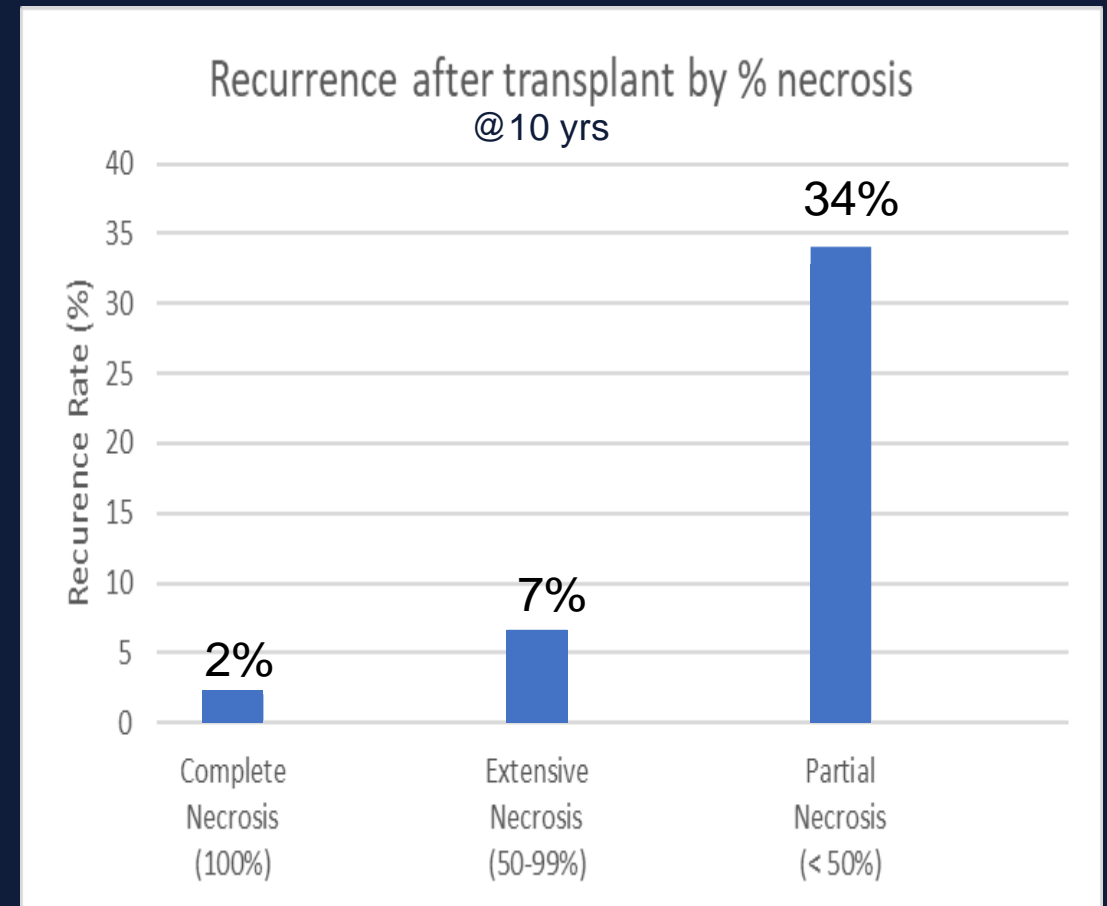
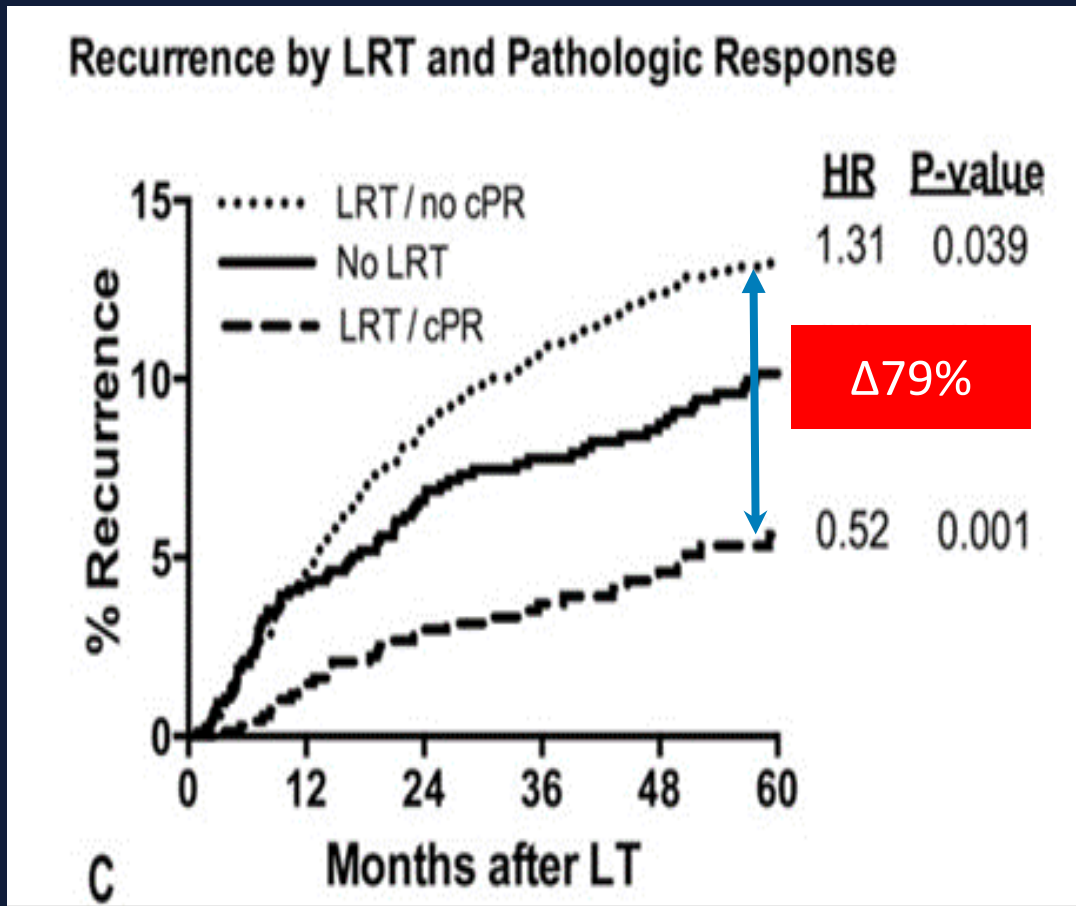
Legacy: 100% of patients with > 400 Gy had CPN  
(UCSD 74% overall, 93% > 400 Gy)

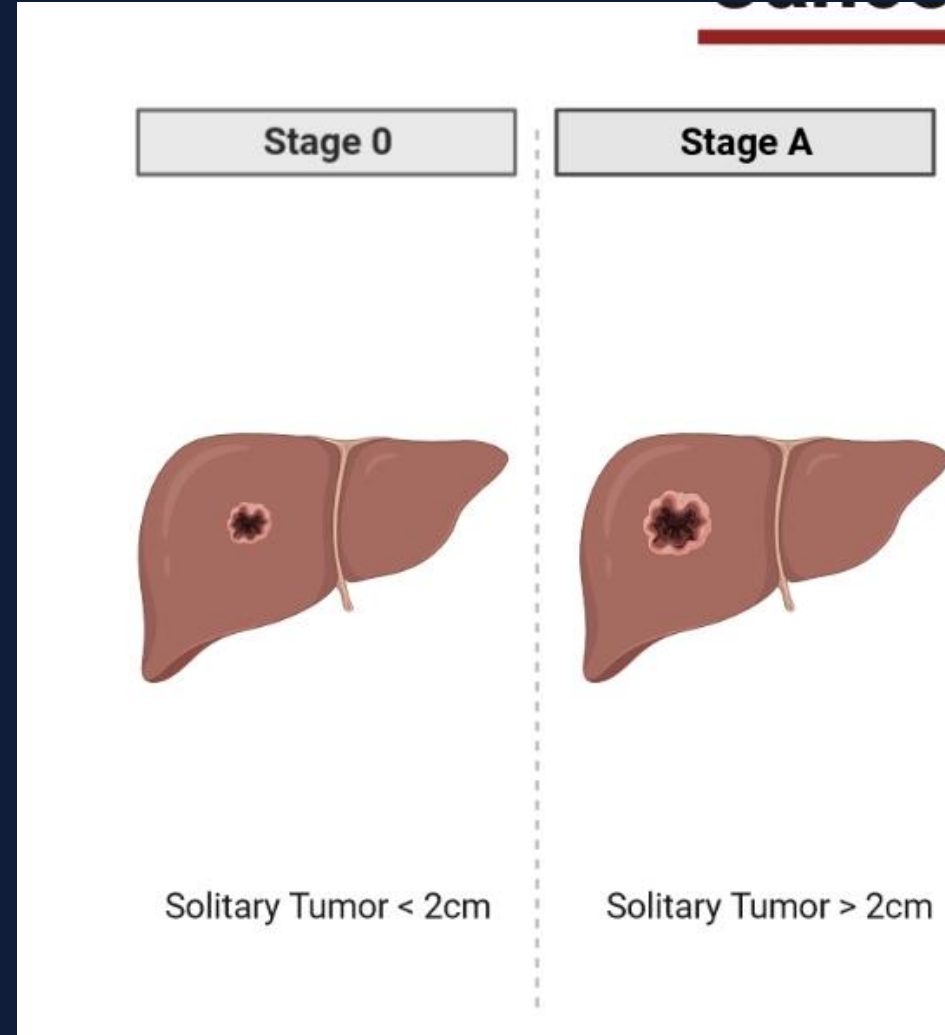
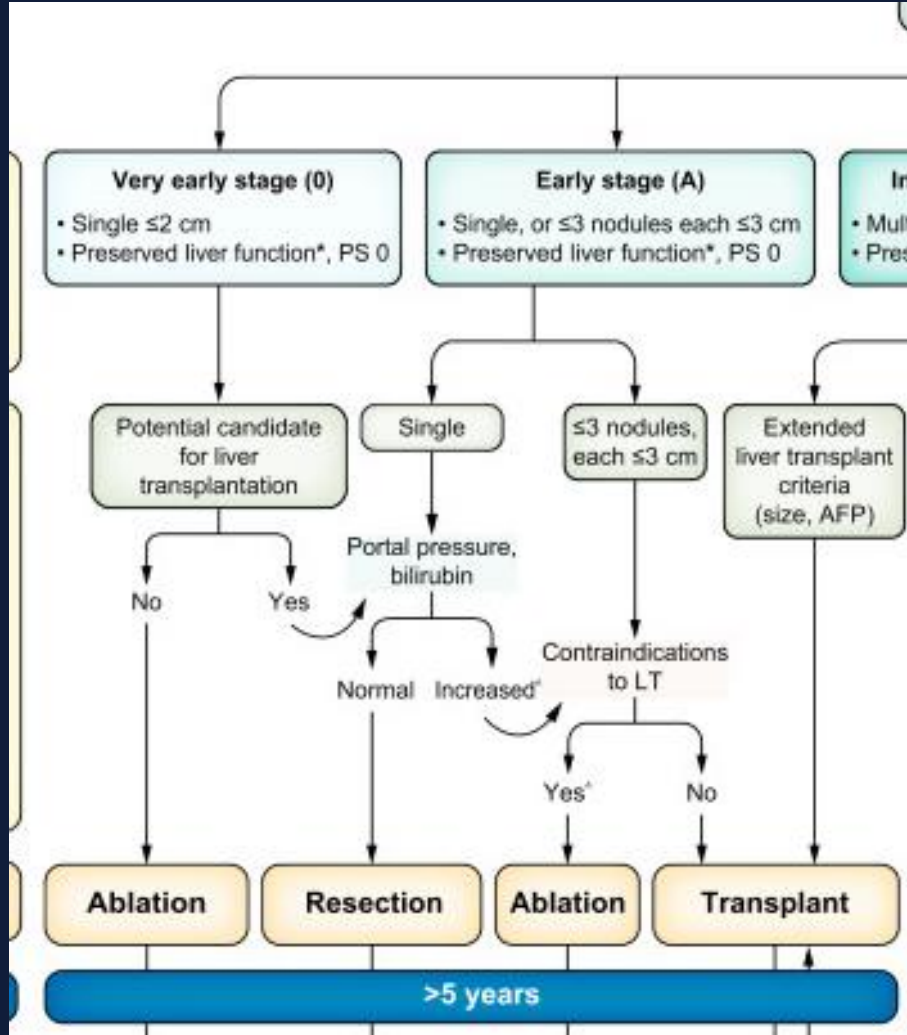
In context CPN rates:

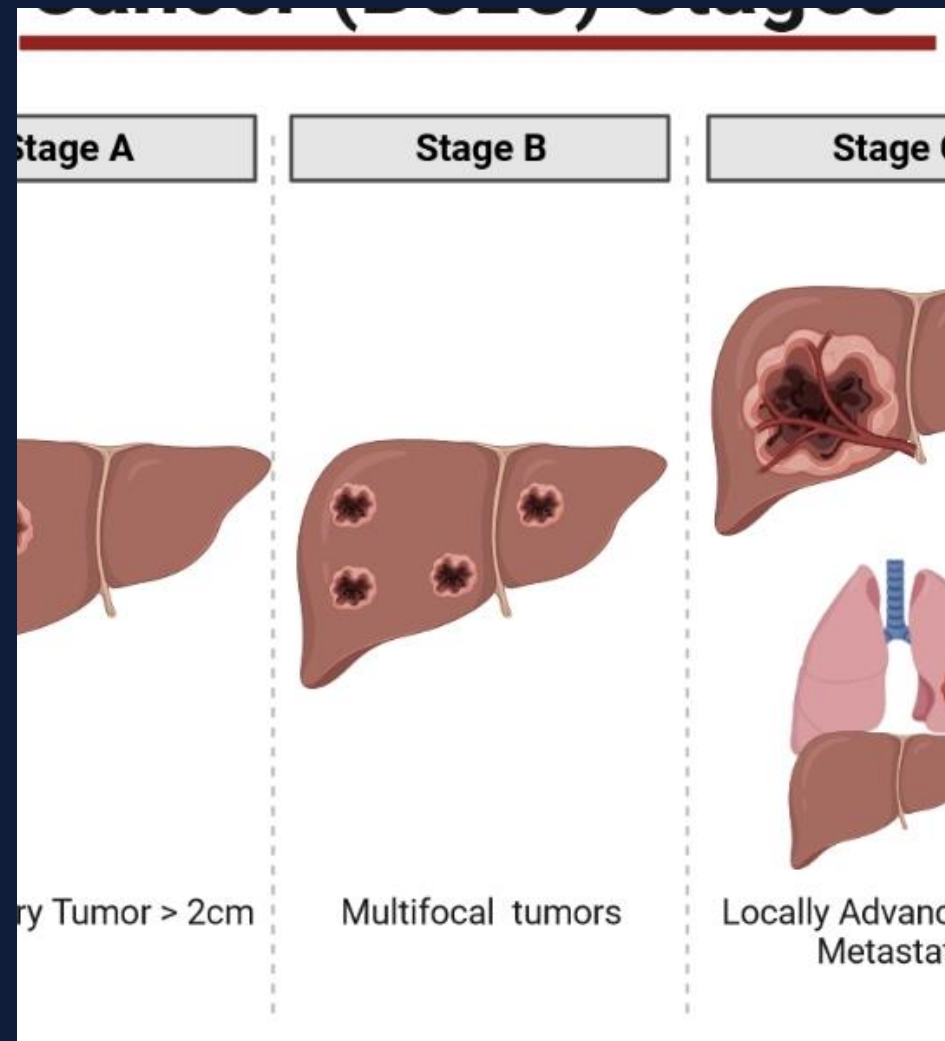
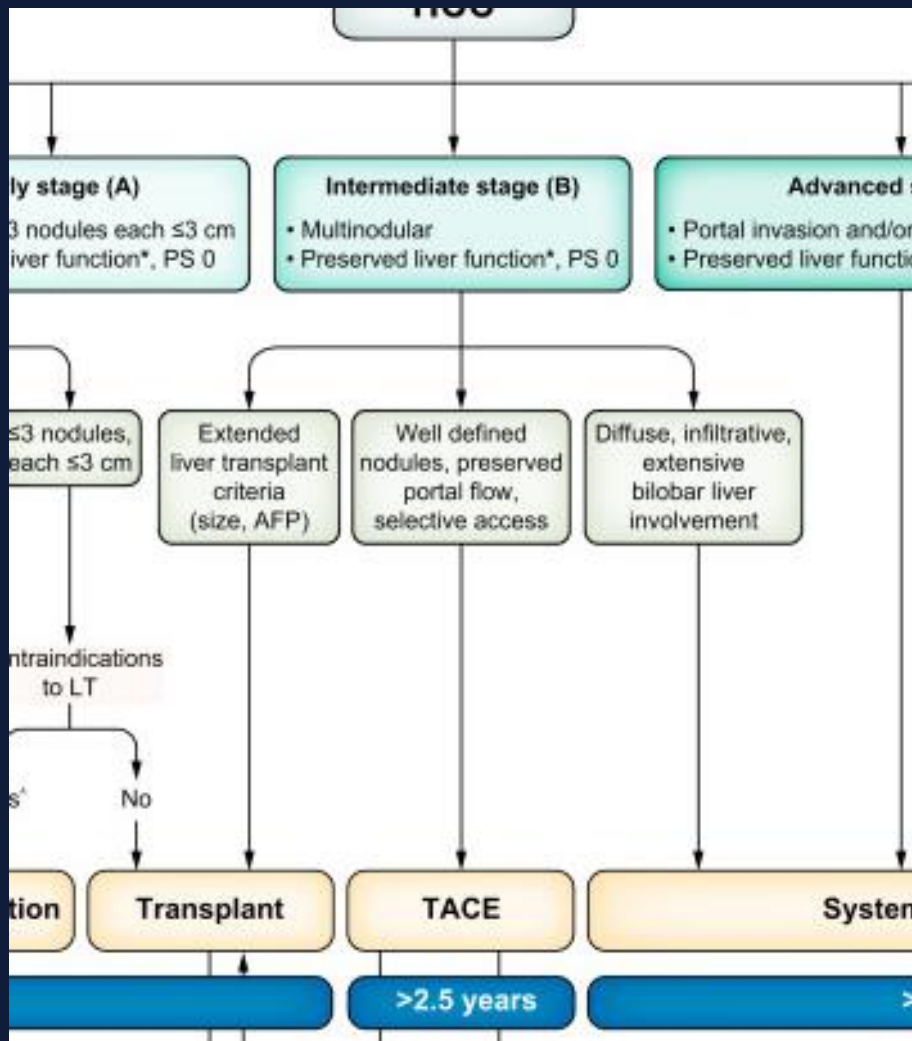
- Ablation – 55-100%
- SBRT – 13-50%
- TACE – 20- 57%



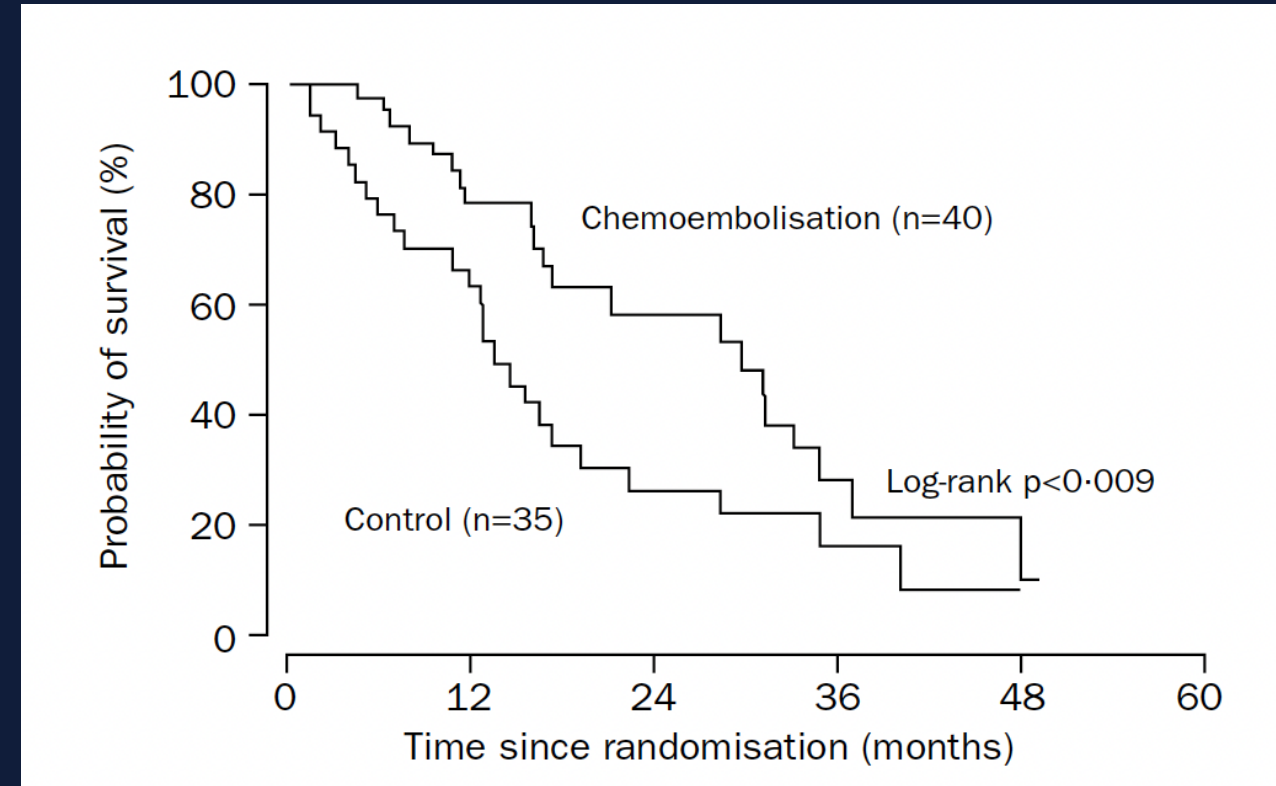
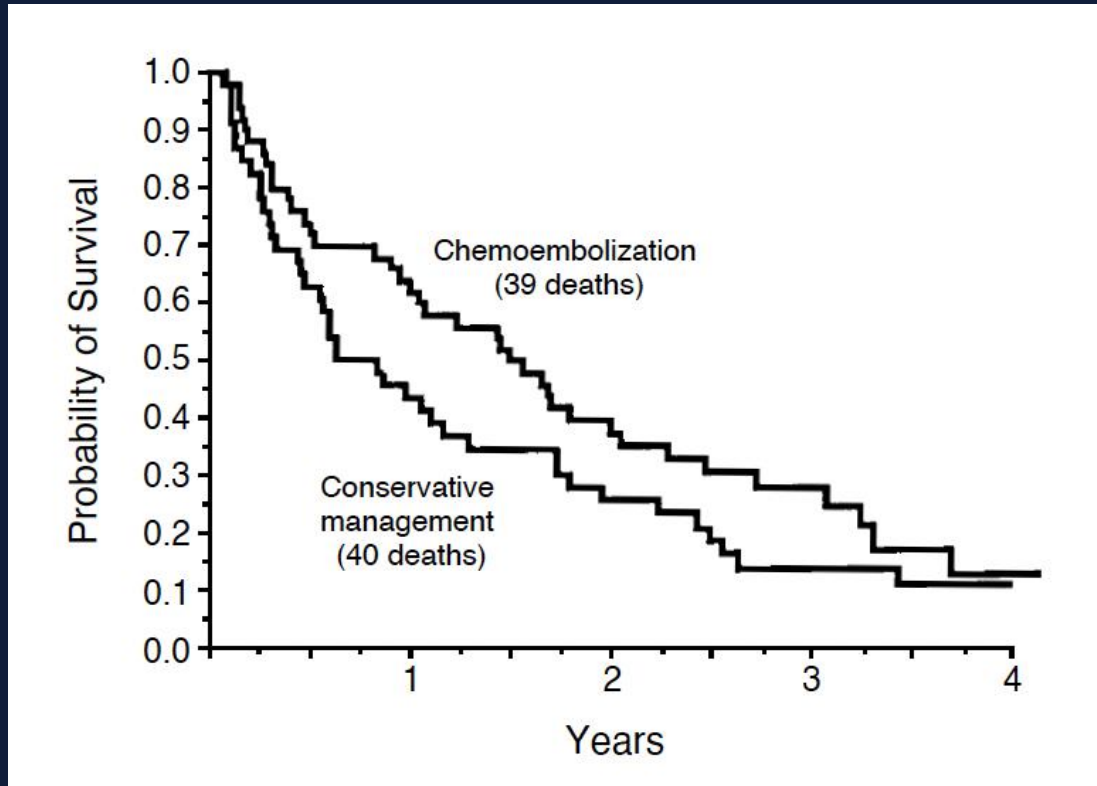
# Why is CPN important if they're going to transplant?



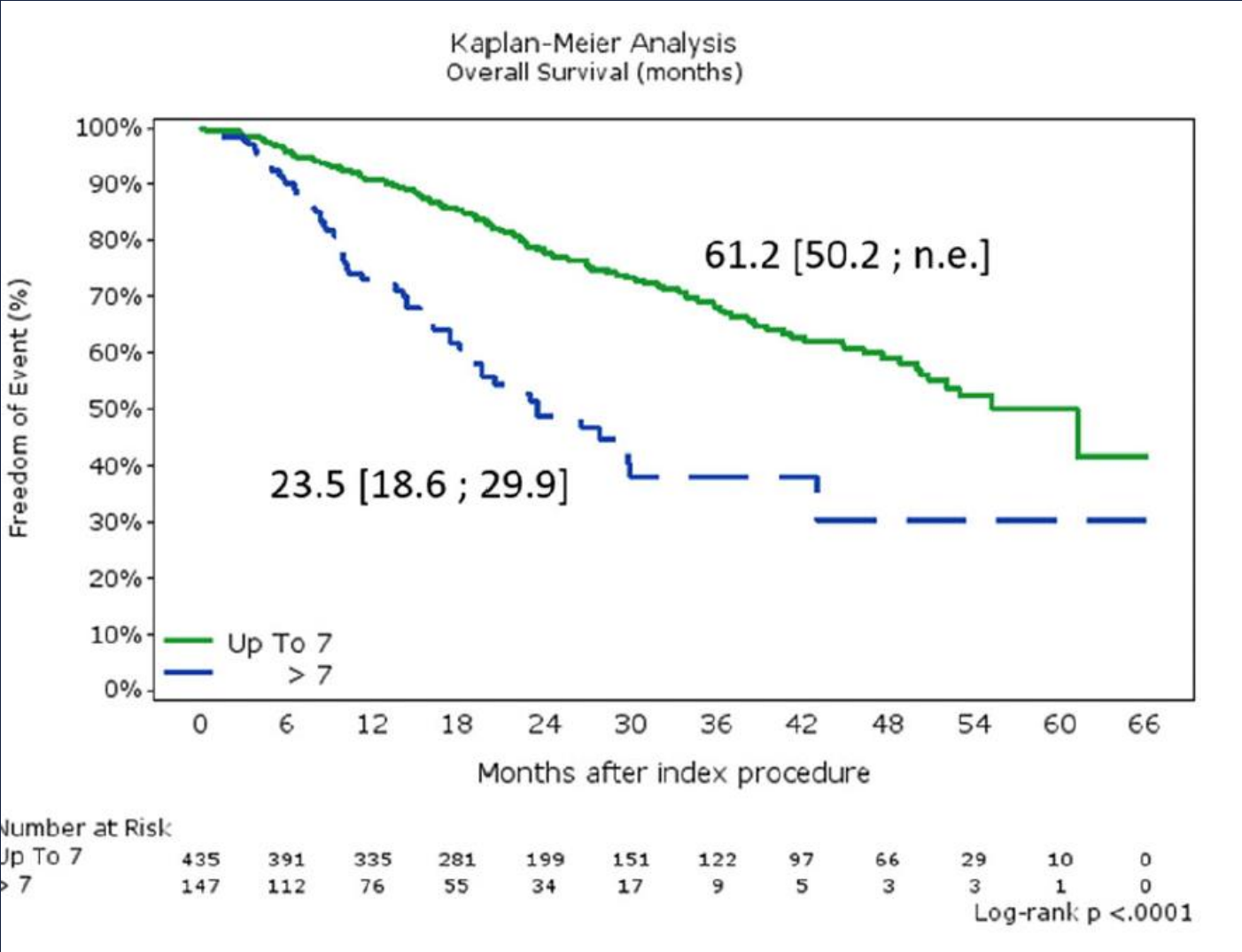




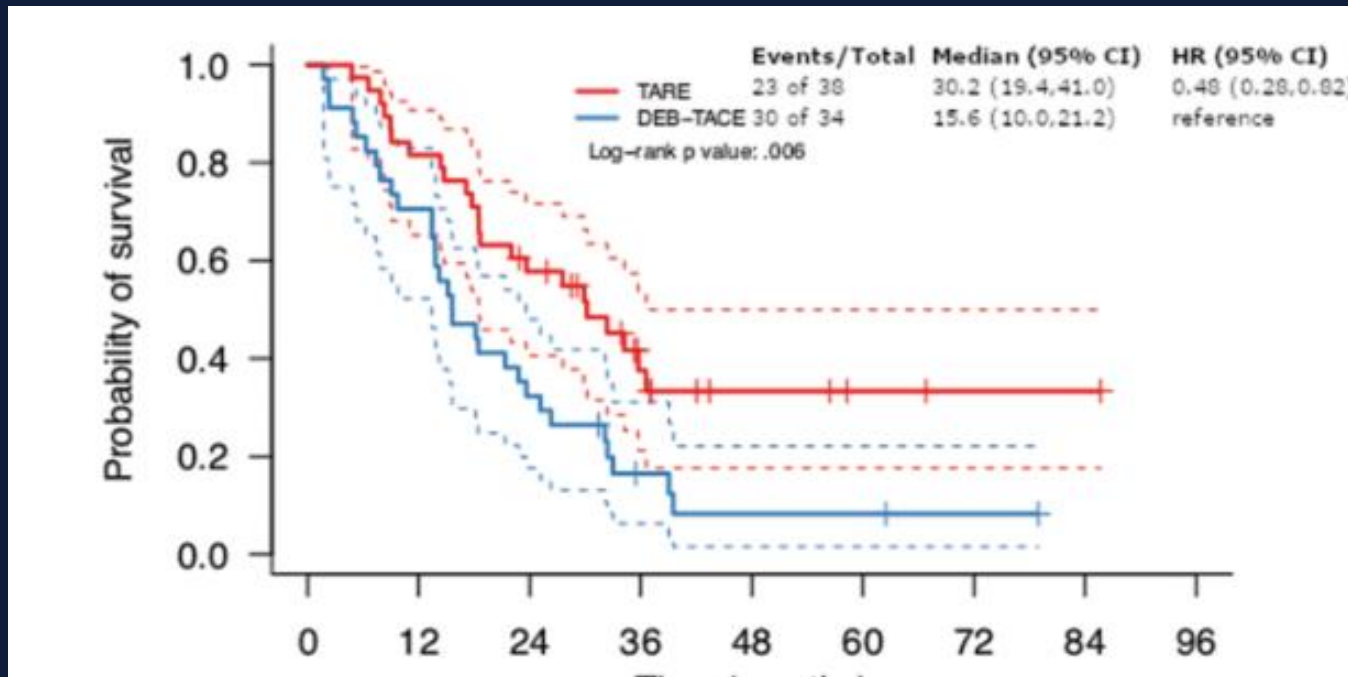
# Initial Trials ~2000



# Contemporary TACE

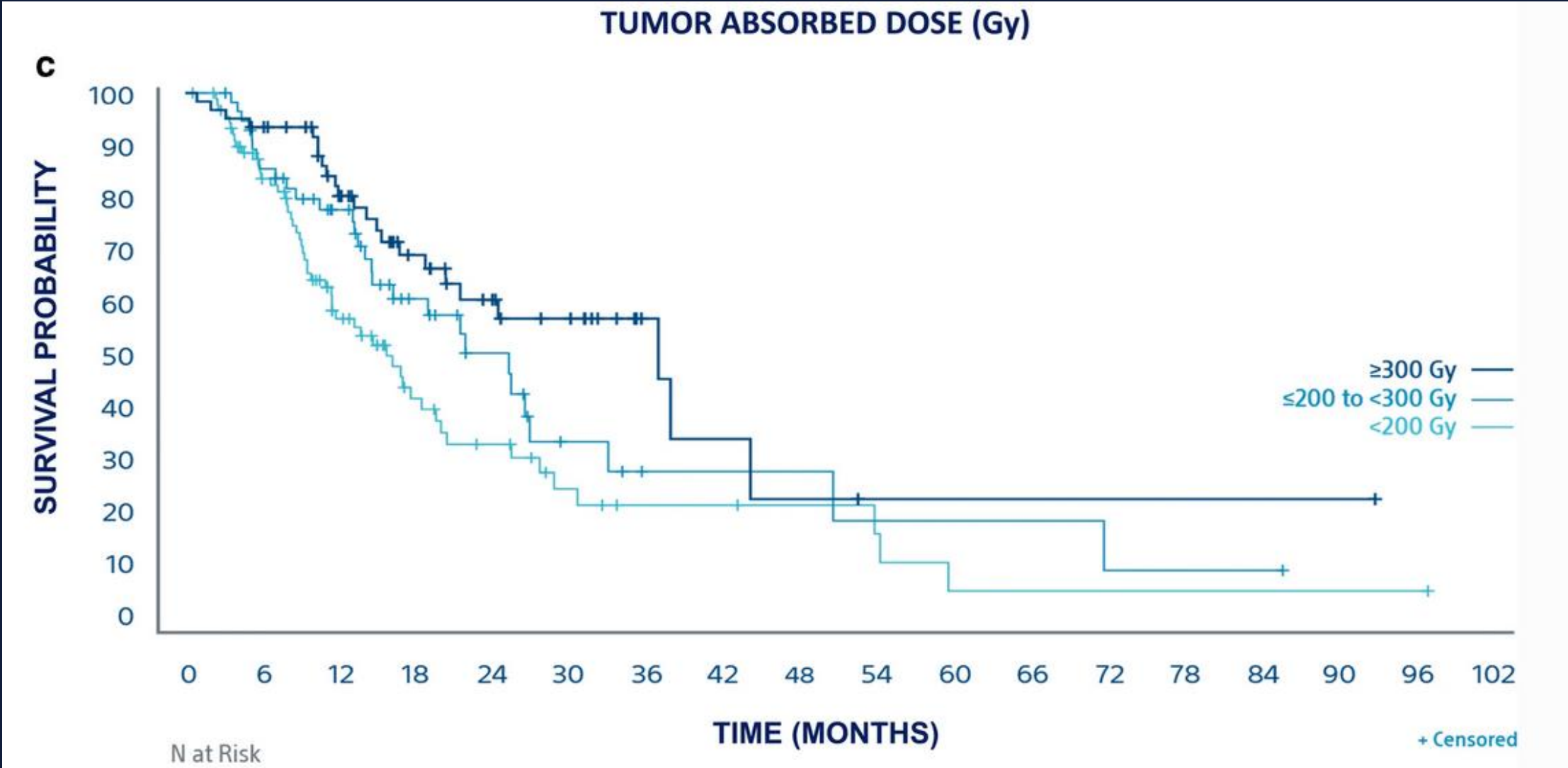


# TRACE Trial

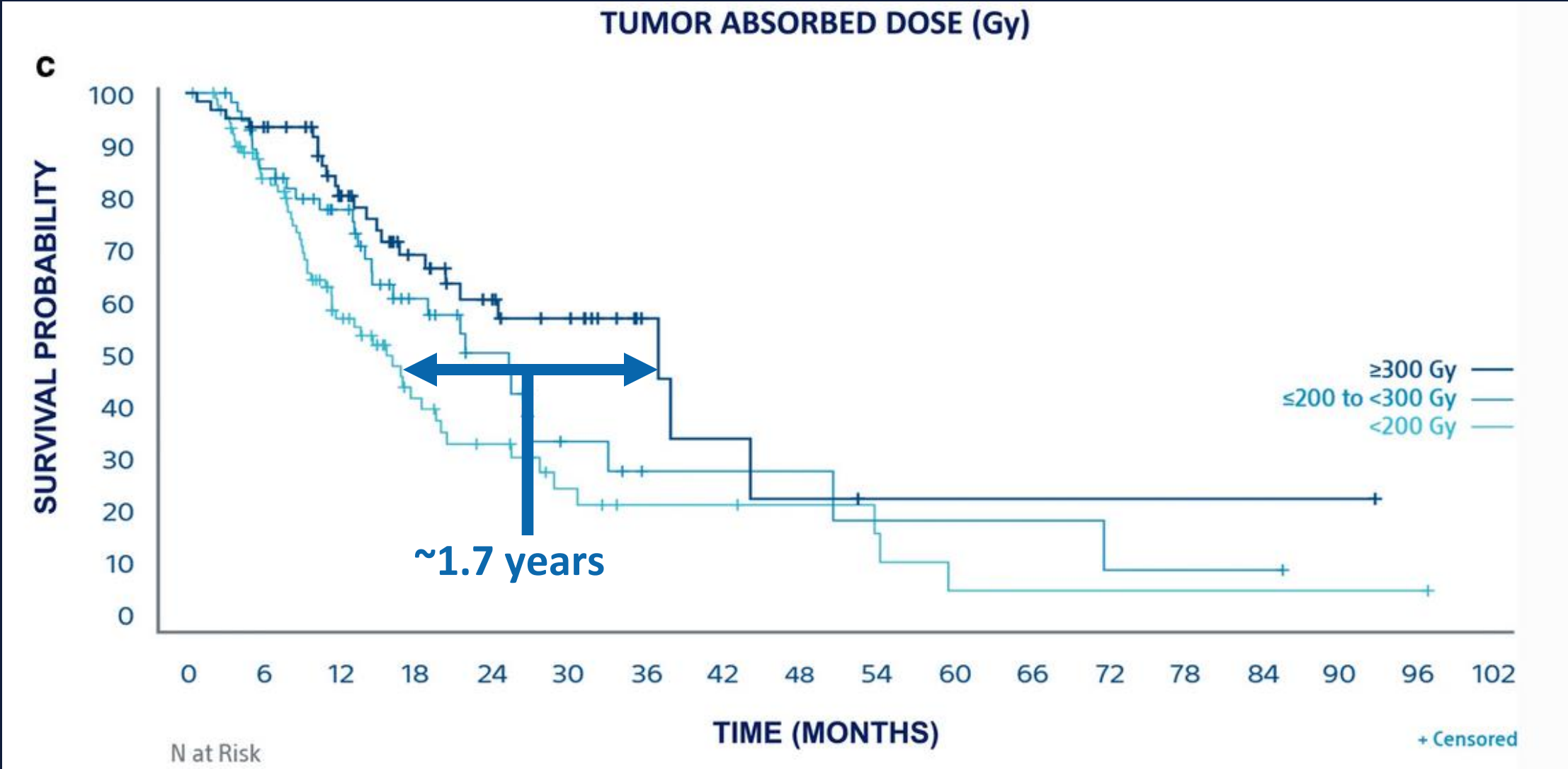


- Prospective phase II randomized controlled trial
  - Median OS was 30.2 months after TARE versus 15.6 months after TACE (HR 0.48)
- TTP was 17.1 months in the TARE arm (n = 38) versus 9.5 months in the TACE arm (n = 34)
- Terminated at first safety analysis for efficacy

# Overall Survival by Dose Thresholds



# Overall Survival by Dose Thresholds

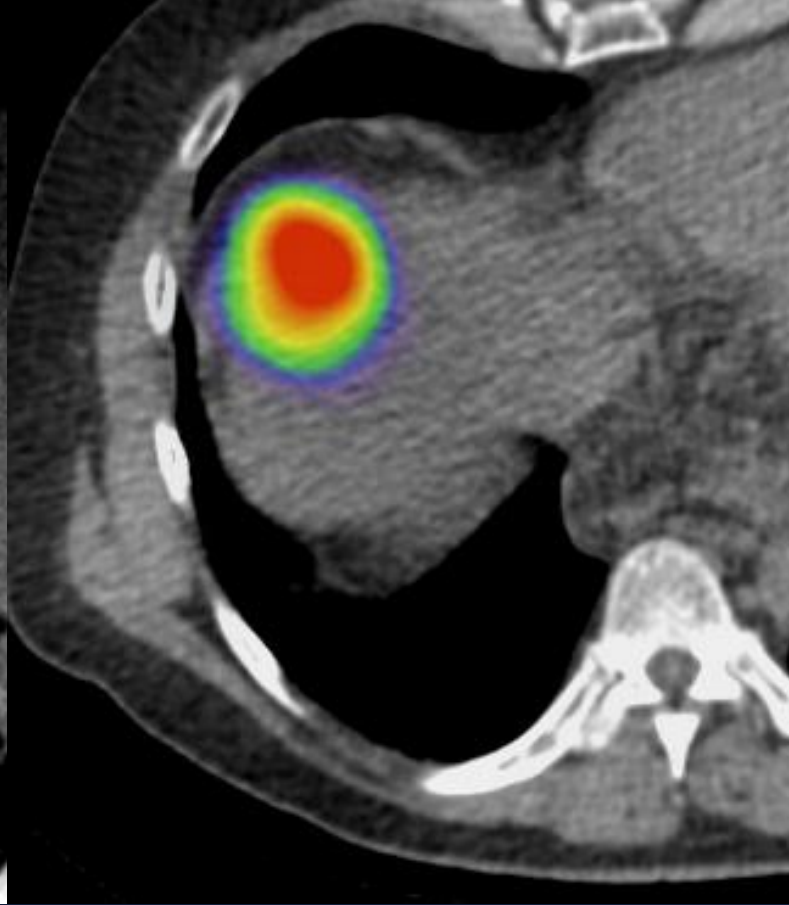


# Modern Boosted Dose Example

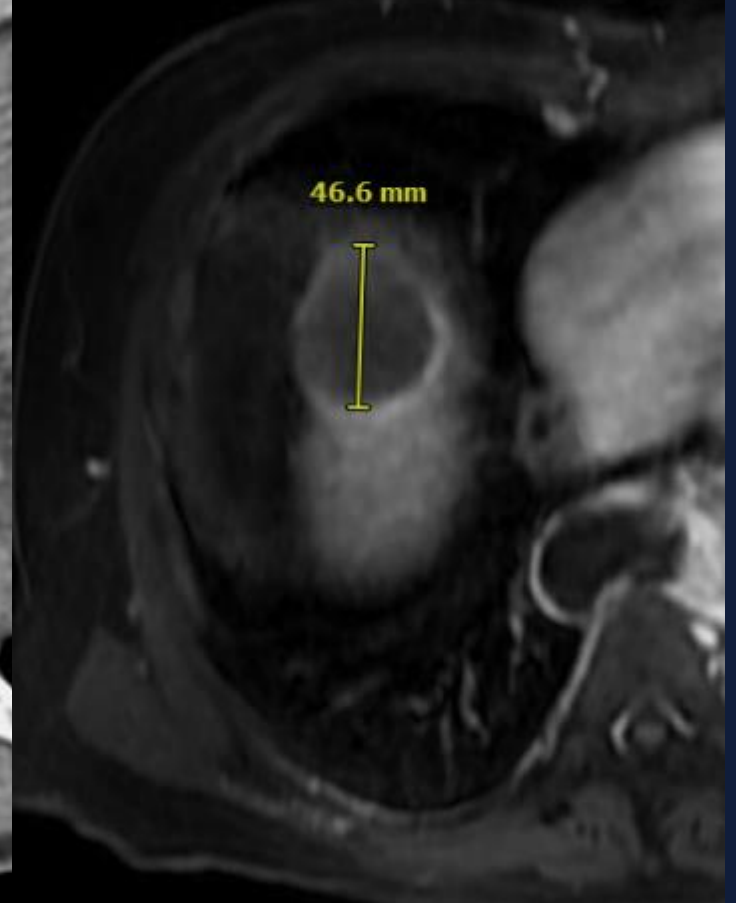
Cone Beam CT of tumor

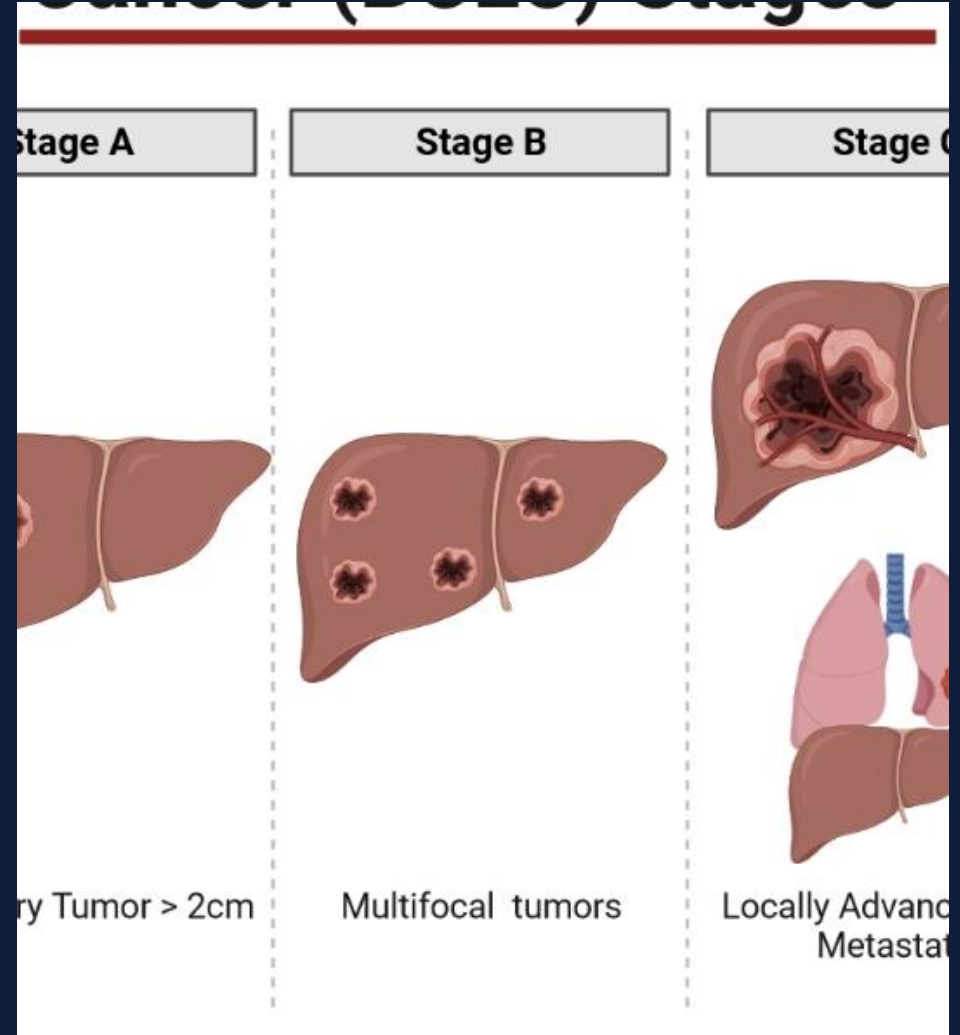
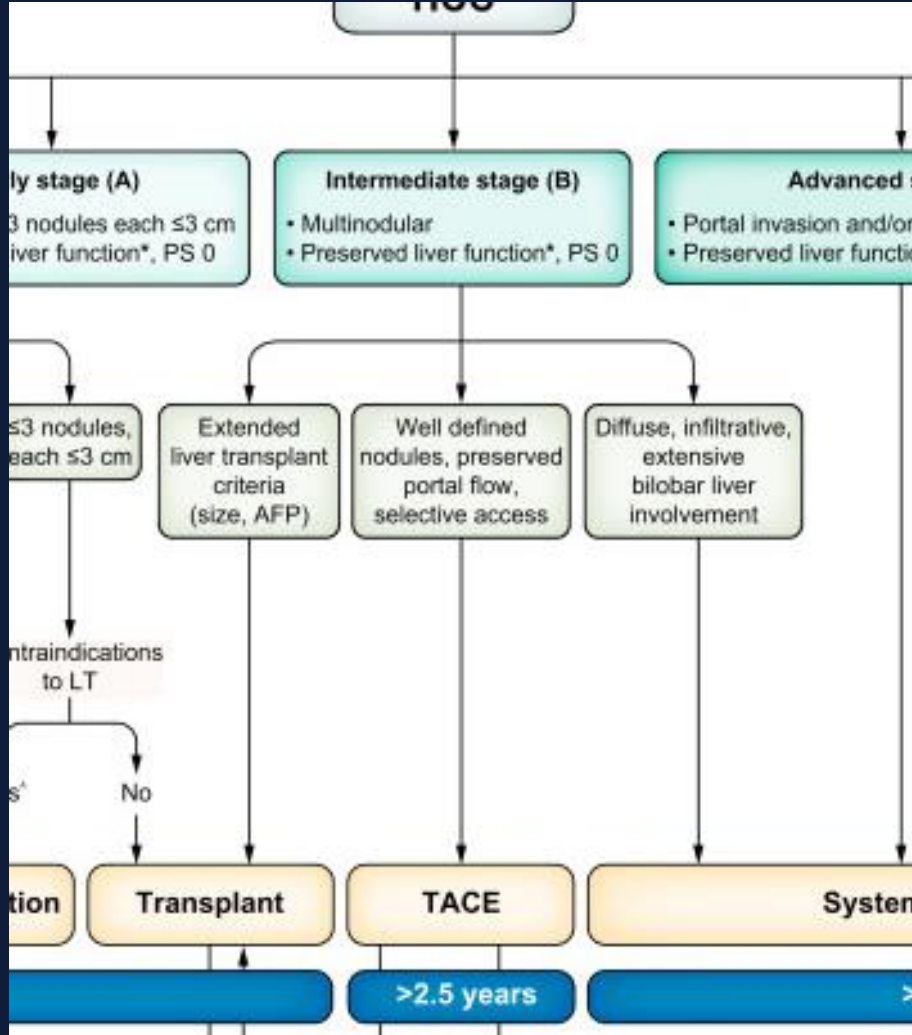


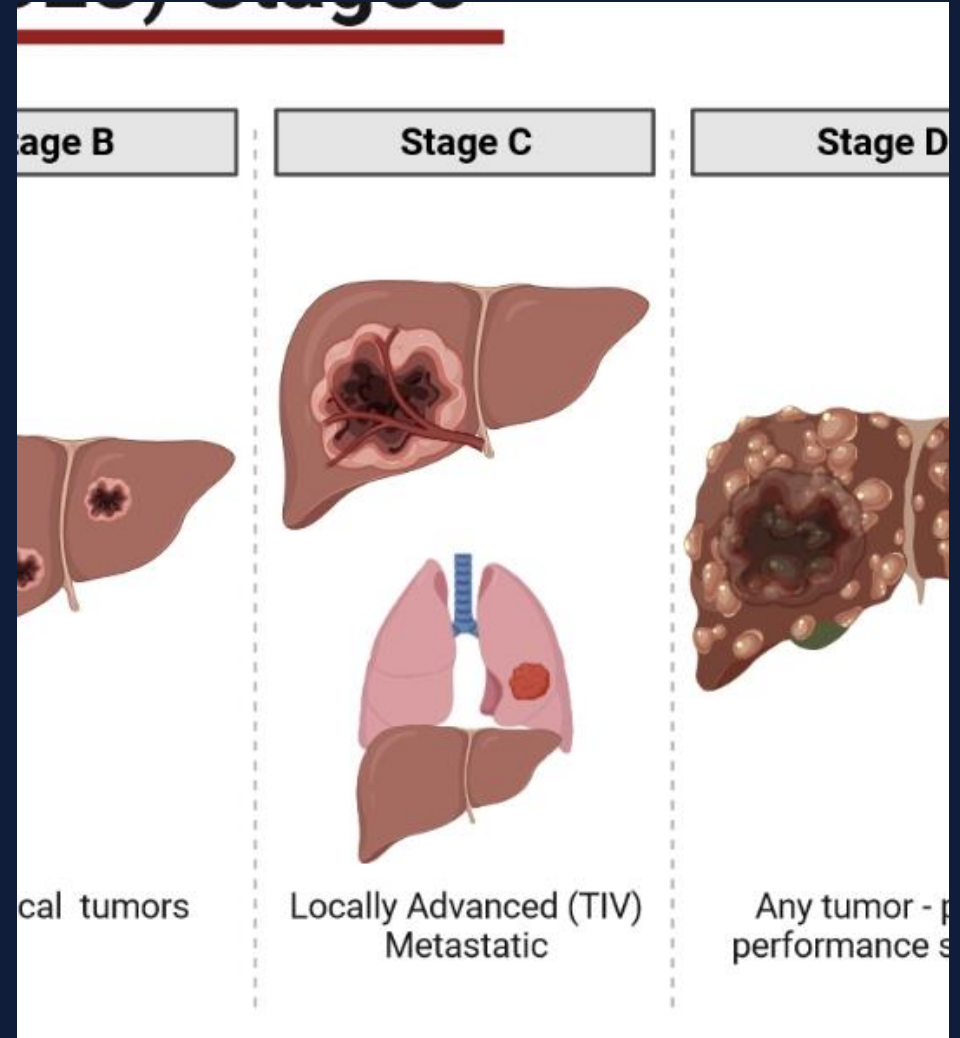
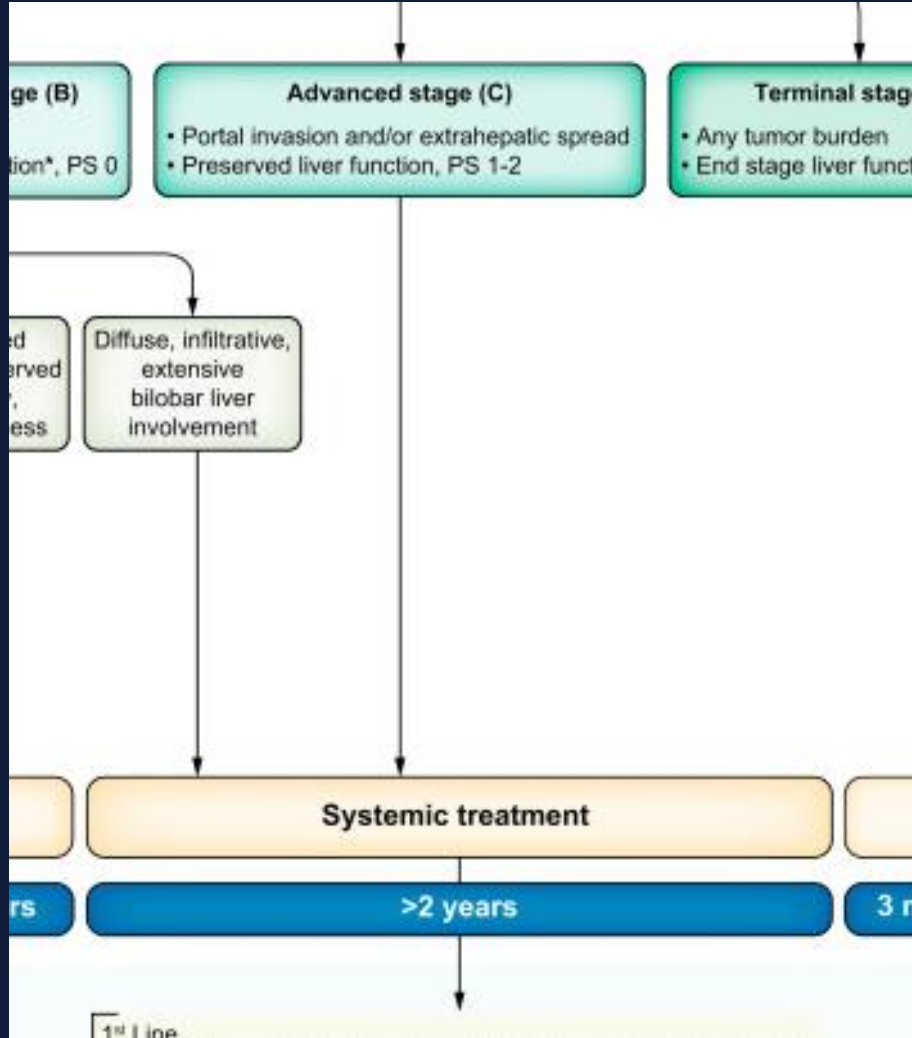
Deposition of dose in tumor on SPECT



2.5 years post

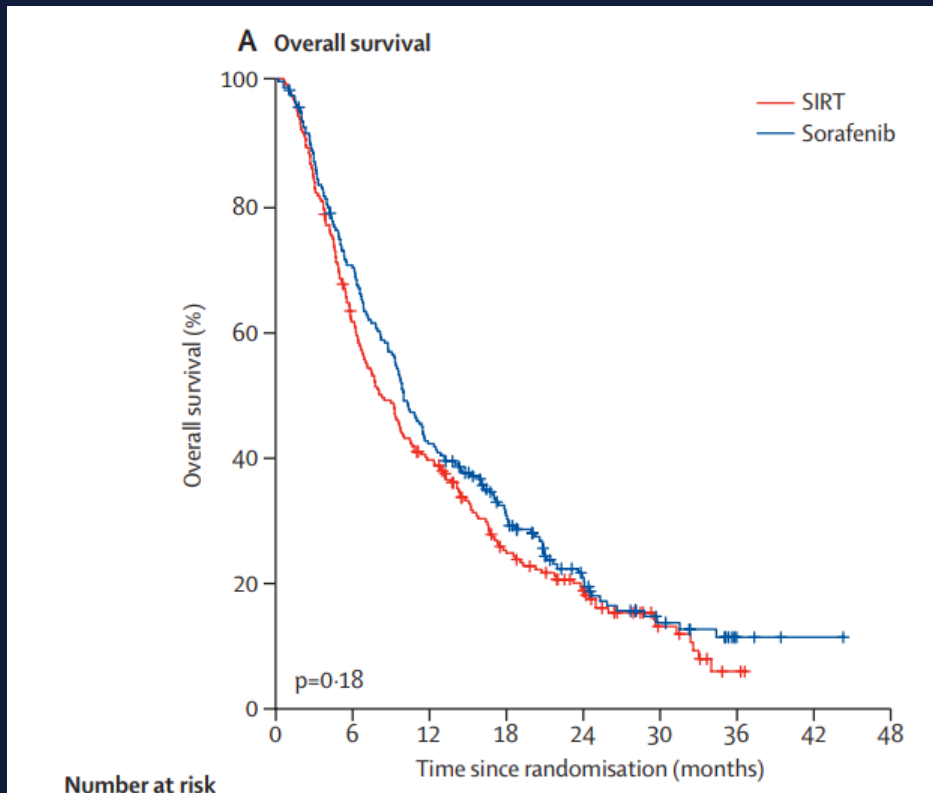




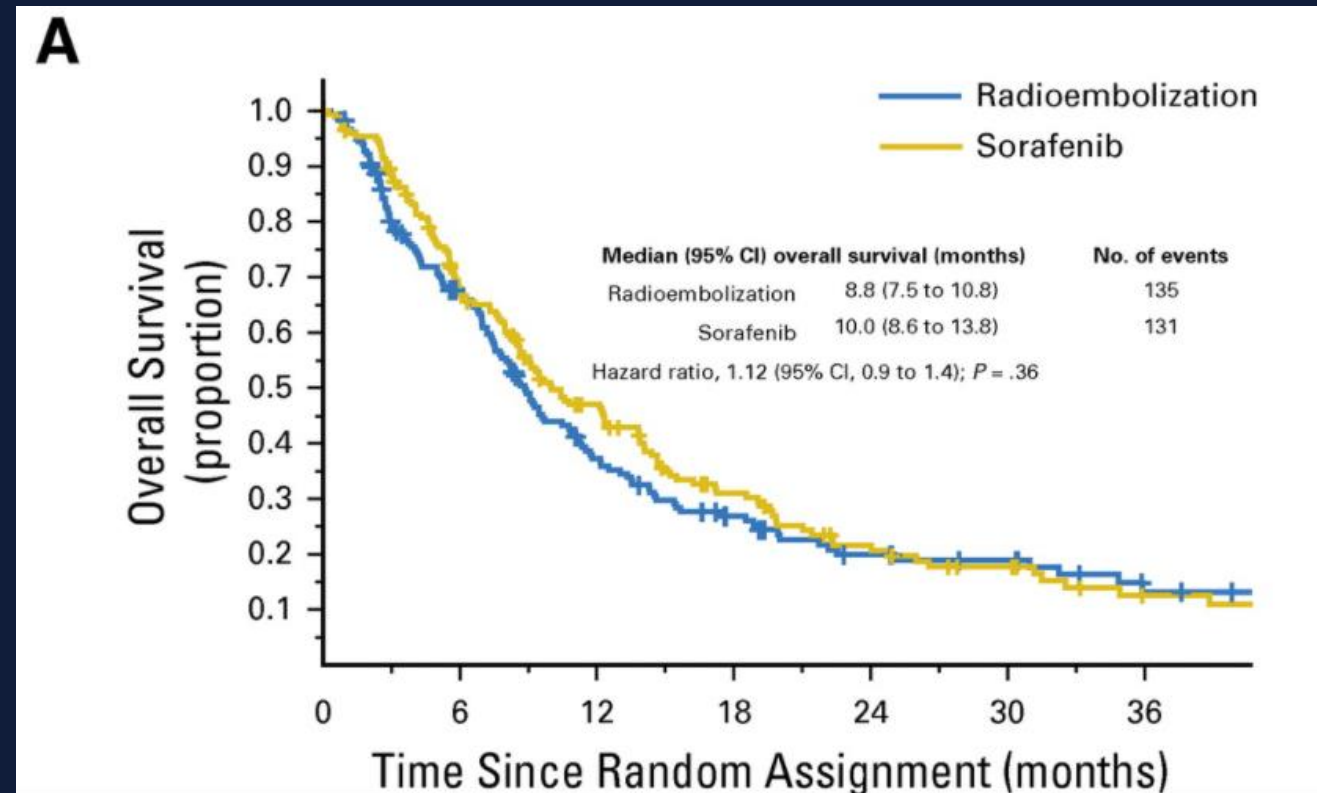


## Where were we?

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

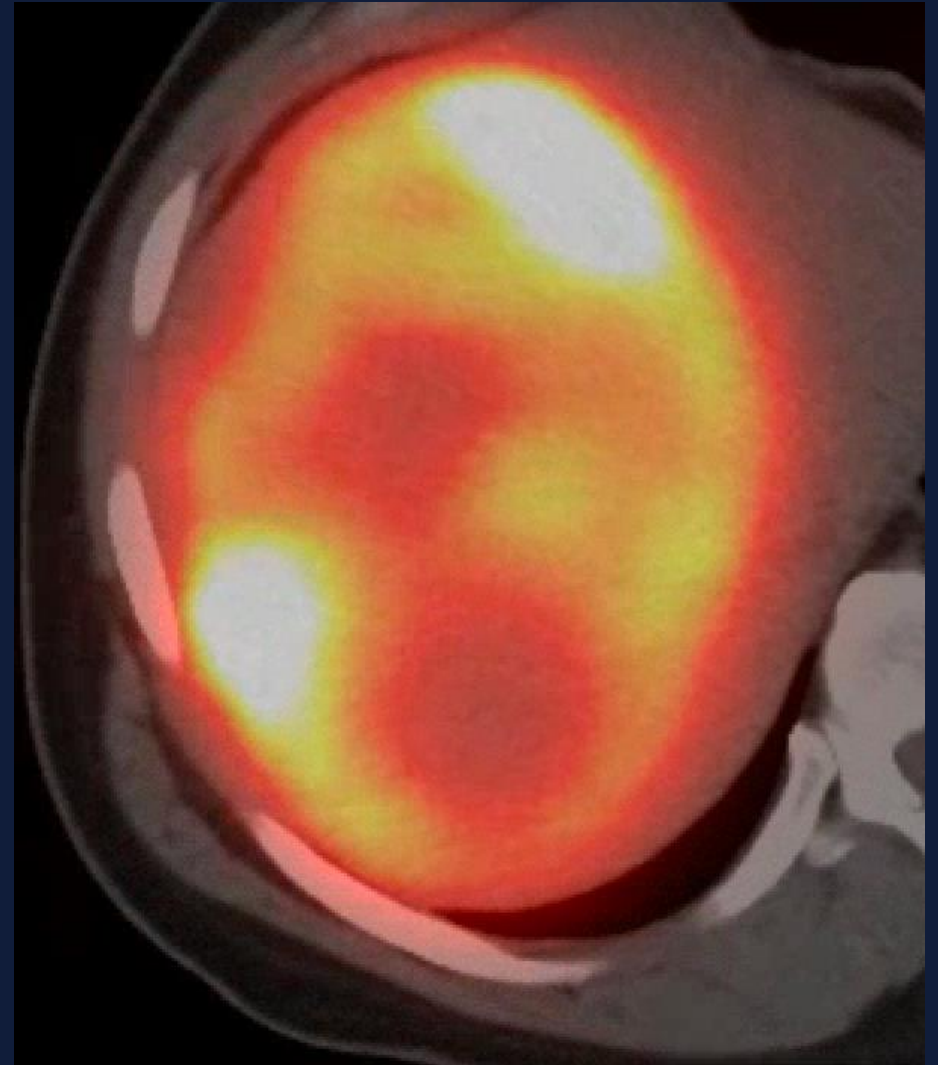


- SIRveNIB Trial (JCO 2017)
  - Resin Y90 vs Sorafenib (median OS ~9 mo)



# Where are we today?

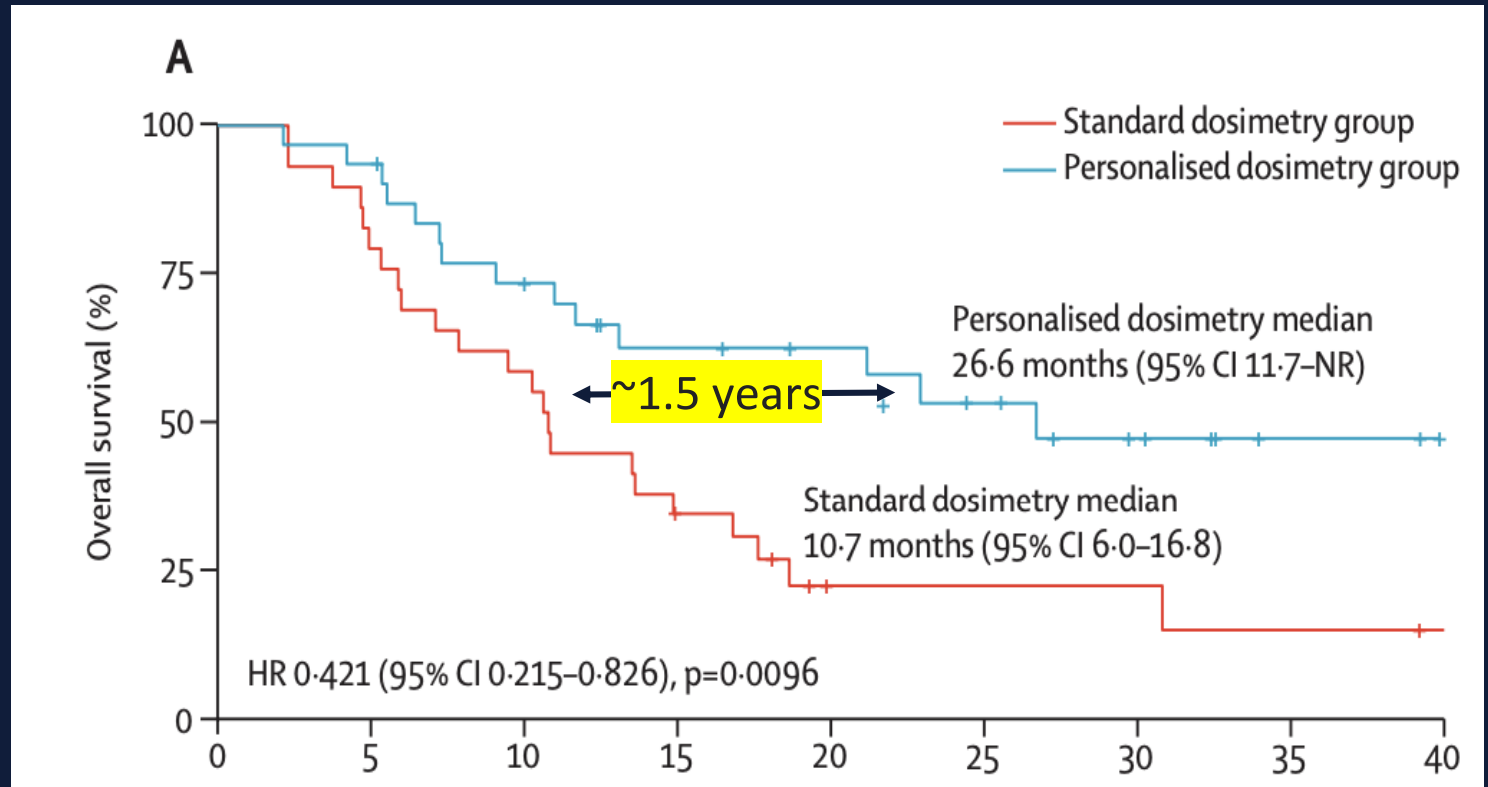
- DOSISPHERE – 01 (Lancet Onc 2021)
  - Randomized, Multicenter
  - Standard vs Personalized (TD > 205 Gy)
  - N=60, Unresectable HCC
  - Median tumor size > 10 cm
  - 64% with TIV
- Halted at first safety analysis due to efficacy (powered for 220 pts)



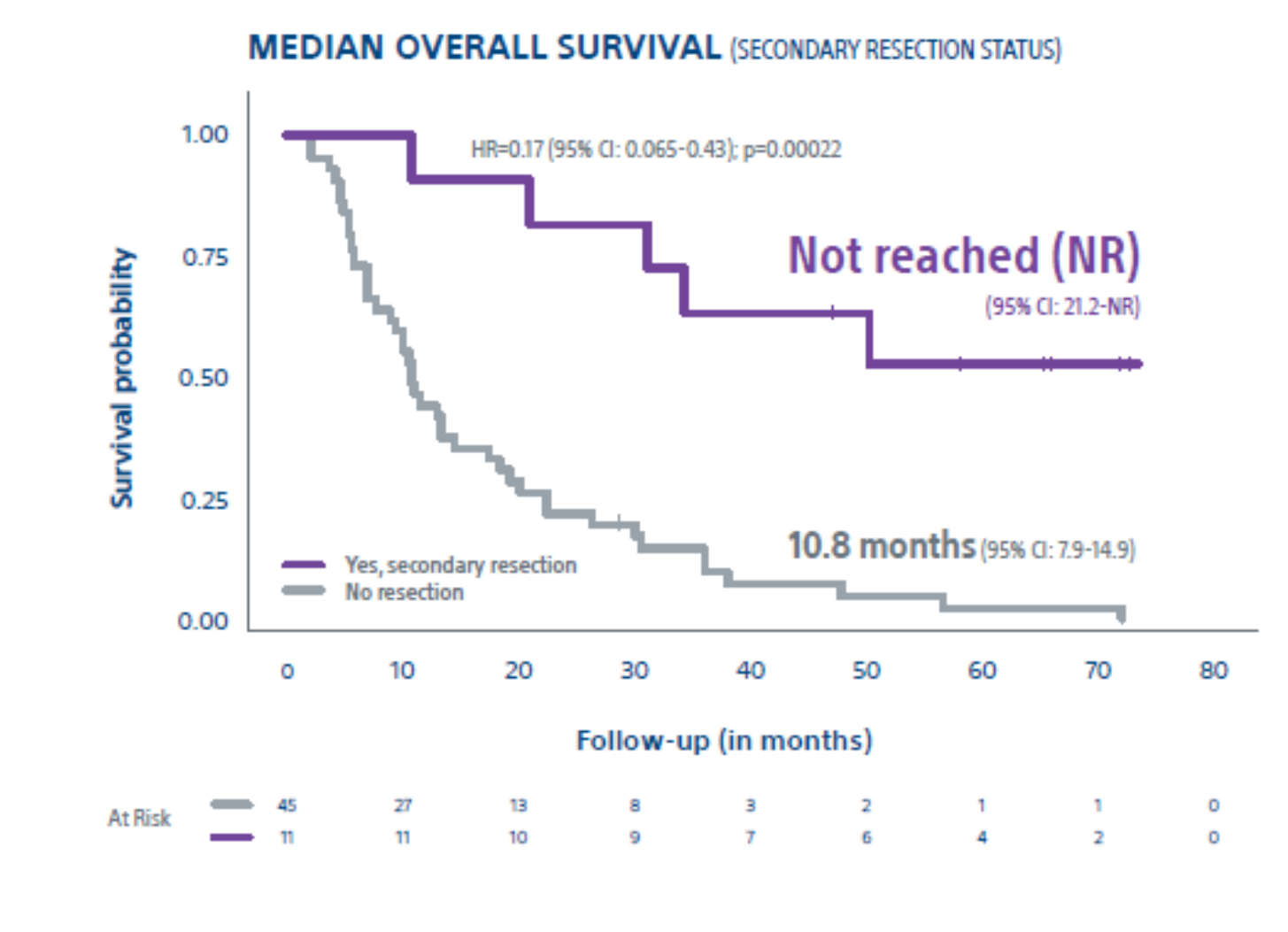
# Dosisphere - 01

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

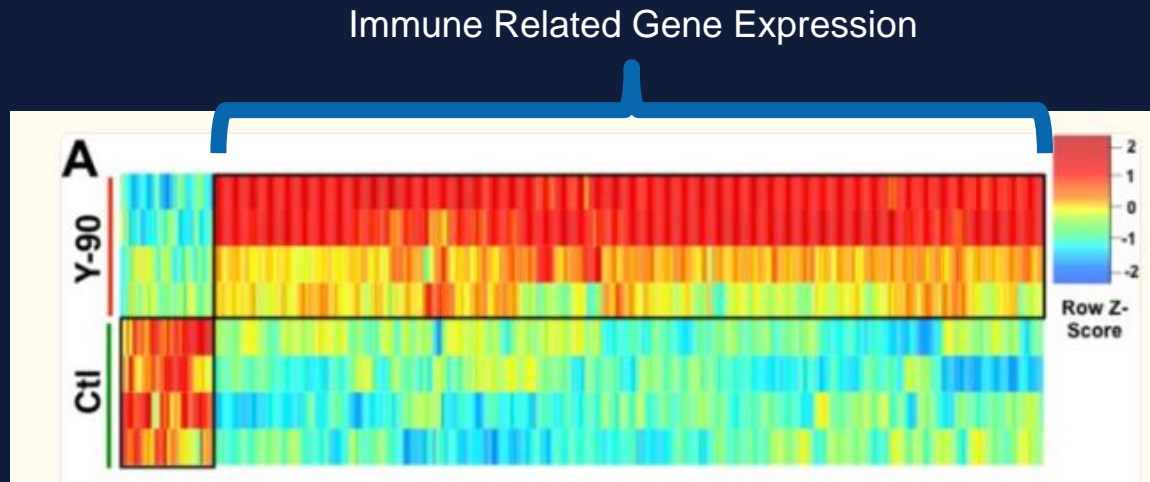
44% of **PVT** in personalized arm  
downstaged to resection



# Why resection is important



LRT or Systemic Therapy → Probably both...



TNF- $\alpha$  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 tumors from a less favorable immune subclass to one that can synergize effectively with immunotherapy.

# 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	Phase II	30	China
NCT03753659	IMMULAB - Immunotherapy With Pembrolizumab in Combination With Local Ablation in HCC	TACE 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 Immune Checkpoint Inhibitor	Phase II	33	Hong Kong
NCT04988945	TACE and SBRT Followed by Double Immunotherapy for Downstaging HCC	TACE SBRT Durvalumab Tremelimumab	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 Y-90 SIRT TACE	Phase II	84	Germany
NCT02638857	Immunotherapy Using Precision T Cells Specific to Multiple Common Tumor-Associated Antigen Combined With Transcatheter Arterial Chemoembolization for the Treatment of Advanced HCC	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	Phase II	30	USA
NCT04981665	A Study to Evaluate TACE Sequential Tislelizumab as Adjuvant Therapy in Participants With HCC at High Risk of Recurrence After Curative Resection	TACE Tislelizumab	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	NA	290	China
NCT04220944	Combined Locoregional Treatment With Immunotherapy for Unresectable HCC.	TACE Surgery	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	MWA, TACE Sintilimab; Bevacizumab Biosimilar	Phase II	34	China
NCT05033522	Immunotherapy for Advanced Liver Cancer	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	DC-TC +GM-CSF	NA	8	China
NCT04268888	Nivolumab in Combination With TACE/TAE for Patients With Intermediate Stage HCC	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

NCT Number	Title	Interventions	Characteristics	Enrollment	Location
NCT04947956	Camrelizumab in Patients With Unresectable Hepatocellular Carcinoma	Camrelizumab	NA	1000	NA
NCT03086564	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	ADCC and TACE	Phase I/II	70	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	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	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 +lenvatinib +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	Nivolumab ipilimumab	Phase III	765	USA

## Conclusions

- 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!

Contact Information:

Zach Berman MD

Interventional Radiology/Oncology

UC San Diego

[ZBerman@health.ucsd.edu](mailto:ZBerman@health.ucsd.edu)

