National University Hospital

Surgical and Interventional Strategies for HCC Recurrence

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No Disclosures

Sites of recurrence

1. Extrahepatic alone : 50–60% (commonly lungs and bone)
2. Combined extrahepatic and intrahepatic: 30–40%
3. Intrahepatic only: 15–40%

Foerster F et al . United European Gastroenterol J. 2019

Unique Challenges

Systemic disease

Immuno-compromised state

Immuno-maintenance phase of the transplant

Anatomical challenges with locoregional treatments

Challenges with Immunotherapy

CASE 1

Background:

59 years / Ch / Female

Premorbidly ADL independent and community ambulant

Non smoker

Non drinker

Past Medical History:

1. Hypertension
2. Hyperlipidemia
3. Type II Diabetes Mellitus
4. Chronic kidney disease with subnephrotic range proteinuria
5. Minor coronary artery disease
6. Cervical spondylosis with previous myelopathy

Diagnosis of HCC

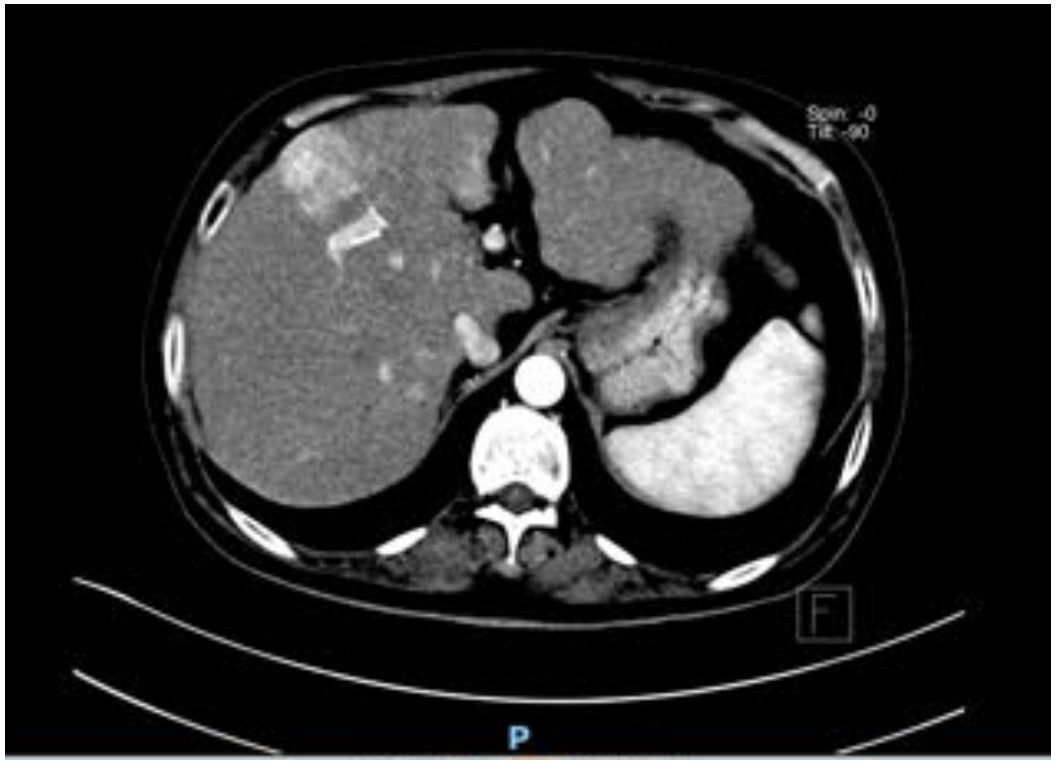
Noted to have thrombocytopenia with transaminitis and prolonged PT during admission with patellar fracture (Oct 2017)

Worked up for possible underlying liver cirrhosis :

Viral hepatitis screen negative

Autoimmune hepatitis screen negative

No evidence of ascites / SBP / EV / HE

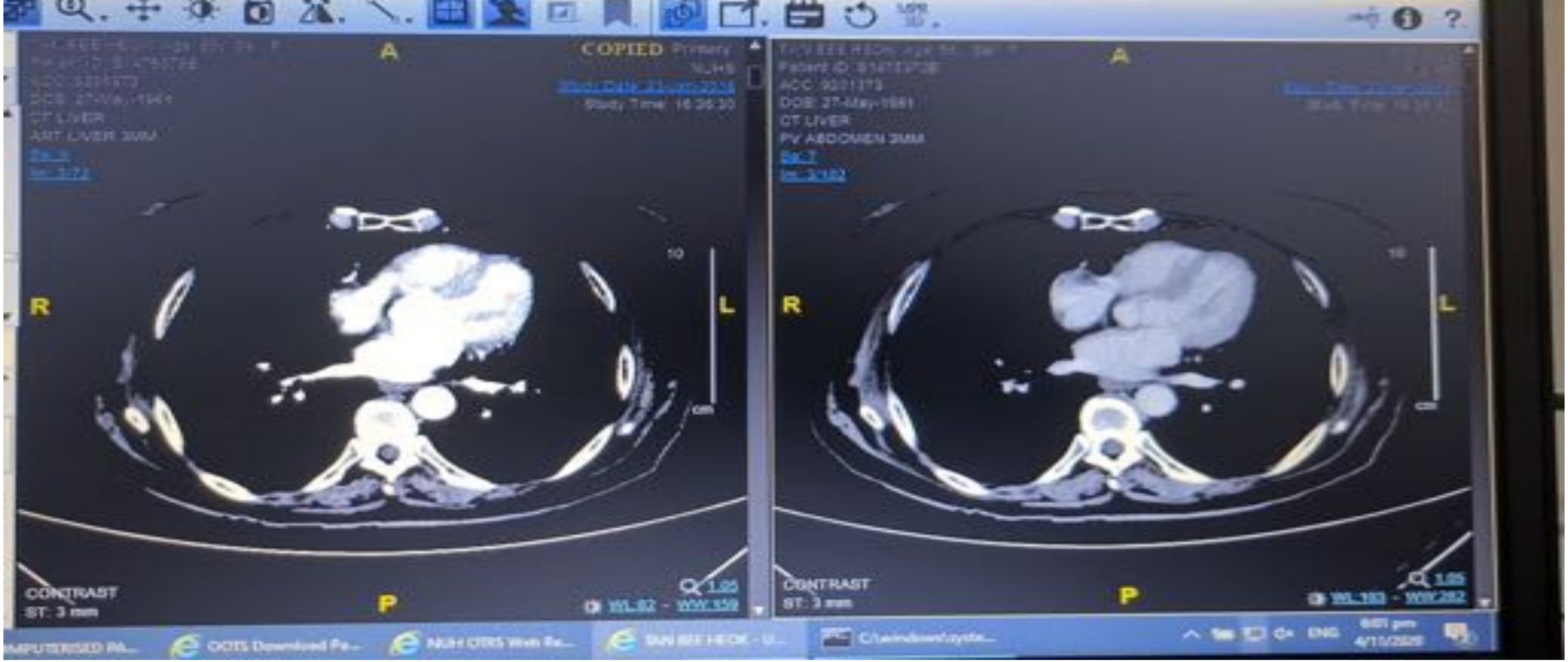


CT Thorax/Abdomen/Pelvis (25/10/2017)

Cirrhotic Liver and regenerative nodules . Splenomegaly indicates underlying portal
A flash-enhancing 3.8 cm mass with slightly irregular margins and showing washout is detected in segment 4A/B, worrisome for a hepatocellular carcinoma (HCC).

AFP 182 -> 203.5
Multifocal HCC, no mets
Discussed in HPB MDT: TACE

Dx : Cryptogenic cirrhosis likely NASH : Childs A6 MELD 10



POST TACE 18/12/2017 CT Liver: In post TACE segment 5, there is arterial enhancement seen within this area with washout noted;

Planned for LDLT in view of residual disease
AFP 182

Criteria	Author	Year	Institution	Criteria	Cases	Outcome	External Validation
Hangzhou	Zheng	2008	Zhejiang University, China	Total tumor diameter less than or equal to 8 cm Total tumor diameter more than 8 cm, with histopathologic grade I or II and preoperative AFP level less than or equal to 400 ng/mL	195	Within Milan: 5-year survival rate: 78.3% Within Hangzohu: 5-year survival rate: 72.3%	◯
Toronto	Dubay	2011	Univ. of Toronto, Canada	No vascular invasion on imaging studies HCC is confined to the liver, and not poorly diffentiated on biopsy.	294	Within Milan: 5-year survival rate: 72% Within Tronto: 5-year survival rate: 70%	
AFP model	Duvoux	2012	French Study group, France	HCC size (cm): ~3 (0)/3.1~6 (1)//6.1~ (4) Number of HCC: ~3 (0)/4~ (2) AFP (ng/mL): ~100 (0)/101~1000 (2)/ 1001~ (3)	537 435 (validation)	Less than score 2: 5-year survival rate: 70%	◯
TTV+AFP	Toso	2015	Univ. of Alberta, Canada	TTV less than 115 cm^3 AFP less than 400 ng/mL	233	Within TTV/AFP but beyond Milan: 4-year survival rate: 74.6%	
Metroticket 2.0 model	Mazzaferro	2018	Multicenter, Italy Fudan Univ., Chila	Up-to-7 & AFP < 200 ng/mL Up-to-5 & AFP 200–400 ng/mL Up-to 4 & APP 400–	1018 341 (validation)	5-year survival rate: 79.7%	◯

Criteria	Author	Year	Institution	Criteria	Cases	Outcome	External Validation
AP criteria	Todo	2007	Multiceter, Japan	AFP (<200 ng/mL) and PIVKA-II (<100 mAU/mL) to the Milan criteria	653	5-year survival rate: 82.0%	
Kyoto	Takada	2007	Univ. of Kyoto, Japan	Maximum diameter of < 5 cm, <10 tumors, and PIVKA-II < 400 mAU/mL	136	5-year survival rate: 87%	◯
Kyushu	Shirabe	2011	Univ. of Kyushu, Japan	PIVKA-II < 300 mAU/mL, regardless of the number of tumors, as long as it is less than 5 cm in diameter	109	5-year disease free survival rate: 80%	
MoRAL score	Lee	2016	Multicenter, Korea	MoRAL Score (11 × √PIVKA-II + 2 × √AFP) < 314.8	566	Low Moral but beyond Milan: 5-year survival rate: 82.6%	◯
Japan	Shimamura	2019	Multicenter, Japan	Nodule size < 5 cm in diameter, nodule number < 5, and AFP < 500 ng/mL	965	Within 5-5-500: 5-year overall survival rate: 75.8% Within Milan or 5-5-500: 5-year	

Prediction for HCC recurrence and survival after transplantation

Criteria	Author	Year	Institution	Risk Factors	Cases	Cut-Off	External Validation
MORAL score	Halazun	2017	Weill Cornell Medical college, USA	Pre-MORAL: Max size > 3 cm (3), AFP ≥ 200 ng/mL (4), NLR ≥ 5 (6) Post-MORAL: Grade 4 tumor (6), Vascular invasion (2), Max size > 3 cm (3), Number > 3 (2) Combo-MORAL: Pre-MORAL+Post-MORAL	339	Low risk ≤ 2 Mod. risk 3–6 High risk 7–10 very High risk >10	
RETREAT score	Mehta	2018	Univ. of California, USA	Max size + Number: 0 (0)/ 1~4.9 (1)/5~9.9 (2)/≥ 10 (3) AFP (ng/mL): 0~20 (0)/21~99 (1)/ 100~999 (2)/≥ 1000 (3) Presence of microvascular invasion: − (0)/+ (2)	3276	3-year recurrence rate Score 0 = 1.6% Score 1 = 5.0% Score 2 = 5.6%	◯

Prediction for HCC recurrence and survival after transplantation

Criteria	Author	Year	Institution	Risk Factors	Cases	Cut-Off	External Validation
HALT-HCC	Sasaki K	2017	Cleveland Clinic SRTR	HALT-HCC score = 1.27 × (TBS (tumor burden score)) + 1.85 × 1n (AFP) + 0.26 × (MELD-Na)	420 13,717 (validation)	5-year overall survival Q1: 78.7% Q2: 74.5% Q3: 71.8% Q4: 61.5%	◯
Recalibrated HALT-HCC	Firl DJ	2020	4 centers in North America 10 centers in Europe 2 centers in Asia	Recalibrated HALT-HCC score = 1.33 × TBS + 2.31 × 1n (AFP) + 0.25 × (MELD-Na) − (5.57 in Asia)	4089	lowest-risk patients (HALTHCC 0–5) highest-risk patients (HALTHCC > 35)	

LDLT 1/2/2018

- Multifocal hepatocellular carcinoma, moderate to poorly differentiated
- Largest tumour 3.0 cm in size, with effects of presurgical therapy (TACE)
- Multiple (5 to 10) smaller tumour nodules, ranging in size from 0.3 to 1.1 cm
- Tumour nodules limited to liver, and involving mainly the right hepatic lobe
- No vascular invasion seen
- Background of established cirrhosis with steatohepatitis and hepatic glycogenosis

Accuracy of preoperative assessment of HCC

Non-invasive diagnostic criteria of hepatocellular carcinoma: Comparison of diagnostic accuracy of updated LI-RADS with clinical practice guidelines of OPTN-UNOS, AASLD, NCCN, EASL-EORTC, and KLSCG-NCC

1–2 cm lesions, sensitivity decreased for all criteria in the following order: EASL-EORTC (59.1%), KLCSG-NCC (58.3%), LI-RADS, AASLD, NCCN (all 56.5%), and OPTN-UNOS (22.7%) criteria.

LI-RADS had the highest sensitivity and accuracy among the guidelines. OPTN had the highest specificity for cirrhotic livers.

Burcu Erkan et al PLOS ONE | December 10, 2019

LTX for HCC- Any difference in DDLT and LDLT?
Impact of GRWR and SFS? Is there a minimum for HCC

No difference in outcomes for HCC between LDLT and DDLT

LDLT provided better survival benefits to HCC patients especially in regions that suffer from low deceased organ availability.

Small for Size – has implications on graft and patient outcomes and needs to be anticipated and managed

No impact on HCC recurrence

Zhu B et al . 2019 Feb;21(2):133-147.

Lee EC. Liver Transpl. 2018 Jan;24(1):35-43.

Elkomos BE. Hepatol Int. 2023

Post LT surveillance

No standardized protocols

Highest rate : within 2-3 years but can occur much later,

Poor prognosis :

- **Early recurrence (defined as <1 year post-LT)**
- **AFP >100 ng/ml**
- **Not Amenable to treatment**

Surveillance improves survival

- **Lee D, et al. Transplantation. 2020**

No difference in 3 or 6 monthly

- **Liu D et al. Transplantation. 2017**

Duration – nor clear

- **at least 3 years**
- **Based on risk of recurrence Eg RETREAT Score**

		Follow up
Low	Year 1	Every 3/12 CT/MRI abdomen and thorax Bone scan AFP
	Year 2-3	Every 3/12 AFP/US scan
	Years 4-5	Every 6/12 AFP/ US scan / CXR
High	Year 1	Every 3/12 CT/MRI abdomen and thorax Bone scan AFP
	Year 2-5	Every 3/12 AFP/US scan Every 6/12 CT/MRI abdomen and thorax Bone scan AFP
	>6	Yearly : AFP /US scan /CXR 6monthly AFP and US SCAN A. Cirrhosis develops

Pre transplant FP >20ng/ml
Pretransplant biopsy
NUH expanded criteria
Explant Histology
Poorly differentiated
UCSF out
Macro/microvasc invasion
Atypical : cholangio-hcc / sarcomatoid

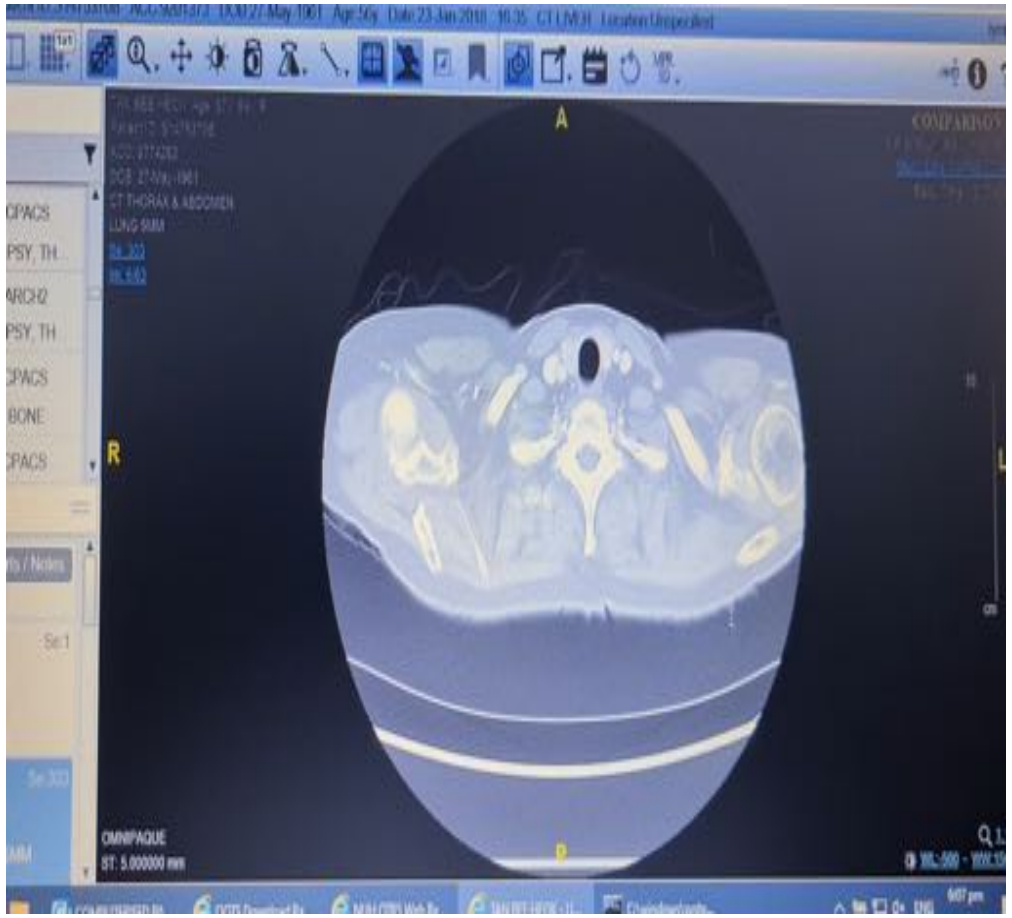
Surveillance 1 Year Post Tx

CT TAP (14/2/19):

The nodule at the anterior segment of the right upper lobe has further increased in size, now measuring ~1 cm, previously 0.4 x 0.36 cm previously .

No HCC in Liver

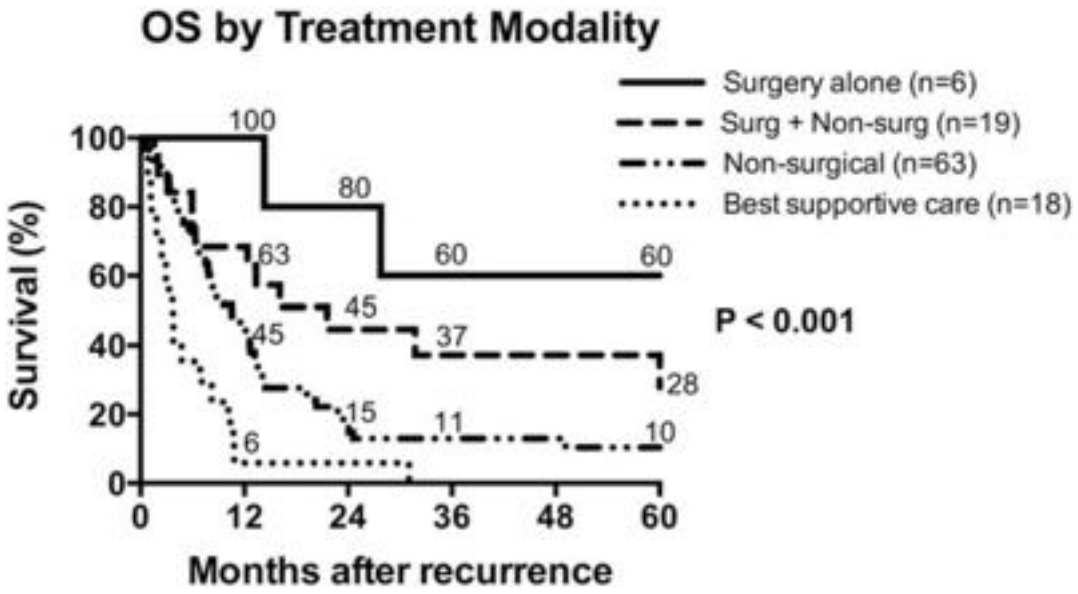
Immunosupression : Prograf 5mg BD, EVL 1.5mg BD



Treatment Options ?

Discussed at transplant meeting : referred to thoracic surgery for consideration of resection

Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation
Impact of Treatment Modality and Recurrence Characteristics

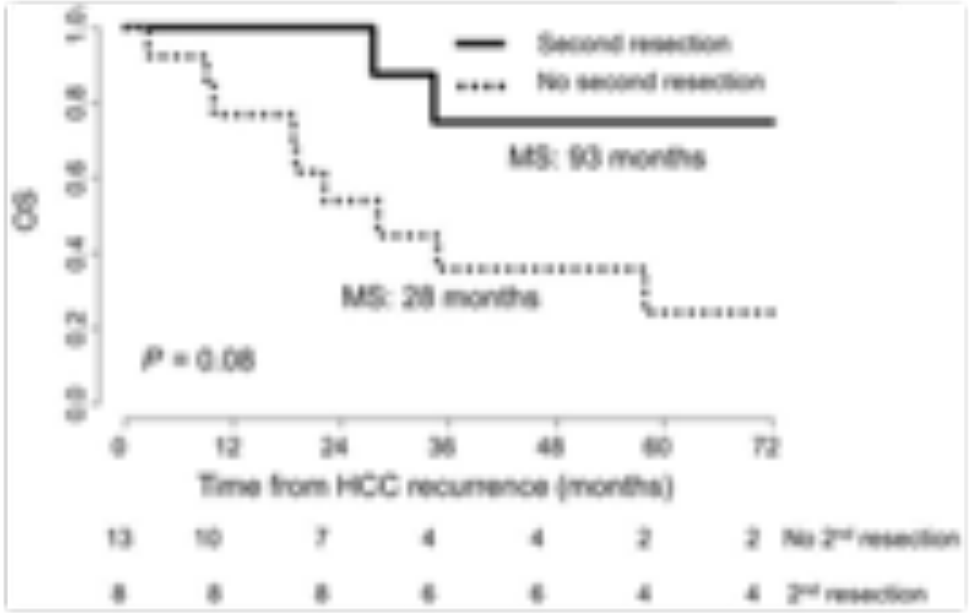


Bodzin et al . Annals of Surgery 266(1):p 118-125, July 2017.

Resection after LT

Recurrence of Hepatocellular Carcinoma After Liver Transplantation: Is there a Place for Resection?

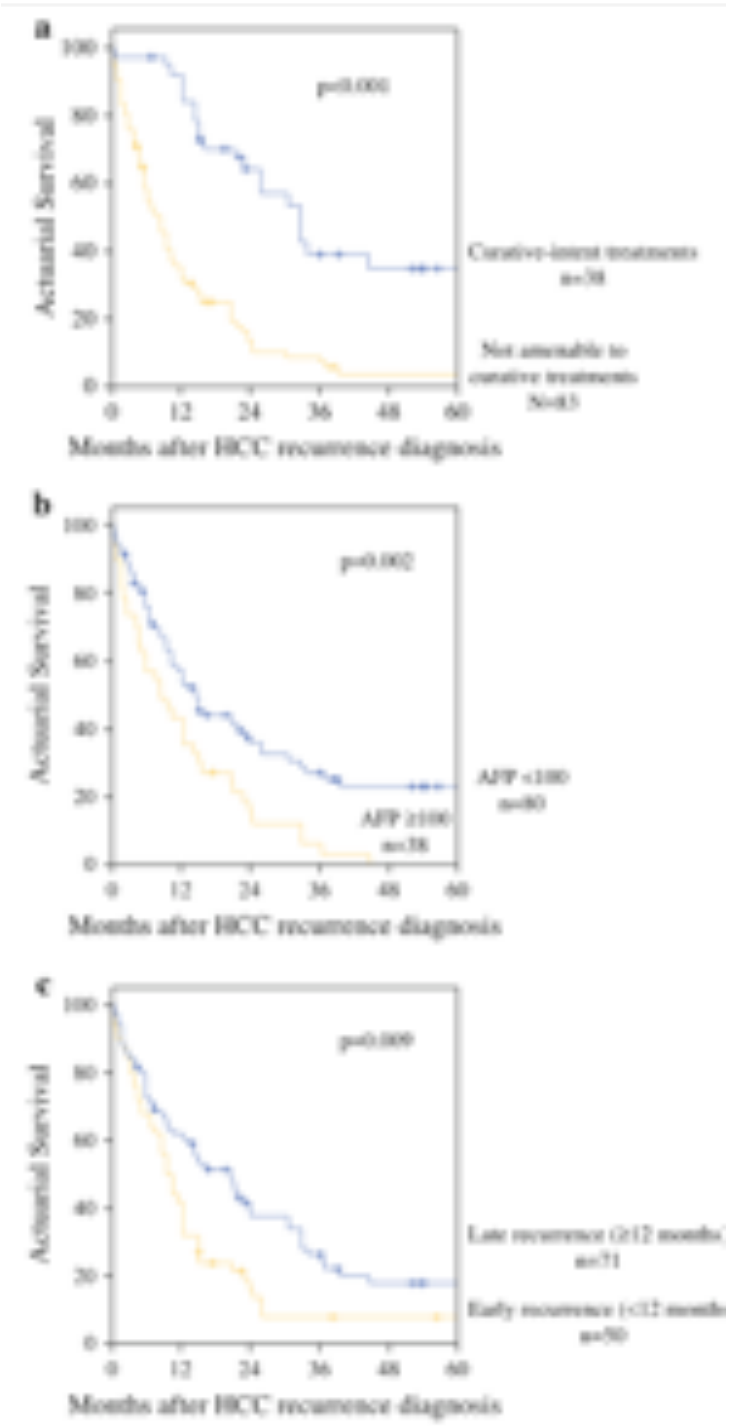
- Fernandez-Sevilla E et al. Liver Transpl. 2017 Apr;23(4):440-447.



Resection of pulmonary metastases from hepatocellular carcinoma following liver transplantation

2-year DF survival rate was significantly greater in the resection group (30.6% vs. 0%, p = 0.007),
Overall 5 year survival rate (44.7% vs. 12.8%, p = 0.017).

Hwang S. World J Surg. 2012



Benefit of Treating Hepatocellular Carcinoma Recurrence after Liver Transplantation and Analysis of Prognostic Factors for Survival in a Large Euro-American Series

Sapisochin et al, Ann Surg Oncol (2015) 22:2286–22

Curative-intent treatments were defined as surgical resection or ablation intended to achieve no evidence of disease

Location of tumor recurrence	
Hepatic	18.4 %
Extrahepatic	47.4 %
Hepatic + extrahepatic	34.2 %

	No. resection/ total (%)	Site of resection	OS	Resection/no resection/ BSC	Selection criteria	Survival benefit
Kornberg *et al* , 2010	7/16 (43.8)	liver(3), lung (2), other (3)	10.5	**65/5**		Yes
Valdivieso *et al* , 2010	11/23 (47.8)	Liver (2), lung (2), adrenal (2), abdominal lymph node - (2)		**32.3 ± 21.5/11.9 ± 6.92,5**	Technical feasibility	
Sapisochin *et al* 2015	38/121 (31.4)			**31/12**	Technical feasibility	Yes
Bodzin *et al* 2017	25/106 (23.6)	lung (*n*8), bone (6), intra-abdominal (4), liver (3), brain (2)	10.6	**27.8/10.6/3.7**		
Fernandez-Sevilla *et al* , 2017	22/70 (31.4)4		19	**35/155**	Technical feasibility and No progression with systemic treatment	Yes

Resection should be considered when feasible.

Recurrence (1)

Underwent Right UVATS excision biopsy of right upper lobe post methylene blue localisation nodule on 10/4/2019

Histology:

Right lung, upper lobe tumour, wedge resection:

- Metastatic hepatocellular carcinoma, moderately differentiated

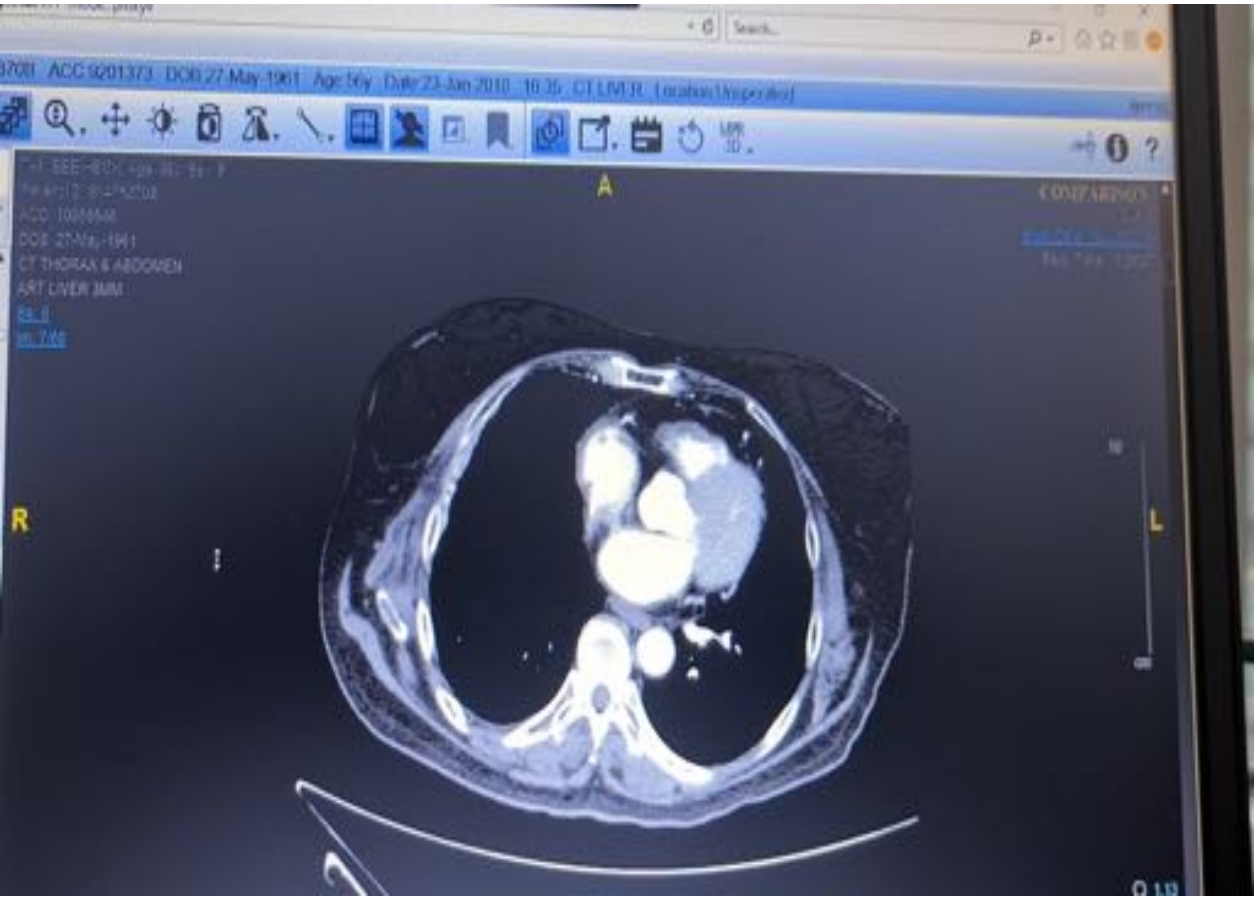
-Excision margin free of tumour

Post op referred to medical oncology post recovery for consideration of TKI (05/2019)

Clinically no evidence of disease

Planned for repeat surveillance scan

Recurrence (2)



CT TAP 13/06/2019 : Status post liver transplant. There is a new 2.1 x 2.2 cm lesion in the graft adjacent to the right hepatic vein which appears arterially enhancing and demonstrating subsequent washout. Appearances highly suspicious for HCC..

AFP 161
Immunosupression
 EVL 2mg BD / SL Prograf 4.5mg BD

Treatment Options ?

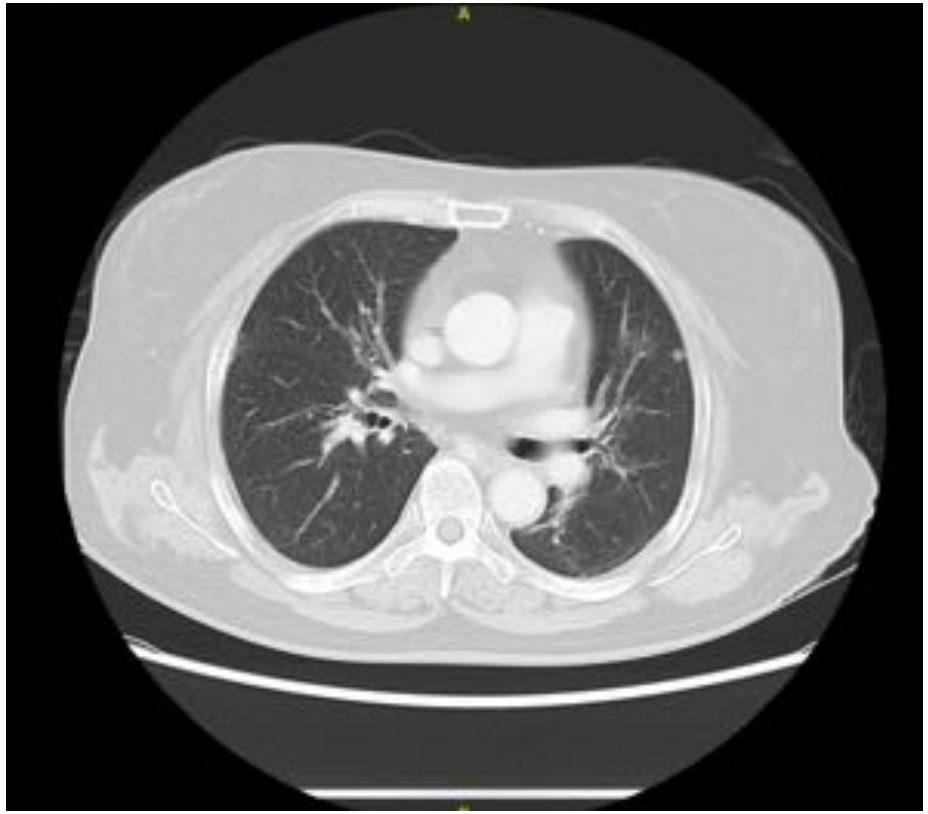
RFA to new 2.2cm HCC in liver graft with good AFP response (1/7/19)

Is radiofrequency ablation applicable for recurrent hepatocellular carcinoma after liver transplantation?

- Huang J et al *J Surg Res* 2016; 200: 122-130

- 15 patients were treated with surgery while 11 received RFA.
- 3-year survival (51% *vs* 51%, *P* = 0.88)
- 5-year survival (35% *vs* 28%, *P* = 0.88)
- However, both hepatic and extra-hepatic recurrences were included,
- Morbidity and mortality after graft resection were not reported.

Recurrence (3)



Surveillance CT TA (09/2019) post RFA

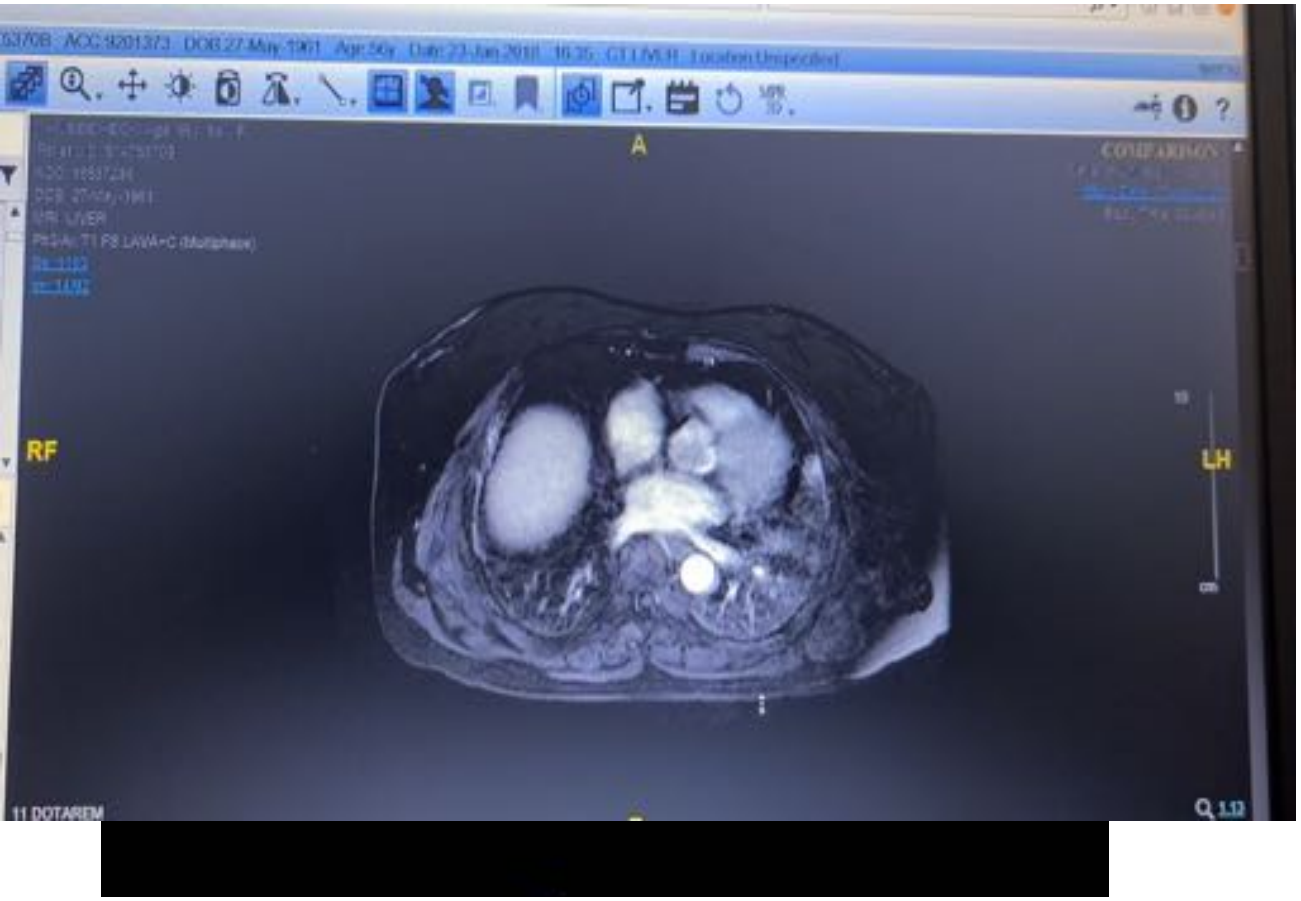
-Previous right UVATS. A left upper lobe lung nodule is now seen, for which metastasis should be considered.
- Status post liver transplant with interval ablation for the right hepatic lesion

- No enhancement of the ablation tract detected.

HPB MTC recommended RFA the lung nodule in view of patient's reluctance for resection and not suitable for TKI for HCC due to nephrotic range proteinurea.

28/11/19 – s/p CT guided ablation

Recurrence (4)



Surveillance MRI 04/2020:

There are 3 new hepatic lesions, which contain fat and show arterial and pseudocapsular enhancement with washout on the delayed phase. One of these abuts the anterior margin of the previously ablated lesion. These are suspicious for foci of HCC.

Also noted new small lung nodules on CT Thorax

Trialled sorafenib, unable to tolerate

CASE 2

Background:

47yo / Male

Premorbidly ADL independent and community ambulant

Married – 3 children

Non smoker

Non drinker

Past Medical History:

1. Hypertension
2. Osteopenia
3. Hep B carrier

HCC History

Hep B carrier

AFP 21.5

CT 19/03/2007 hypervascular lesion in segment III and VII ?HCC : 3 cm ad 1.5 cm

s/p excision of segment VII and III nodules

Histology:

HCC, moderately differentiated ; 3cm Tumour not breaching capsule, margins clear

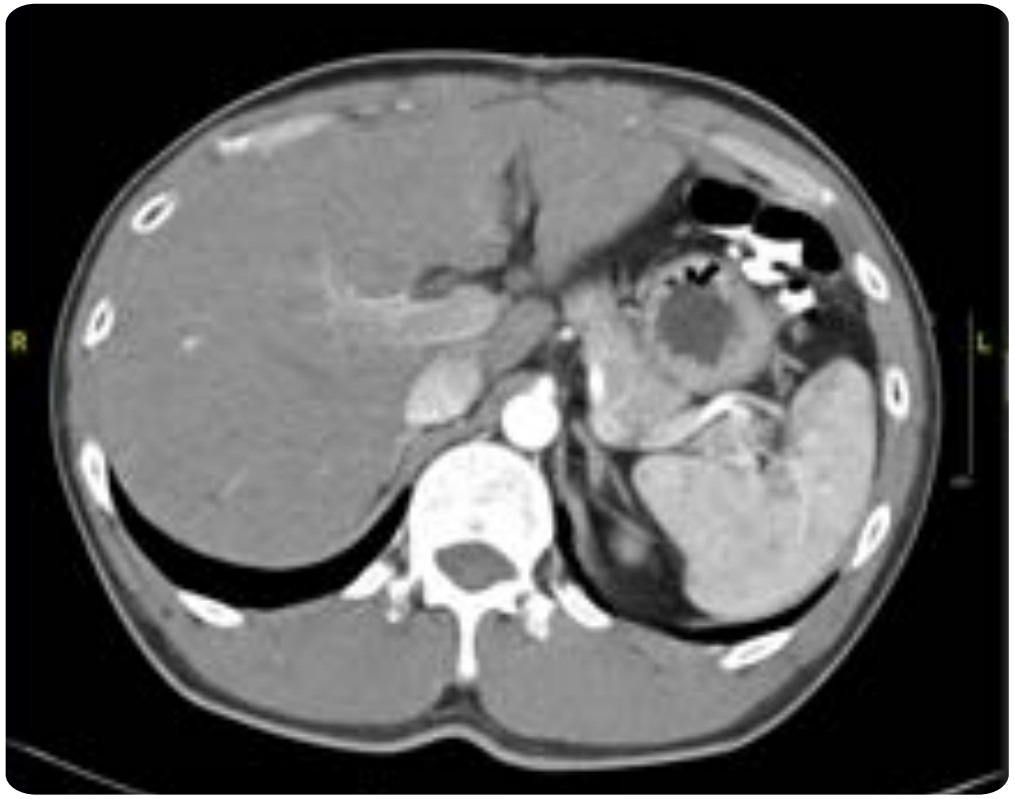
Cavernous hemangioma 1.2cm

Chronic hep B with minimal activity and focal bridging fibrosis

Lesion at segment VII - HCC 1.4cm, not breaching liver capsule

Lesion at segment VI - bile duct adenoma, no vascular invasion

Follow Up



MRI Liver 12/09/2007 : Lesion at segment VI suspicious for HCC

s/p TACE to segment 6 lesion

CT 14/11/07:Interval transarterial chemoembolisation of the hepatic 6 hepatoma. A hypodense nodule in segment 5 anterior to the right portal vein has increased in size, with the suggestion of rim hypervascularity, and is suspicious for a hepatoma.

CT thorax 5/10/07: no lung mets.

AFP Normal

s/p DDLT (Dec 2007)

DDLT , full liver, Piggy-back

Explant Histology:

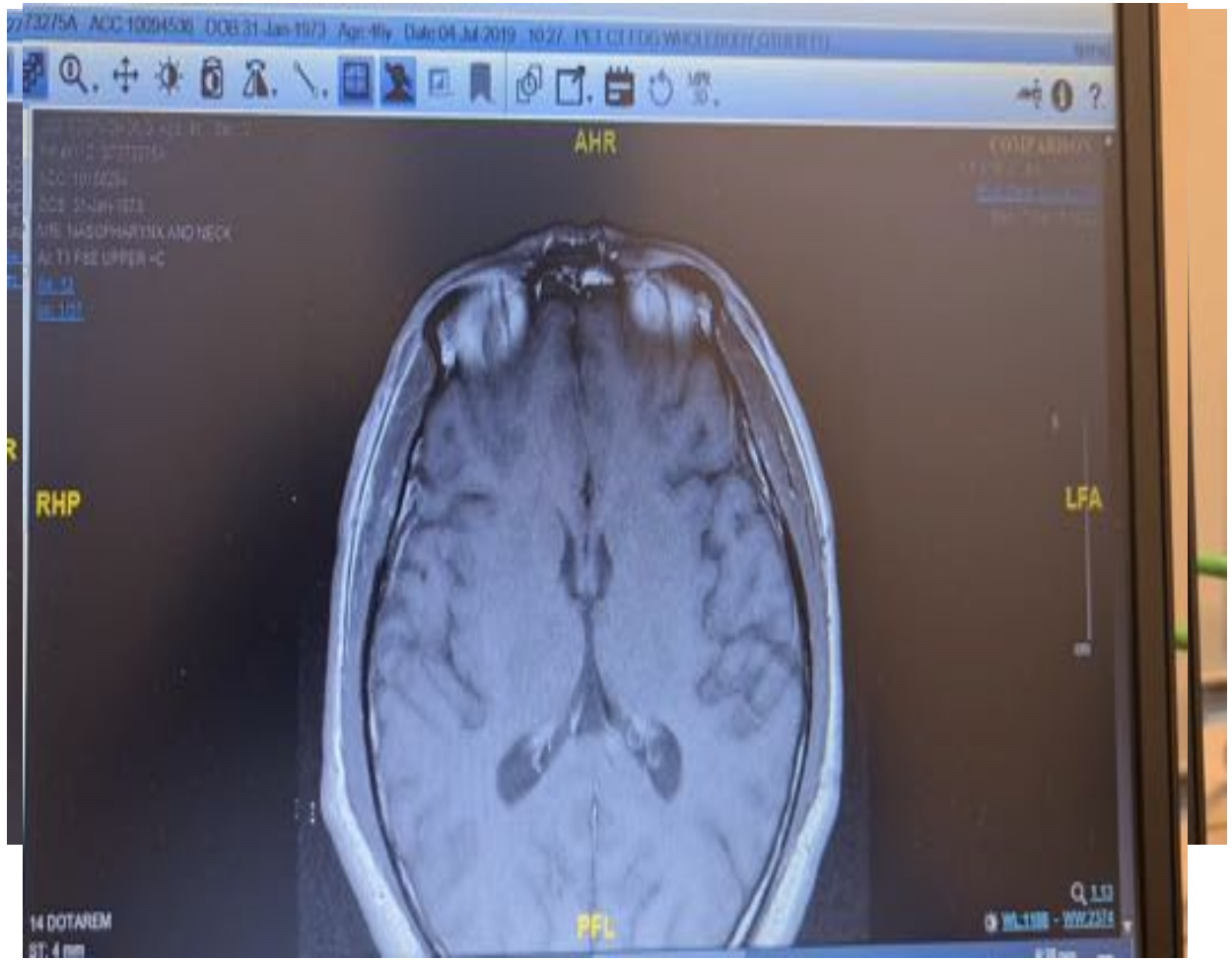
3 tumors (1.0cm, 1.3cm, 0.7cm)
complete coagulative necrosis

Well differentiation

No vascular invasion

AFP normal

Recurrence (1) June 2019



AFP rose to 66.8 (June 19)

cellcept 250mg BD tacrolimus 1mg BD tenofovir 300mg EOD

CT scan – No disease in Liver and Thorax

PET CT 4/7/19: Hypermetabolic soft tissue mass centered in the left side of the **hyoid bone** with possible bony destruction and FDG-avid adenopathy seen in the left parapharyngeal region.

FNAC 22/7/19: **Metastatic carcinoma, favoured diagnosis is of metastatic hepatocellular carcinoma**

Treatment Options ?

Left selective neck lymph node dissection, excision of left parapharyngeal tumor 27/8/19

Histo: Metastatic hepatocellular carcinoma within soft tissue. Some reactive bone present within tumour raising possibility that this is a bone metastasis. Carcinoma seen in fibrocartilage, adjacent soft tissue and focally within bone marrow of hyoid bone.

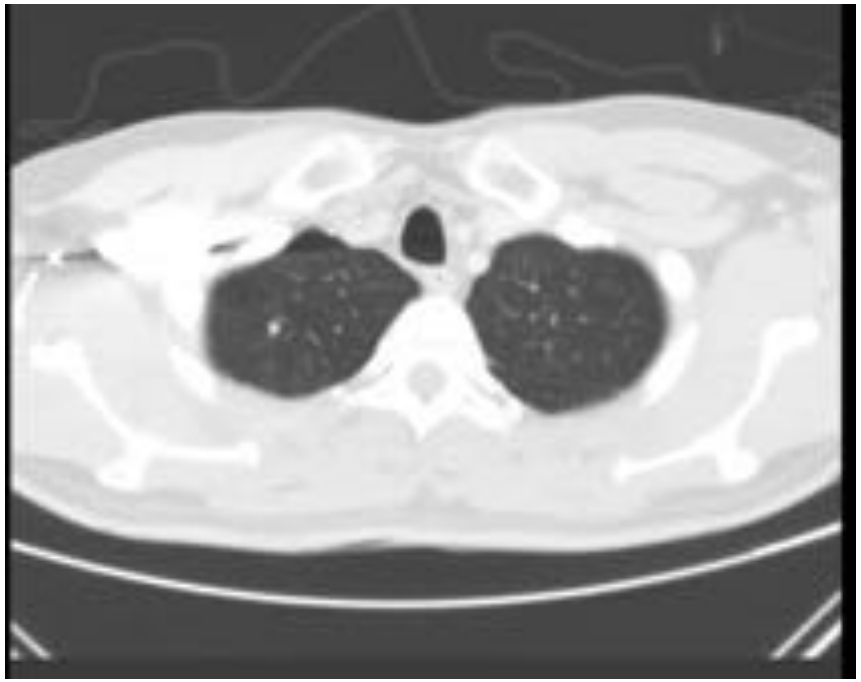
LN negative

Treatment Options ?

Med Onco: RT for local control; currently there is no evaluable disease, and the role of adjuvant TKI is limited

adjuvant RT 66Gy/ 33 fractions – started 14/10/19

Recurrence (2)



CT Thorax 14/10/2019

There are several new subcentimetre nodules scattered within the right lung, approximately 10 in number, thus are suspicious for being metastases. No pleural effusion is seen.

There is no axillary, supraclavicular or mediastinal lymphadenopathy of note.

The liver is smooth and homogenous with no suspicious lesions seen.

AFP rising from 4.2 --> 7.9 --> 7.5

Cellcept 250mg BD Prograf 1mg BD Tenofovir 300mg EOD

Treatment Options ?

Started on lenvatinib at 8mg OD

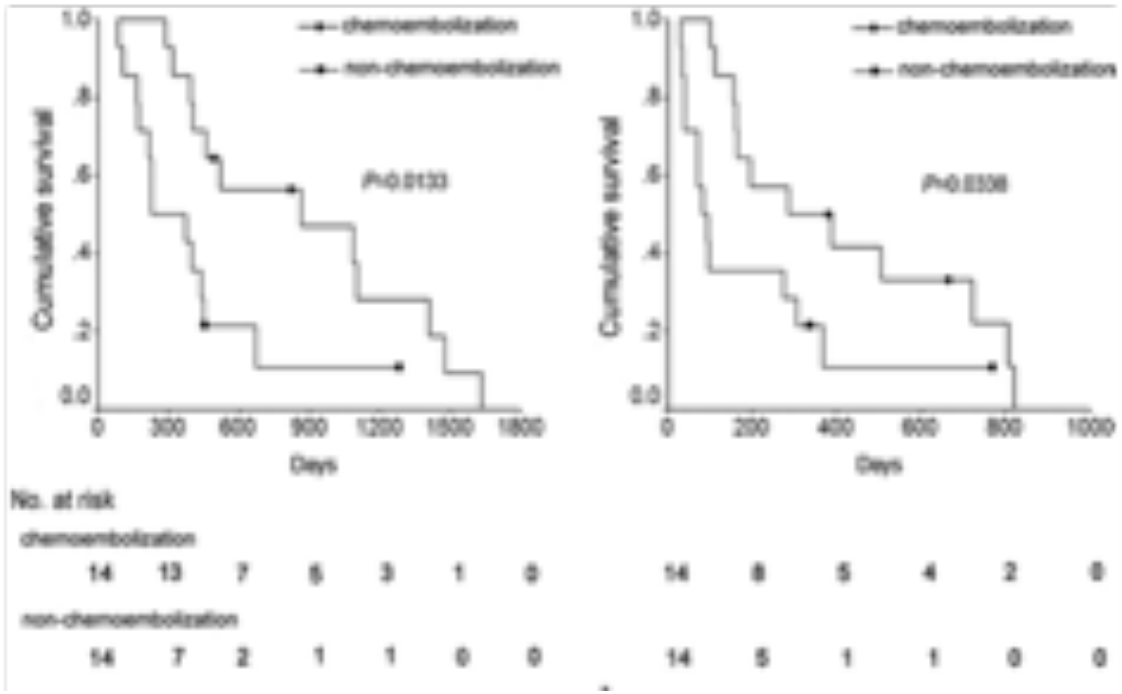
Recurrence (3)

Noted level 3, left neck palpable lymph nodes in medical oncology clinic on 02/11/2020

AFP 41

Lenvatinib 8mg OM Tacrolimus 0.5mg BD

Transarterial chemoembolization



Lobaplatin Mixed with Iodized Oil

The 6-, 12-, and 24-month overall survival rates from diagnosis of HCC recurrence chemoembolization group: 64.3%, 50%, and 22.2%,

Non-chemoembolization group : 35.7%, 21.4%, and 10.7%

Zhou B,. J Vasc Interv Radiol. 2010

Other Locoregional treatments

TARE limited to case reports

SBRT

- Upregulates anti-tumour immunity
- Stimulates antigen-presenting cells, activation and proliferation of tumour-specific cytotoxic T cells

Limited data in post transplant setting

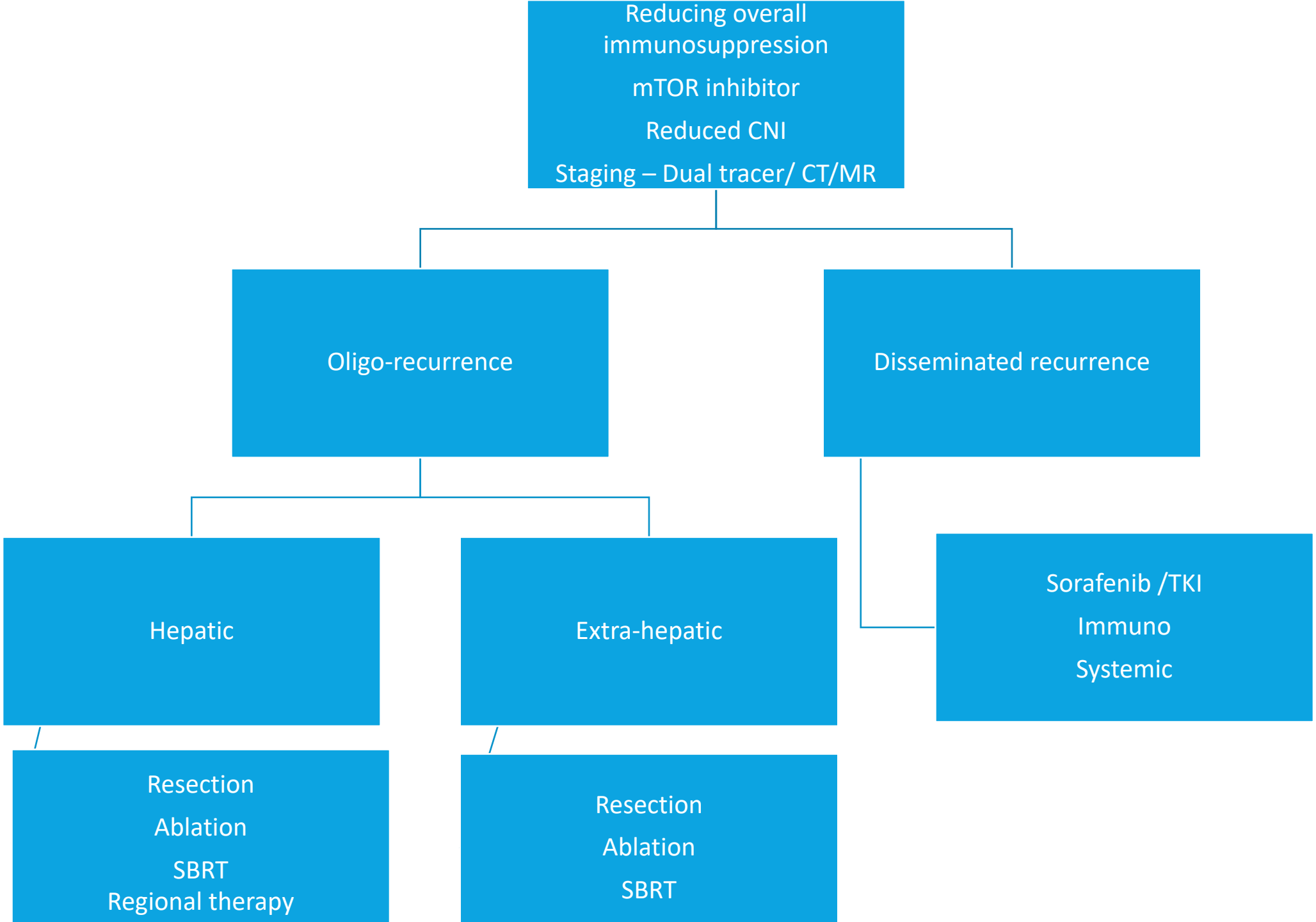
In Summary

Surveillance for HCC improves survival after transplant

Curative intent treatments- surgery/ ablation if feasible for recurrence

Locoregional treatments may offer survival benefit

Most case series don’t have a control arm


Reducing overall immunosuppression
mTOR inhibitor
Reduced CNI
Staging – Dual tracer/ CT/MR
Oligo-recurrence
Disseminated recurrence
Hepatic
Extra-hepatic
Sorafenib /TKI
Immuno
Systemic
Resection
Ablation
SBRT
Regional therapy
Resection
Ablation
SBRT

Thank you.


NUHS
National University Health System
National University Hospital
Ng Teng Fong General Hospital
Alexandra Hospital
Jurong Community Hospital
National University Polyclinics
Jurong Medical Centre
National University Cancer Institute Singapore
National University Heart Centre Singapore
National University Centre for Oral Health Singapore
NUHS Diagnostics
NUHS Pharmacy
NUS Yong Loo Lin School of Medicine
NUS Faculty of Dentistry
NUS Saw Swee Hock School of Public Health

Immunotherapy

Immune checkpoint modulation of cell- mediated immunity is implicated in transplant organ tolerance .

Downregulation of these pathways may lead to transplant rejection .

Clinical trials for immune checkpoint inhibitors often exclude solid organ transplant recipients due to the fear of graft injury .

Current experience in immunotherapy after liver transplantation is confined to case reports and small series with limited survival

The salvage nature of immunotherapy must be considered while interpreting the results. Most patients had developed disease progression