2017 CST-Astellas Canadian Transplant Fellows Symposium

Case Study: Liver Transplantation

Karim Qumosani, MD, FRCPC, ABIM, MdMEd

Dr. Qumosani is Assistant Professor, Medical Director of the Advanced Hepatology and Liver Transplantation Fellowship, and is now Program Director of Gastroentrology Training (starting July 2017) at Western University. He attended medical school at King Abdulaziz University, Saudi Arabia; and he studied internal medicine, as well as received his gastroenterology training and an advanced hepatology and liver transplantation fellowship, at Western University. He also has a Diploma of Medical Education from the University of Dundee, UK. His research interests include hepatocellular carcinoma and nonalcoholic steatohepatitis.

Liver Transplant Cases Discussion

Karim Qumosani

MD, FRCPC, ABIM, MdMEd

Multi-organ Transplant Unit, London

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Clinical Scenario

Mr ML 58 years old gentleman

- HCV diagnosed 2000
  - Liver biopsy 2004 (Staging) showed stage 4/4 fibrosis
  - Peg-interferon and Ribavirin = Null responder
- Well compensated
- No other comorbidities

Clinical Scenario

PMHx

- No other chronic medical illness

PSHx

- Unremarkable

Drugs

- None

Clinical Scenario

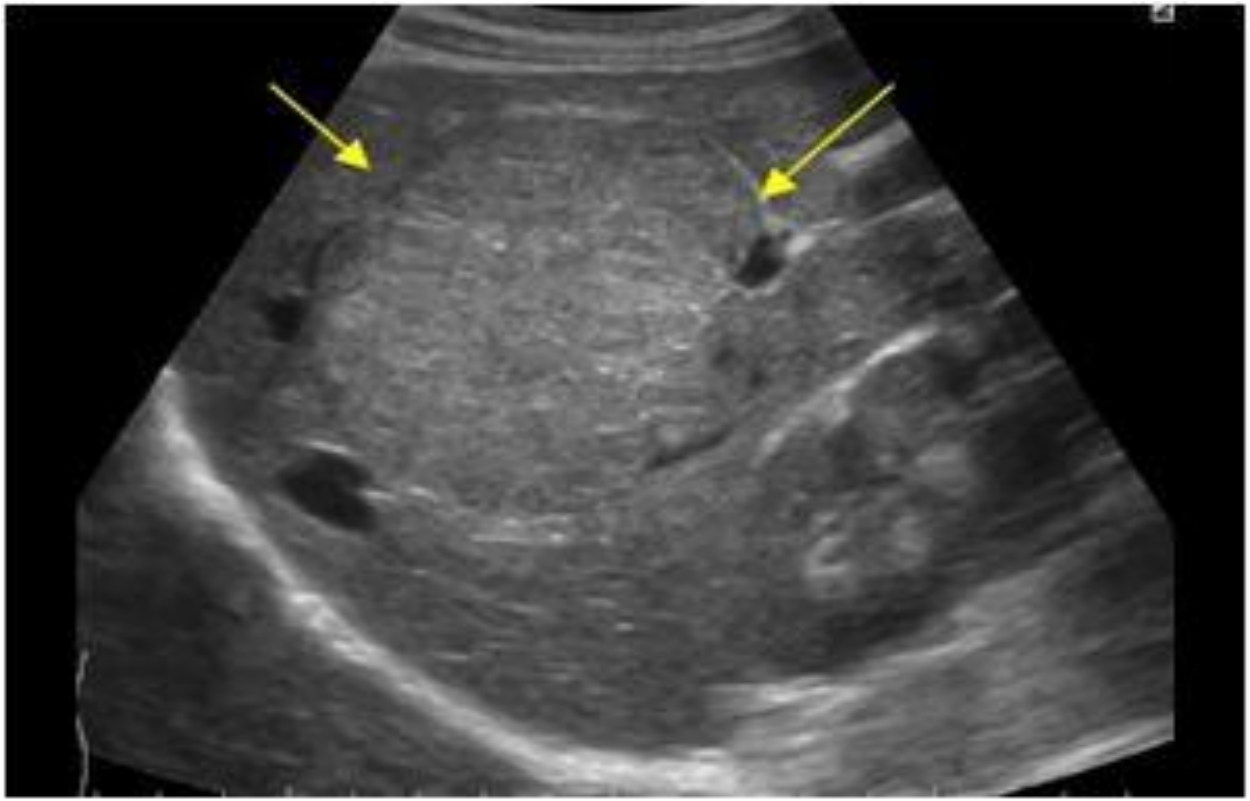
Social Hx

- Remote IVDU, no EtOH misuse
- Smoker 1 p/day for 25 years

Family HX

- Brother had liver transplant for HCV cirrhosis, died within first year after transplant

Clinical Scenario



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Discussion

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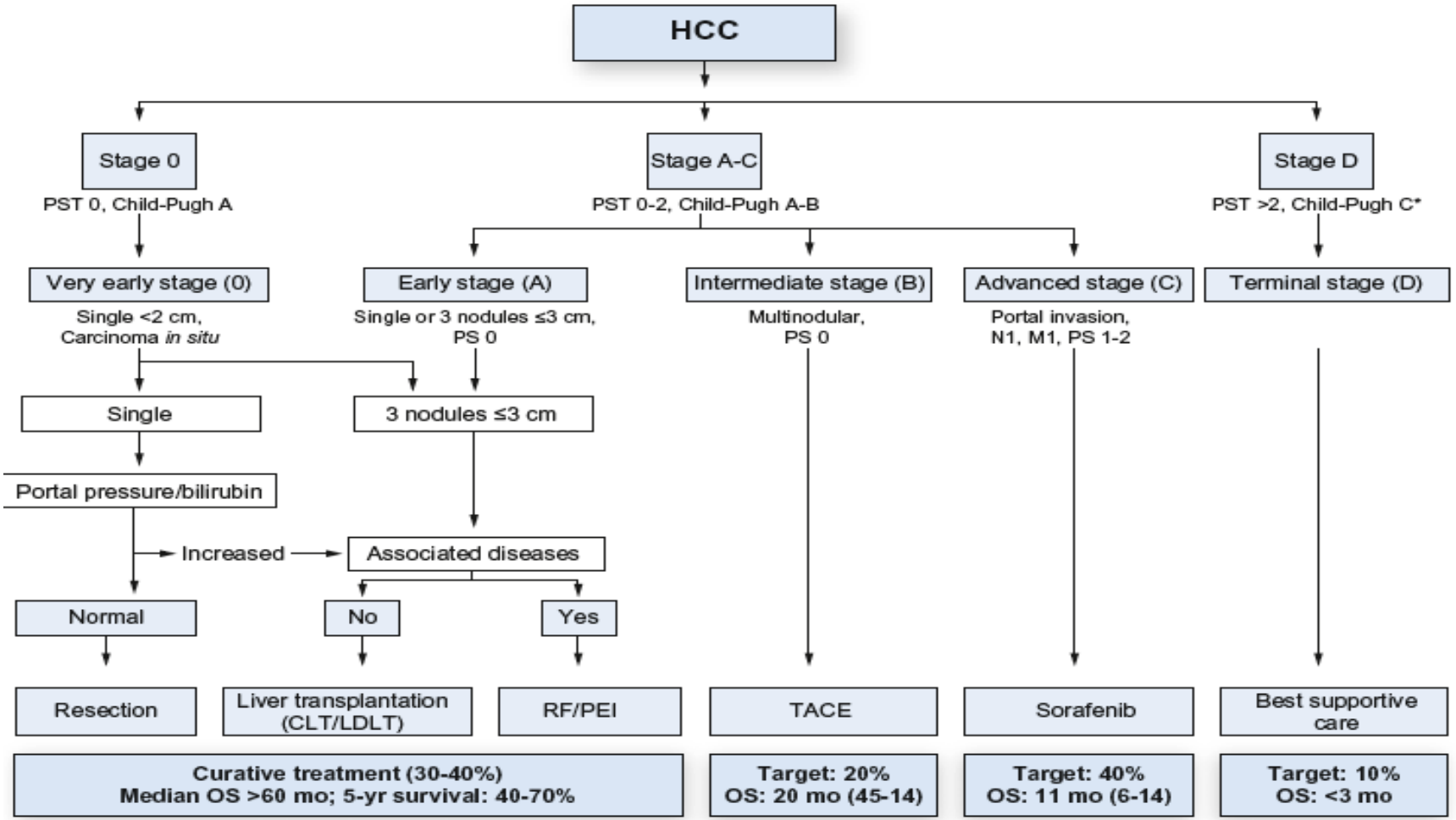
HCC – Staging



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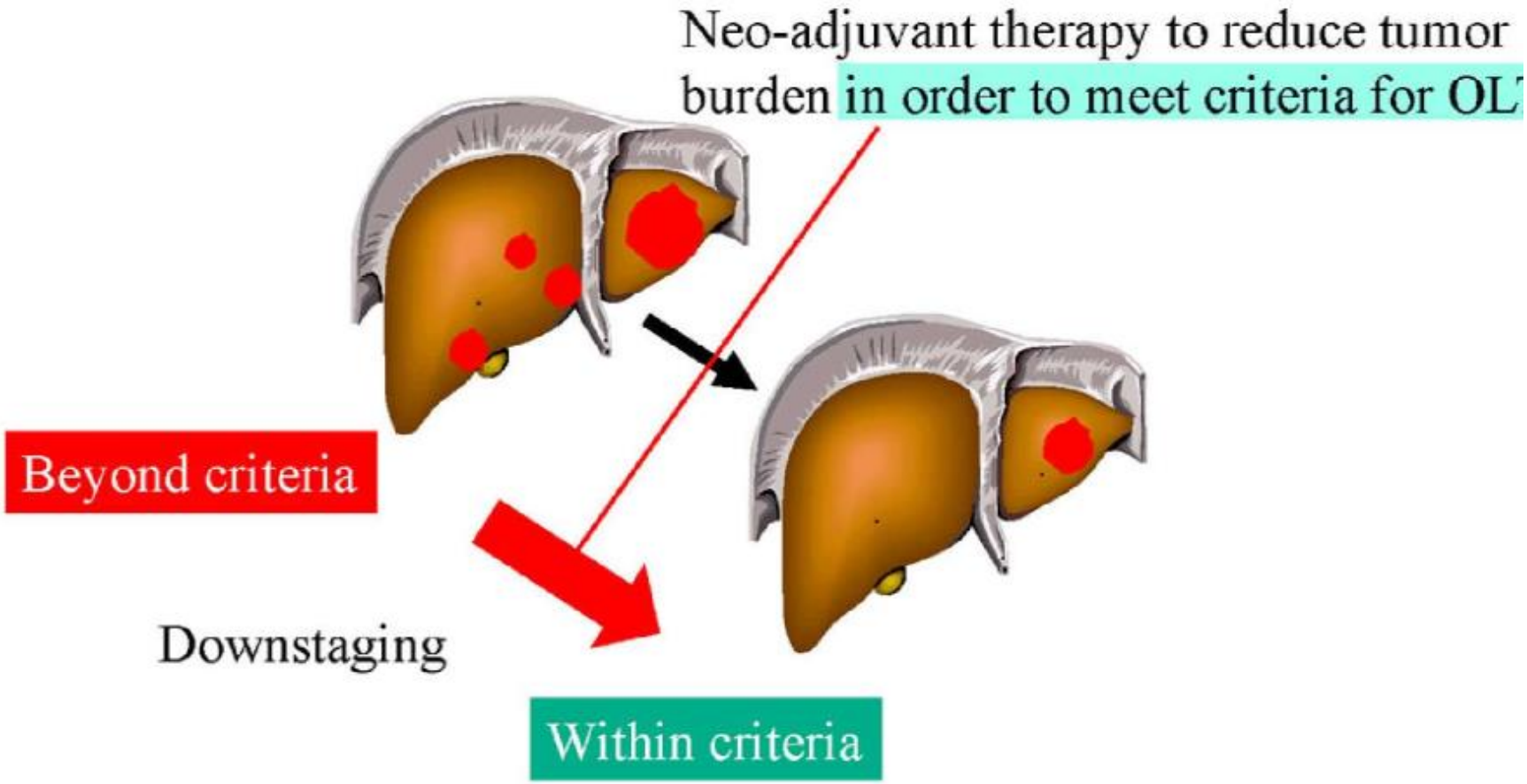
Clinical Scenario



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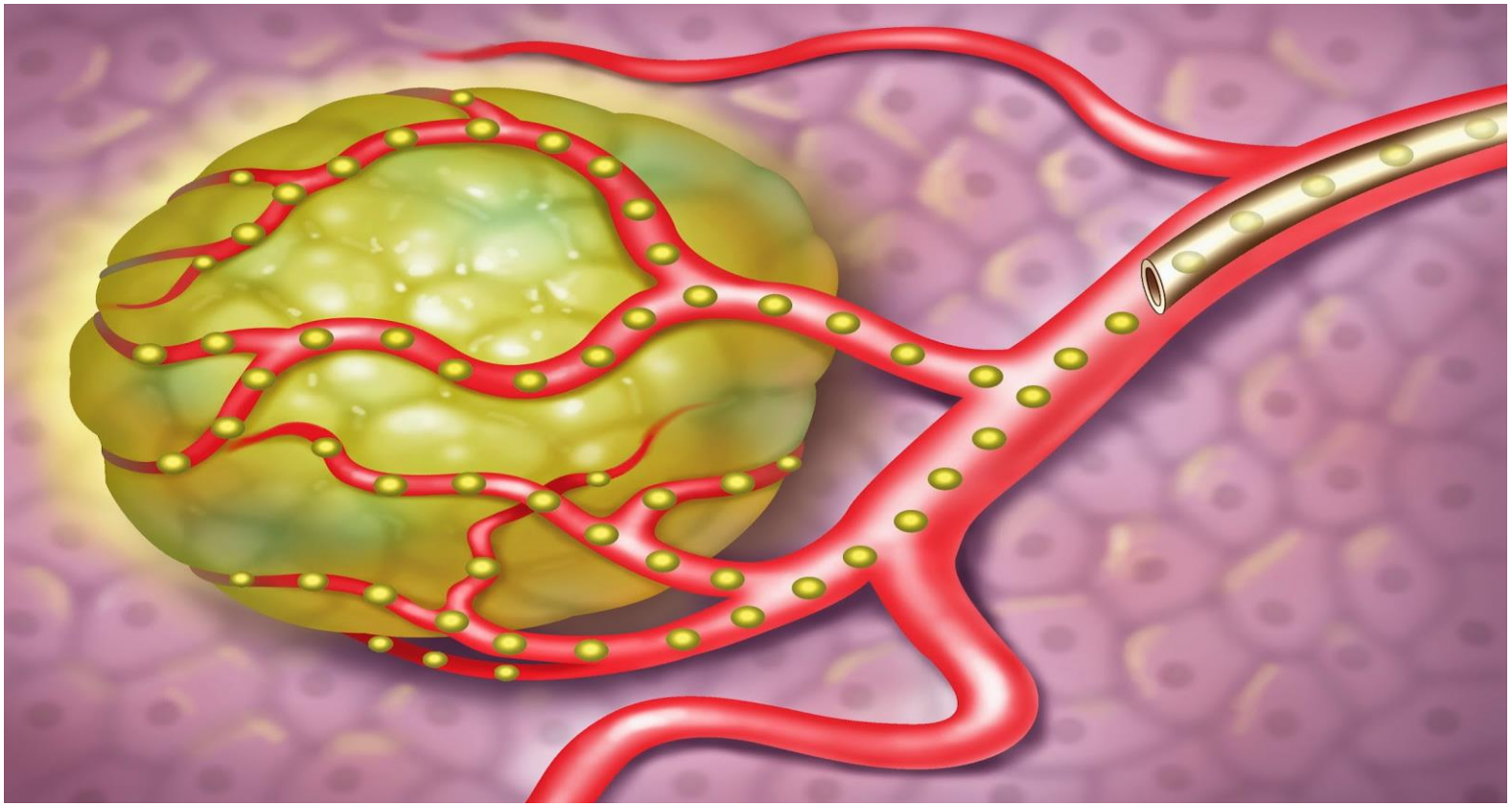
Clinical Scenario



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Clinical Scenario

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Clinical Scenario

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Clinical Scenario

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Clinical Scenario

August 2007; Liver Transplant Assessment

- No medical or psychosocial contraindication for liver transplantation
- Down staged to Milan criteria

Clinical Scenario

September 2007; Liver Transplantation

- NDD
- Cold ischemia time 5 hours
- No intraoperative complications
- Hospital stay was uneventful
- Discharged home 9 days after transplant

Clinical Scenario

SYNOPTIC REPORT - LIVER CANCER

Tissue(s) Received:
liver, gallbladder

Specimen Type:
total hepatectomy (explant liver) and cholecystectomy

Focality:
multiple (two nodules in right lobe)

Tumour Size:
greatest dimension 2.1 cm

Histological Type:
hepatocellular carcinoma

Histological Grade:
moderately differentiated (grade 2/4, modified Edmondson and Steiner grading system)

Venous (Large Vessel) Invasion:
present, microscopic

Lymphatic Invasion:
absent

Primary Tumour (pT):
multiple tumours, none greater than 5 cm (pT2)

Resection Margins:
Vena Cava: uninvolved by invasive carcinoma
Porta Hepatis: uninvolved by invasive carcinoma
Distance of tumour from closest margin: 30 mm, porta hepatis margin, larger nodule)

Lymph Node Status
no lymph nodes present

Additional Pathological Findings:
Immediately adjacent to the larger nodule, tumour is present in thin-walled vascular spaces. No vascular invasion is identified in association with the smaller nodule.

Pathological Stage:
pT2NXMX

B: The slide shows histologically normal gallbladder.

Discussion

High Risk Features of HCC recurrence

- Outside Milan criteria
- HCC more than 5 cm
- Microvascular invasion
- Moderately – Poorly differentiated HCC
- AFP more than 200

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Sotiropoulos GC, *et al* Eur J Med Res. 2007;12:527–534

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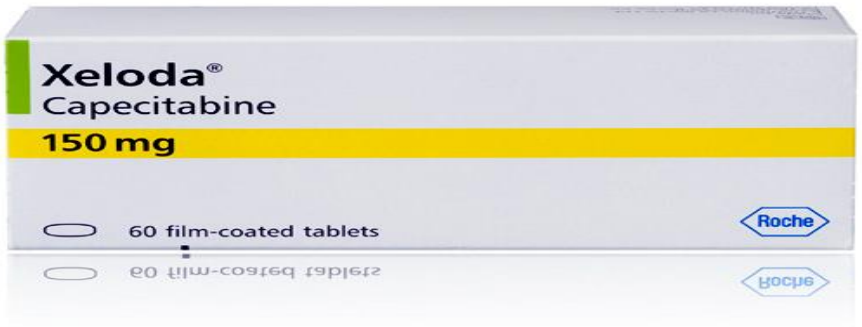
Clinical Scenario – Follow up

October 2007; Transplant Clinic

- No major complains
- Unremarkable post operative course
- Discussion about Xeloda



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Clinical Scenario – Follow up

April 2008; CT Chest/Abdomen/Pelvis

- No evidence of HCC recurrence
- Normal Liver Enzymes and Function

Clinical Scenario – Follow up

October 2008; CT Chest/Abdomen/Pelvis

- No evidence of HCC recurrence

July 2009; CT Chest/Abdomen/Pelvis

- No evidence of HCC recurrence

Clinical Scenario – Follow up

February 2010; CT Chest/Abdomen/Pelvis

- Liver; Clear
- No lymph nodes
- Lungs; 3 new nodules in the left upper lobe measuring 11, 7, and 5 mm. Also new 4 mm nodule in the left lower lobe
- AFP 9.3

Discussion

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Clinical Scenario – Follow up

March 2010; FNA

- Left upper lobe
- Suspicious for malignancy

May 2010; CT Guided Biopsy

- Left upper lobe
- HCC

Clinical Scenario – Follow up

August 2010; Medical Oncology

- No chemotherapy
- Surgical resection would be ideal

September 2010; Thoracic Surgery

- Resection feasible

Clinical Scenario – Follow up

October 2010; Surgical Resection

- Wedge resection of apical nodule
- Wedge resection of 2 nodules in the left upper lobe
- Wedge excision of the lung nodule in the posterior basal segment
- Wedge resection of lung nodule in the superior segment of the left lower lobe

Clinical Scenario – Follow up

October 2010; Hospital Stay

- No post operative complications
- Total hospital stay 5 days
- No changes in his immunosuppressive medication

Clinical Scenario – Follow up

Diagnosis

A: Left upper lobe, apex, wedge resection:
- one focus of metastatic hepatocellular carcinoma;
- tumour size: 0.6 cm;
- distance to parenchymal resection margin: 0.4 cm.

B: Left upper lobe, anterior segment, wedge resection:
- two foci of metastatic hepatocellular carcinoma;
- tumour sizes: 1.6 cm, 1.0 cm;
- distance to parenchymal resection margin: 0.6 cm.

C: Left lower lobe, wedge resection:
- one focus of metastatic hepatocellular carcinoma;
- tumour size: 0.8 cm;
- distance to parenchymal resection margin: 0.4 cm.

D: Left lower lobe, wedge resection:
- one focus of metastatic hepatocellular carcinoma;
- tumour size: 0.4 cm;
- distance to parenchymal resection margin: 0.4 cm. smc/CH/smc

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ORIGINAL ARTICLE

Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation

Impact of Treatment Modality and Recurrence Characteristics

Adam S. Bodzin, MD,† Keri E. Lunsford, MD, PhD,*‡ Daniela Markovic, MS,§*
Michael P. Harlander-Locke, MPH, Ronald W. Busuttil, MD, PhD,* and Vatche G. Agopian, MD**

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Bodzit, A *et al*; Annals of surgery; 2016

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TABLE 1. Characteristics of Recurrence Following Liver Transplantation in 106 Patients

Time to recurrence, mo (IQR)	15.8 (6.8–33.1)
Time from recurrence to death, mo (IQR)	10.6 (3.8–20.2)
AFP at recurrence, ng/mL (IQR)	53.6 (7.2–1566)
Number of recurrent nodules, %	
1–3	36.6
4–10	12.9
>10	50.5
Maximum recurrence diameter, cm (IQR)	3.5 (1.7–6.0)
Number of sites of recurrence, %	
1	47.2
2	33.0
3	17.0
4	2.8
Site of recurrence, %	
Liver allograft	37.8
Lung	55.7
Bone	25.5
Abdomen (outside liver)	37.7
Chest (mediastinum, pleural)	14.2
Brain	3.8
Treatment modality for recurrence, %	
Surgery	23.3
External beam radiation	13.6
Ablation	3.9
Chemotherapy (targeted or cytotoxic)	73.5
None	17.0
Treatment modality groups, (%)	
Surgery alone	5.8
Surgery + Nonsurgical (XRT/ablation/chemo)	17.5
Nonsurgical (XRT/ablation/chemo)	59.2
None	17.5

IQR indicates interquartile range; XRT, radiation therapy.

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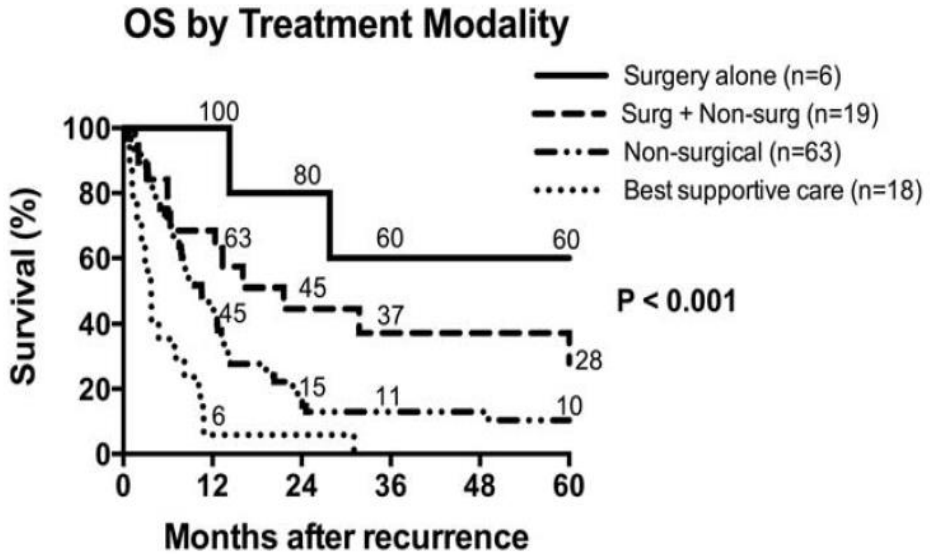

FIGURE 2. Kaplan–Meier overall survival following hepatocellular carcinoma (HCC) recurrence stratified by treatment modality for the HCC recurrence.

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Clinical Scenario – Follow up

December 2011; CT Chest

- No recurrence

March 2012; CT Chest/Abdomen/Pelvis

- No recurrence

September 2012; CT Chest

- No recurrence

Clinical Scenario – Follow up

March 2013; CT Chest/Abdomen/Pelvis

- No recurrence

October 2013; CT Chest

- No recurrence

May 2014; CT Chest

- No recurrence

Clinical Scenario – Follow up

December 2014; CT Chest

- No recurrence

May 2015; CT Chest/Abdomen/Pelvis

- No recurrence

December 2015; CT Chest

- No recurrence

Clinical Scenario – Follow up

May 2016; CT Chest/Abdomen/Pelvis

- No recurrence

May 2017; CT Chest/Abdomen/Pelvis

- No recurrence

May 2017; Transplant Clinic

- Doing well
- Working full time

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Clinical Scenario

Mr DT 43 year old male with hepatitis C virus (HCV) cirrhosis

- Refractory Ascites (LVP Biweekly)
- Esophegeal varices
- Muscle wasting

Clinical Scenario

PMHx

- No other chronic medical illness

PSHx

- Unremarkable

Social Hx

- He is married with 2 children and has been off work from his job as a carpenter for 10 months

Clinical Scenario

Current/previous medications	Duration	Response, other relevant information
Nadolol 40 mg/day	12 months	Pulse at target (60/min)
Spironolactone 200 mg/day	6 months	Stopped due to lack of effect
Furosemide	6 months	Stopped due to lack of effect
Vitamin D	12 months	
Multivitamin	12 months	

Clinical Scenario

Investigation	Finding
Hb	110 gm/L
WBC count	3.8 x 10^9/L
Platelets	85 x 10^9/L
Bilirubin	110 µmol/L
Creatinine	105 µmol/L
PT INR	2.1
MELD Na	28
US and MRI abdomen	• Cirrhosis with portal HT • No HCC or portal venous thrombosis

Hb, hemoglobin; HCC, hepatocellular carcinoma; HT, hypertension; PT INR, prothrombin time, international normalized ratio; MELD Na, model for end-stage liver disease - sodium; MRI, magnetic resonance imaging; US, ultrasound; WBC, white blood cell count

Clinical Scenario

Liver Transplant

- He undergoes an appropriately sized matched, ABO-identical cadaveric liver transplant without technical complications
- Immunosuppression:
  - Steriod for induction
  - Tacrolimus 3 mg BID
  - Mycophenolate mofetil (MMF) 1 g BID

Clinical Scenario

Post Liver Transplant Course

- Patient extubated Day 1, oriented and alert; off all pressors
- Good initial graft function
- Poor urine output on Day 1 (20 cc/hr)
- Creatinine 170 µmol/L
- Tacrolimus level 4.5 µg/L

Clinical Scenario

Did the patient have pre-op risk factors for renal dysfunction post liver transplant?

Clinical Scenario

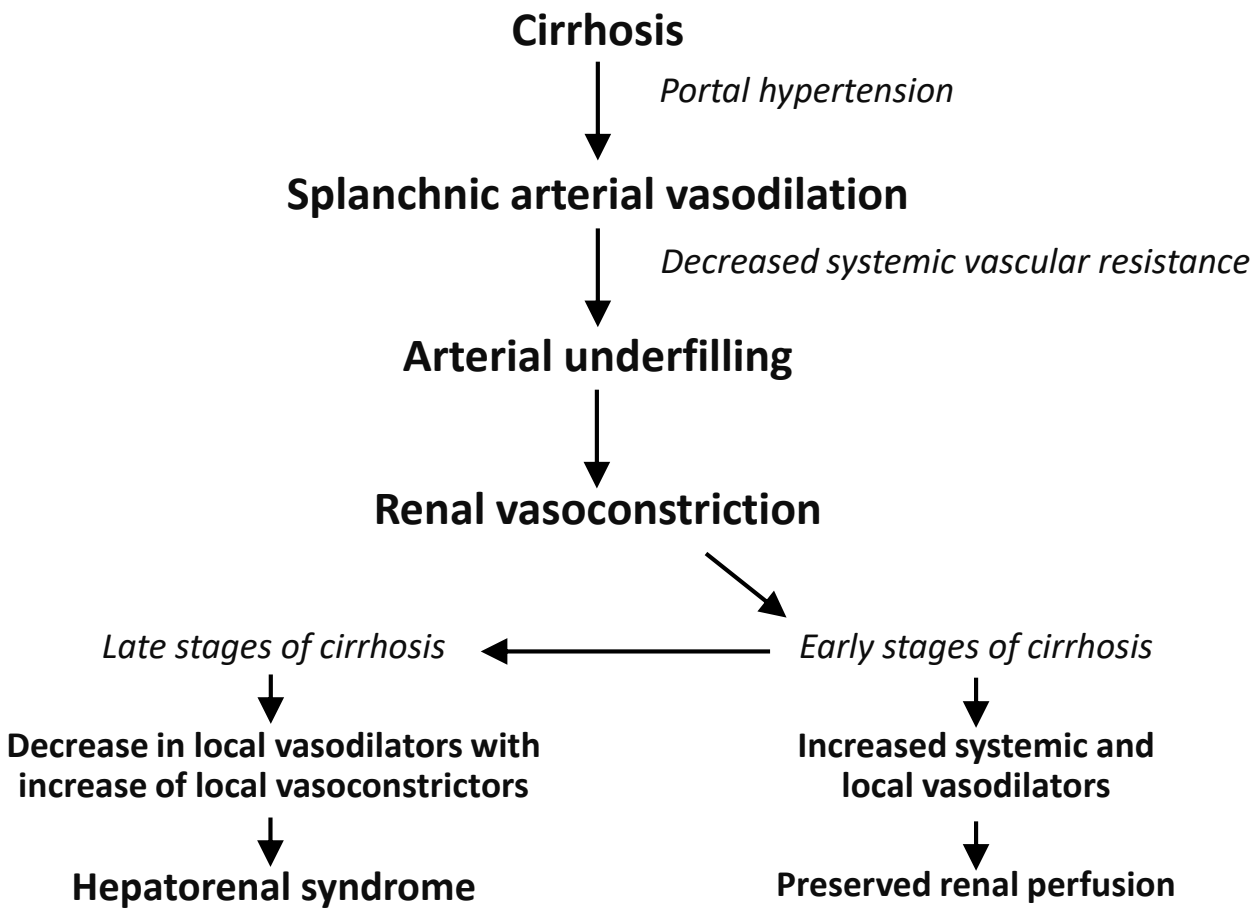
Risk factors for post liver transplant renal dysfunction:

- Reduced glomerular filtration rate (GFR) pre-transplant, including hepatorenal syndrome
- Hepatitis C
- Use of full-dose calcineurin inhibitor
- Diabetes mellitus
- Hypertension
- Nonalcoholic steatohepatitis (NASH)

Clinical Scenario

Are liver transplant recipients more vulnerable to renal dysfunction?

Clinical Scenario



Cardenas A. *Am J Gastro* 2005;100:460-467

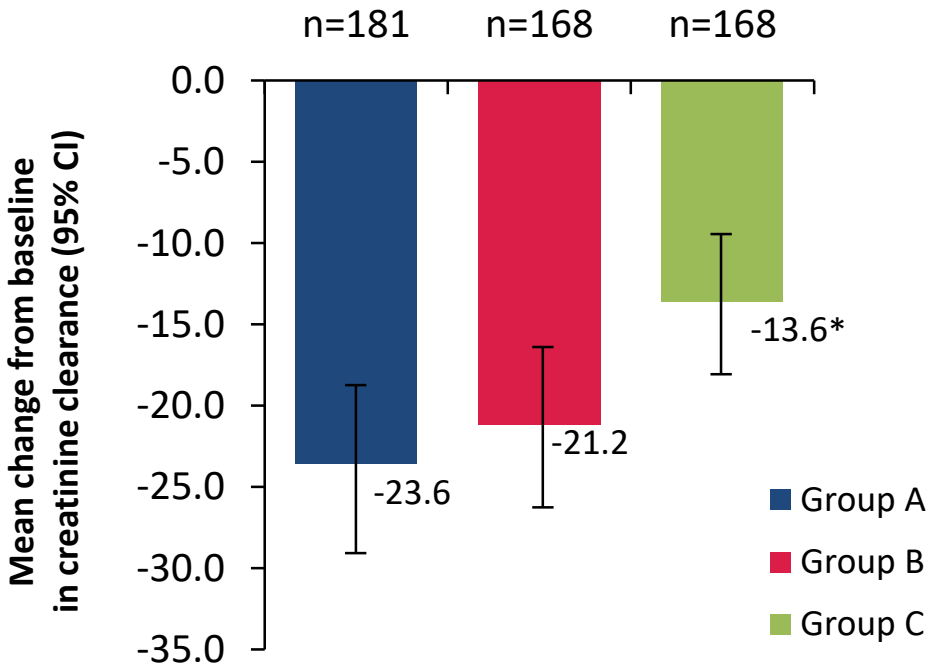
Clinical Scenario

What could have been done differently?

1. Reduced dose of tacrolimus
2. Delayed initiation of tacrolimus
3. Both 1 and 2
4. Alternate immunosuppression, e.g., sirolimus
5. Other

Change in creatinine clearance in liver allograft recipients

Mean change in creatinine clearance (Cockcroft–Gault) at 52 weeks



*p< 0.05 vs. Group A

Group A: Standard dose TAC [target trough levels >10 ng/mL], corticosteroids
Group B: MMF 2 g/day, reduced-dose TAC (target trough levels ≤8 ng/mL]), corticosteroids
Group C: Daclizumab induction, MMF, reduced-dose TAC delayed until 5th day post-Tx, corticosteroids

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Neuberger JM, et al. *Am J Transplant* 2009;9(2):327-336

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Clinical Scenario

What should be done now?

1. Assess fluid status
2. Exclude obstructive causes
3. Hold tacrolimus
4. Carefully monitor and consider adding back low-dose tacrolimus if improvement occurs

Clinical Scenario

Renal function post-transplant according to pre-transplant GFR

	Group 1	Group 2	Group 3	Group 4
Time	Average GFR, mL/min (n)			
Pre-transplant	47±13 (109)	80±9 (106)	108±7 (114)	140±20 (114)
3-month GFR	44±16 (54)	58±23 (50)	63±30 (53)	74±31 (46)
1-year GFR	45±16 (55)	57±20 (49)	68±29 (54)	68±23 (45)
2-year GFR	44±18 (31)	54±19 (26)	67±24 (38)	70±29 (30)
3-year GFR	35±16 (8)	57±34 (4)	86±37 (5)	78±27 (5)
4-year GFR	**49±8 (10)**	**51±22 (11)**	**75±44 (8)**	**49±15 (4)**

GFR determined by iothalamate clearance. Group 1 had pretransplant GFR ≤67 mL/min; Group 2, 67–95 mL/min; Group 3, 96–120 mL/min; Group 4, ≥121 mL/min. Data are average 6 SEM (no. of patients)

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Davis CL, et al. *Liver Transpl* 2002;8(3):193-211

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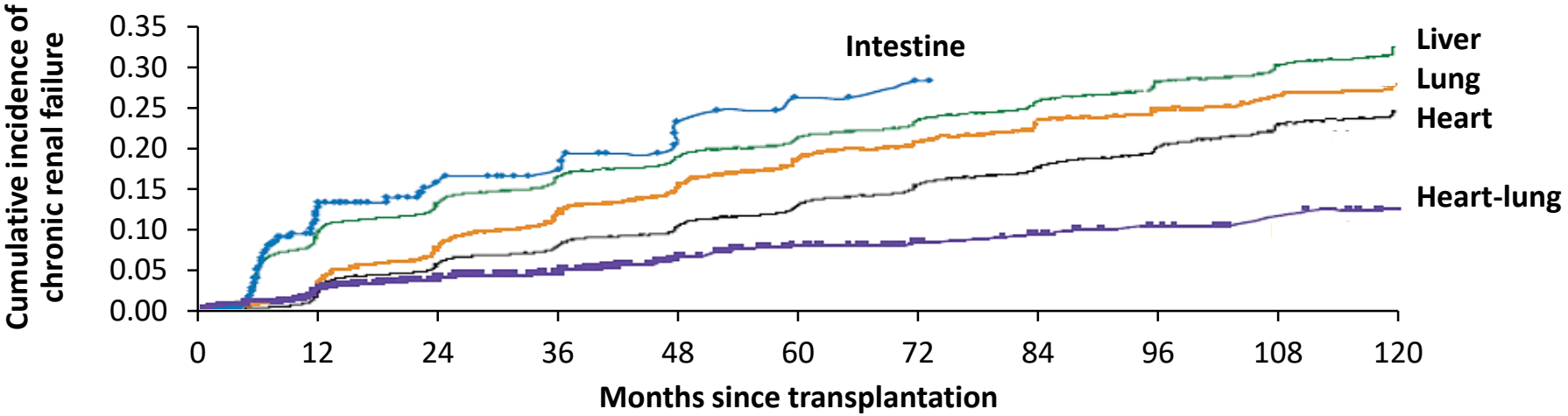
Chronic renal failure in nonrenal organ transplants

Cumulative incidence of chronic renal failure among US nonrenal organ transplants



No. at tisk											
Heart-lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7,997	6,104	4,526	3,096	1,991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9,844	7,345	5,292	3,614	2,261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1,136	745	468	258	133

N = 69 321 persons who received nonrenal organ transplants in US (1990-2000)
Renal function measurements obtained at 6-month intervals during the first year and annually thereafter

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Ojo AO, el al. *N Engl J Med* 2003;349:931-940

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Clinical Scenario

Patient management and follow-up

- Serum creatinine (Cr) peaks on Day 2 at 155 µmol/L
- Day 3 (still off tacrolimus) urine output improves to 70 cc/hr and serum Cr starts to decline
- Low-dose tacrolimus 1 mg BID is reintroduced and titrated to a trough level of 5–7 µg/L

Take Home Messages

- Renal function is often worse than it appears in patients with decompensated liver cirrhosis
- Early AKI is highly prevalent post liver transplant, but risk factors have been identified that help predict which patients are most vulnerable
- Liver transplant patients are uniquely sensitive to CNIs in the immediate post-op period
- Strategies exist to minimize post-op renal injury

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