HCC and Post-Transplant Malignancy

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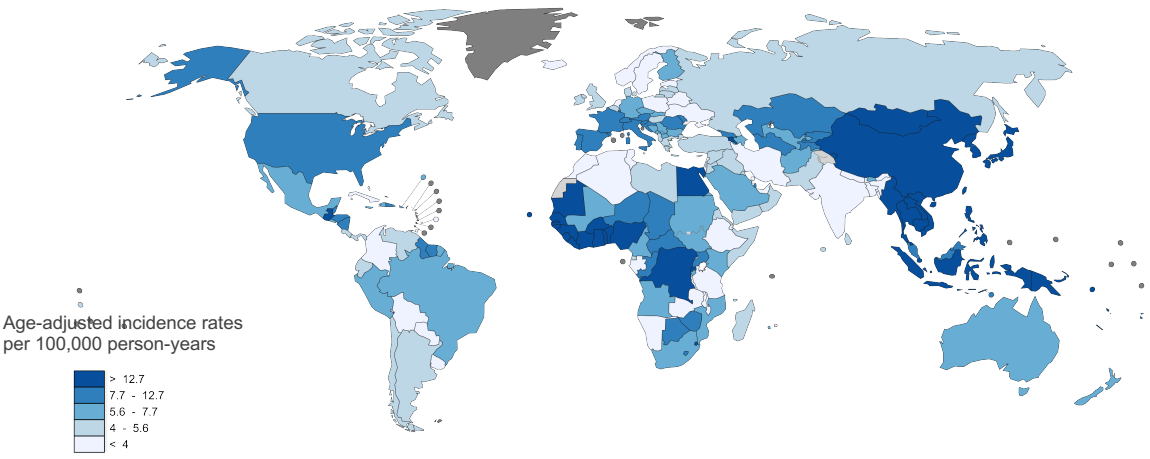
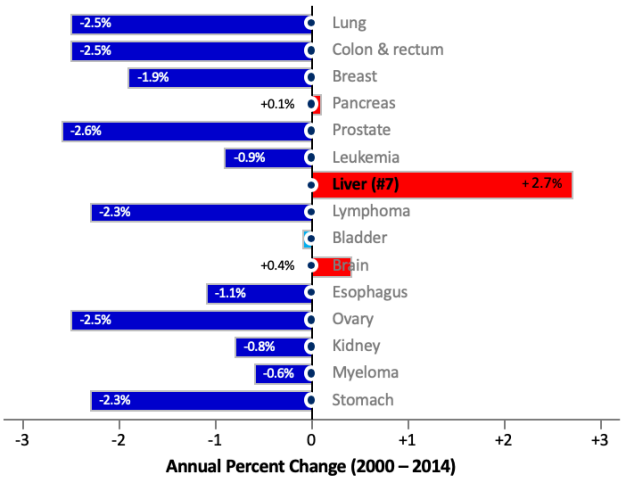
Hepatocellular carcinoma is the 4th leading cause of cancer-related death worldwide



GLOBOCAN 2012

HCC mortality in the United States is increasing

Top 15 causes of cancer death United States 2000-2014



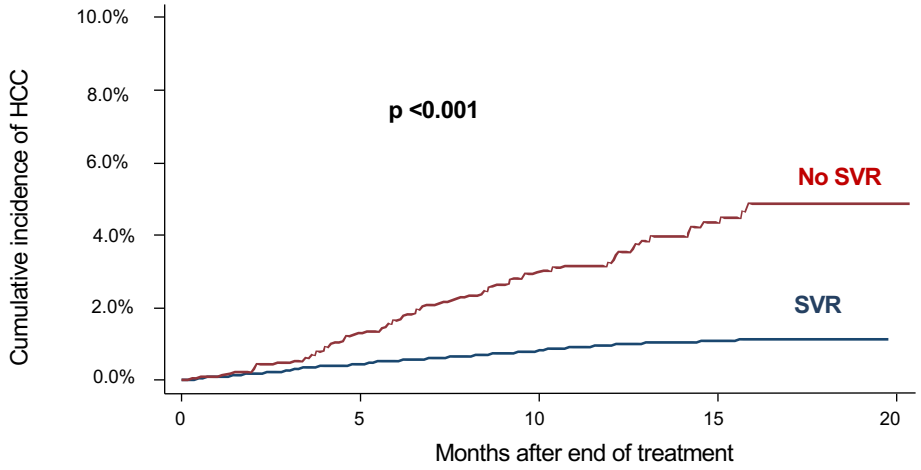
http://seer.cancer.gov

Chronic HBV and cirrhosis are primary at-risk groups

Population Group	Annual incidence
HBV carriers	
Asian male ≥40 years	0.4 – 0.6%
Asian female ≥50 years	0.3 – 0.6%
Blacks at younger age	Occurs at younger age
Family history of HCC	Higher than w/o family history
Cirrhosis	3 – 8%
Cirrhosis	
Hepatitis C	3 – 5%
Primary biliary cirrhosis	3 – 5%
Hemochromatosis	>1.5%
Alpha-1 antitrypsin	>1.5%
Other (alcohol and NASH)	Unknown

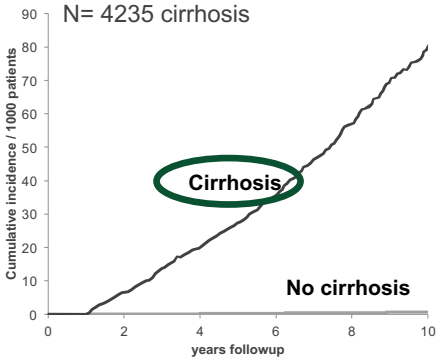
Marrero et al. Hepatology 2018

DAA-based sustained viral response reduces, but does not eliminate, HCC incidence in hepatitis C cirrhosis

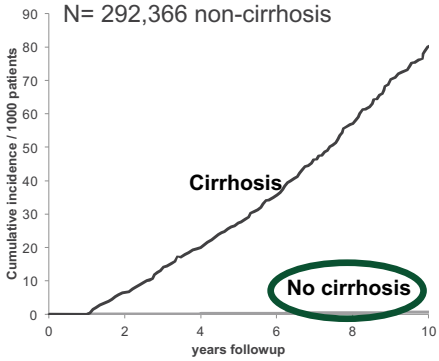


Kanwal et al. Gastro 2017

HCC risk in NASH primarily restricted to those with cirrhosis



1.06 per 100 patient-years

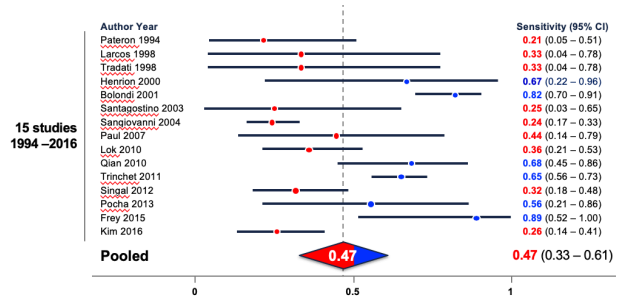


0.008 per 100 patient-years

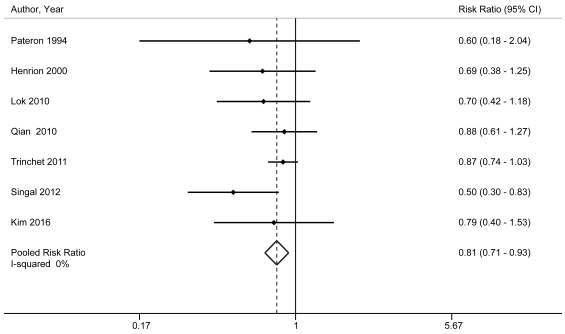
NAFLD defined by exclusion of other etiologies (2004- 2008)

Kanwal et al. Gastro 2018

HCC surveillance recommended using ultrasound +/- AFP



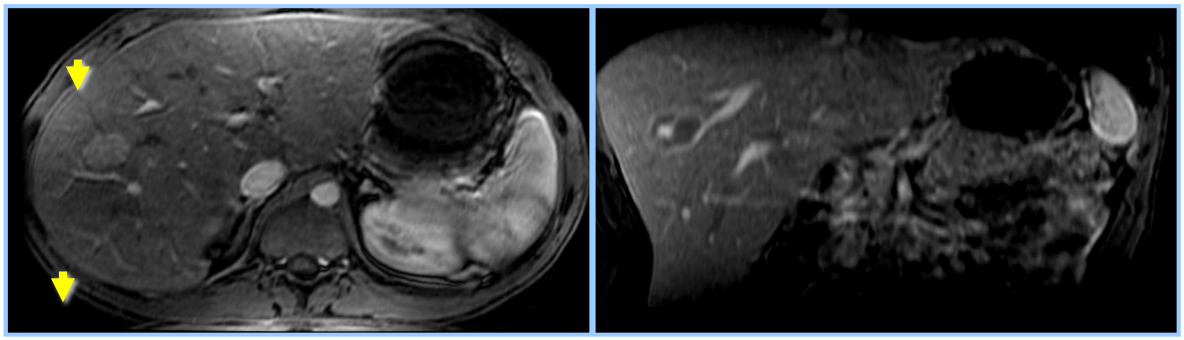
Ultrasound operator dependent and likely suboptimal sensitivity when used alone



Sensitivity of US +/- AFP for early HCC: 63% vs. 45% (*p*=.002)

Tzartzeva et al. Gastro 2018

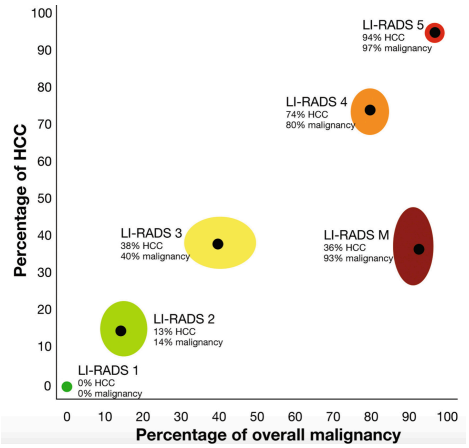
HCC diagnosis typically made by characteristic imaging



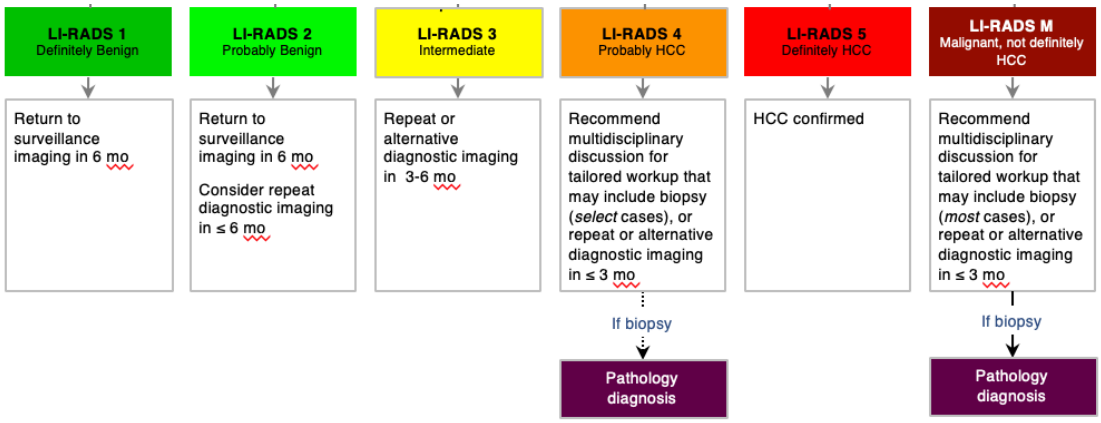
"Arterial enhancement and delayed washout"

LI-RADS provides nomenclature for describing liver lesions

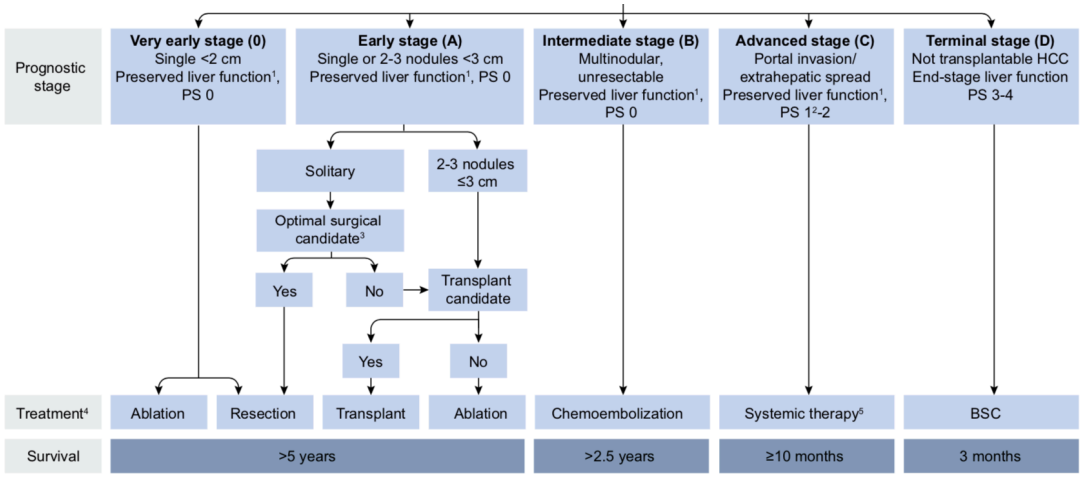
LI-RADS Category	Concept and Definition
LR-1 **Definitely Benign**	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2 **Probably Benign**	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3 **Intermediate probability for HCC**	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4 **Probably HCC**	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5 **Definitely HCC**	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V **Definitely HCC with Tumor in Vein**	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M **Probable malignancy, not specific for HCC**	**Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC. **Definition:** Observation with one or more imaging features that favor non-HCC malignancy.
LR-Treated **Treated Observation**	**Concept:** Loco-regionally treated observation. **Definition:** Observation that has undergone loco-regional treatment



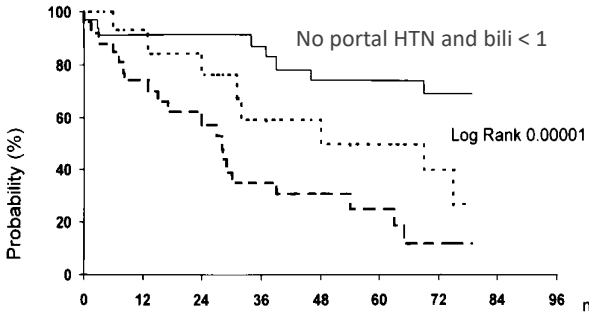
LI-RADS categories are linked to treatment recommendations



BCLC staging system linked to treatment algorithm, with curative treatments restricted to early stage HCC

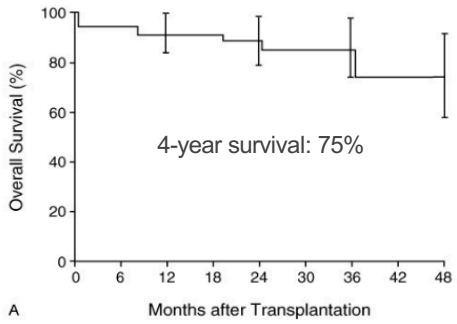


Curative therapy improves survival in well-selected patients



Unifocal lesions of any size in those w/o portal HTN

Surgical resection is treatment of choice in non-cirrhotic patients and those with minimal to no portal HTN

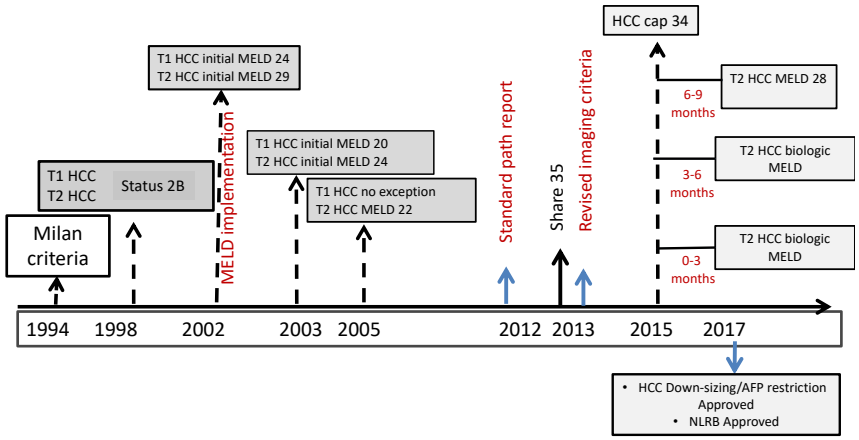


Milan criteria: 1 lesion <5 cm or 2-3 lesions <3 cm each

Transplant is treatment of choice in patients with unresectable disease

Llovet et al. Hepatology 1999
Mazzafeero et al. NEJM 1996)

Timeline of Changes in UNOS Policy

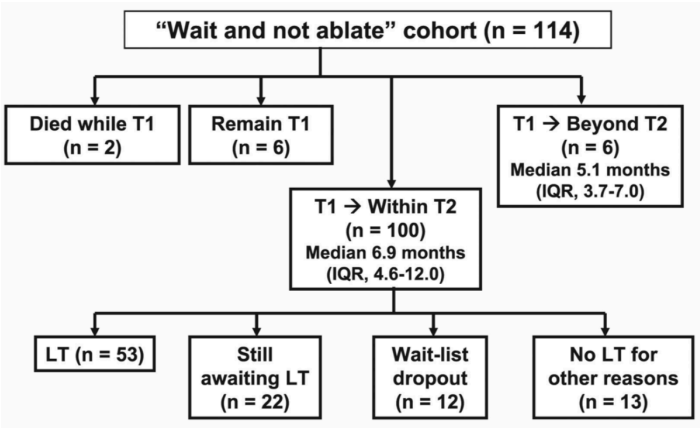


Current Policy

1) Six-month waiting period*
2) Median MELD – 3 points
3) Downstaging eligible for exception

*Salvage transplant patients do not need to wait 6 months if original tumor was within Milan Criteria

Is "wait and not ablate" a good strategy for T1 lesions?

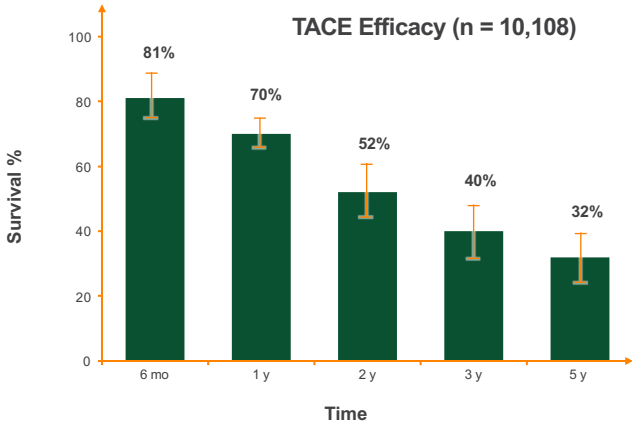


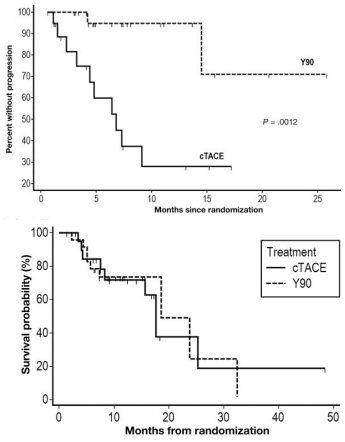
Probability of rapid progression was 4.4% and 9.0% at 6- and 12-months

Predictors of rapid progression included Hispanic etiology and alcohol-related cirrhosis

Mehta et al Liver Transplantation 2016

Locoregional therapy improves survival in intermediate stage HCC



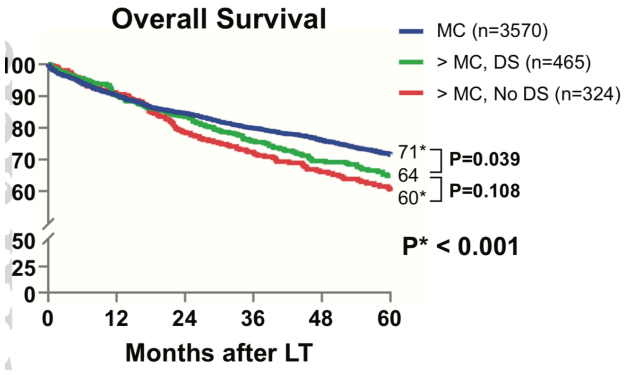


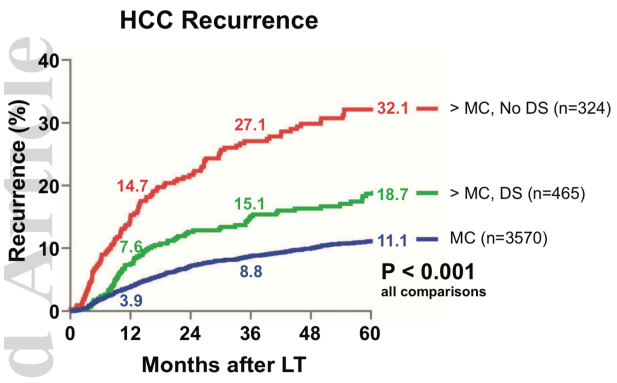
RCT of TARE vs. TACE (n=45)
Time to progression: >26 vs.6.8 months
Median survival: 17.7 vs. 18.6 months

Lencioni et al. Hepatology 2016
Salem et al. Gastro 2016

Downstaging larger tumors can result in good outcomes

Multicenter study of patients undergoing LT from 2002 - 2013





Kardashian et al. Hepatology (in press)

Downstaging incorporated into transplant criteria

- Eligibility for downstaging protocol:
  - One lesion >5 cm and ≤8 cm
  - Two or three lesions each <5 cm and total diameter of all lesions ≤8 cm
  - Four or five lesions *each <3 cm and total diameter of all lesions ≤8 cm*
- *Candidates who are eligible and then complete locoregional therapy must be successfully downstaged into T2 (Milan) criteria to receive a MELD exception* ***without need for special case.***

Patients with tumors beyond UNOS-DS can still be transplanted but are not eligible for exception points

Expanding landscape of first-line and second-line systemic therapies for advanced HCC

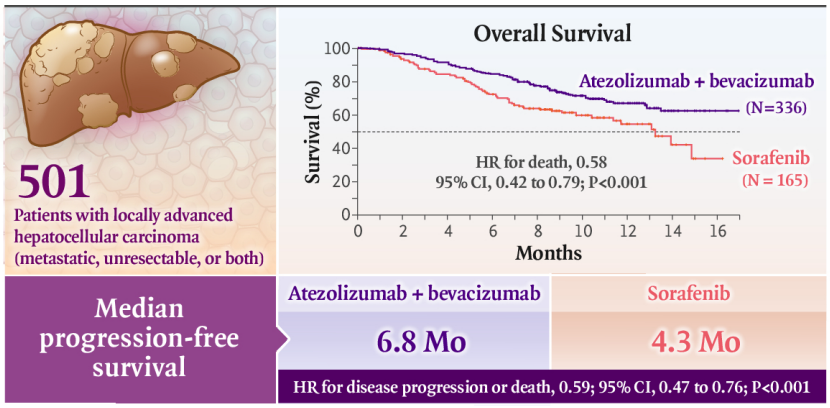
Advanced (BCLC C)

→ **Sorafenib* or Lenvatinib** → **Regorafenib or Nivolumab* or Pembrolizumab or Cabozantinib or Ramucirumab****

** If AFP > 400 ng/mL

* Safety data exists for use in patients with Child B cirrhosis

Atezolizumab/Bevacizumab new standard of care for advanced HCC



Patients were required to have EGD within 6 months and "adequate control" of varices

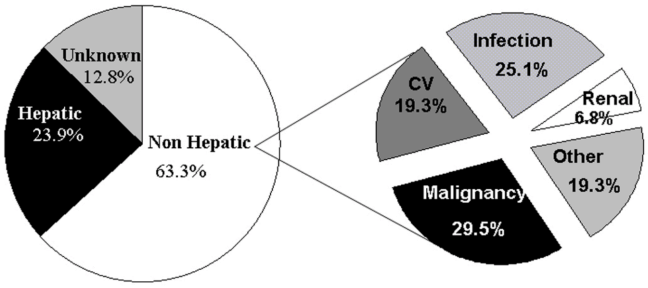
Finn et al. NEJM 2020

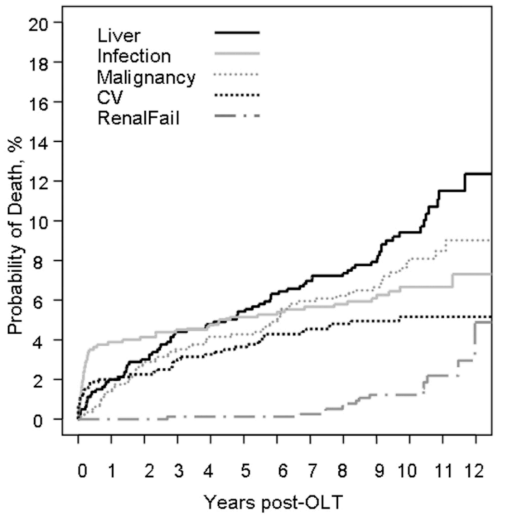
Multidisciplinary care improves HCC outcomes

Study	# Patients	Description	Outcomes
Serper 2017	3988	Multi-specialty evaluation or tumor board	Increase HCC treatment receipt and improve survival
Yopp 2014	355	Single day MDT clinic and conference	Improve early detection, curative treatment, time to treatment, and survival
Zhang 2013	343	Single day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang 2008	183	Fluid referrals and joint conference	Improve early detection, curative treatment, and survival

Malignancy is a common cause of post-LT mortality

Multi-center NIDDK OLT database
Over median 10 year f/u, 327 of 798 LT recipients died
Survival at 1-, 3, and 5-years were 87%, 79% and 75%



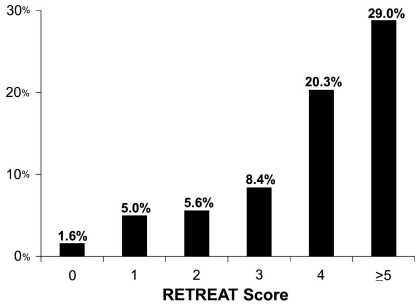


Watt et al. Am J Transplant 2010

Recurrent HCC and Post-LT Surveillance

Variable	RETREAT Score Points
AFP	
0 – 20	0
21 – 99	1
100 – 999	2
>999	3
Microvascular invasion	2
Tumor number plus diameter	
0	0
1 – 5	1
5 – 9.9	2
>9.9	3

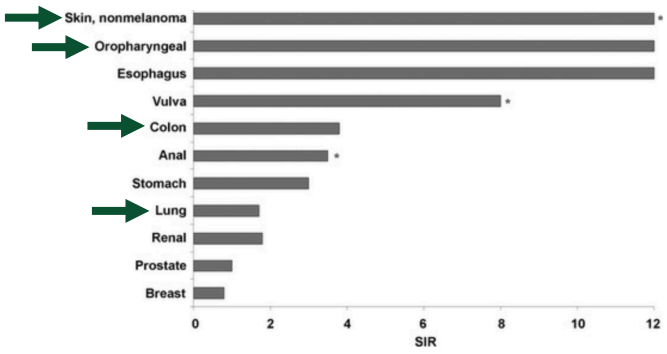
RETREAT score highlights possibility of risk stratification for post-LT recurrence and tailoring surveillance strategies to individual risk



Retreat Score	Possible surveillance strategy
0	No surveillance
1-3	Semi-annual * 2 years
4	Semi-annual * 5 years
5+	Quarterly * 2 years then semi-annual for years 3-5

Mehta et al. Am J Transplant 2018

Non-melanoma skin cancer is most common *de novo* solid malignancy after liver transplantation

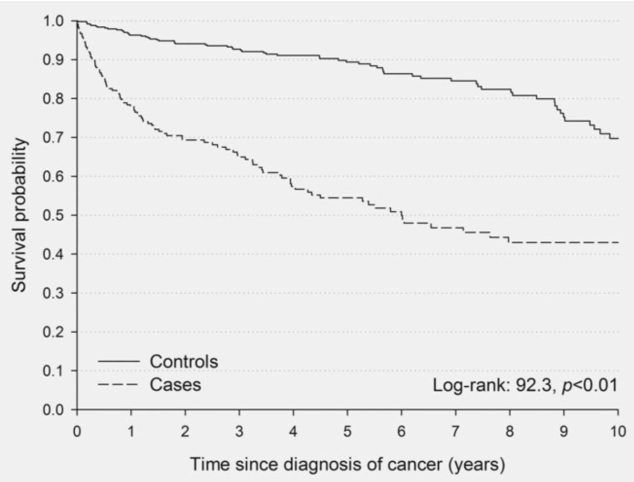


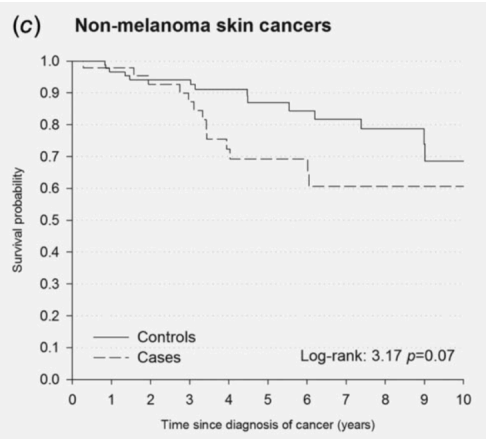
Risk Factors for solid malignancies

Age
Sex
Smoking
LT for alcohol-related cirrhosis or PSC
Excess immunosuppression
Sun exposure
Infections
- HHV8 for Kaposi's sarcoma
- EBV for nasopharyngeal carcinoma
- HPV for cervical, vulvar, anal, and oropharyngeal cancer
- HBV for hepatocellular carcinoma

Chandok et al. Liver Transplant 2012

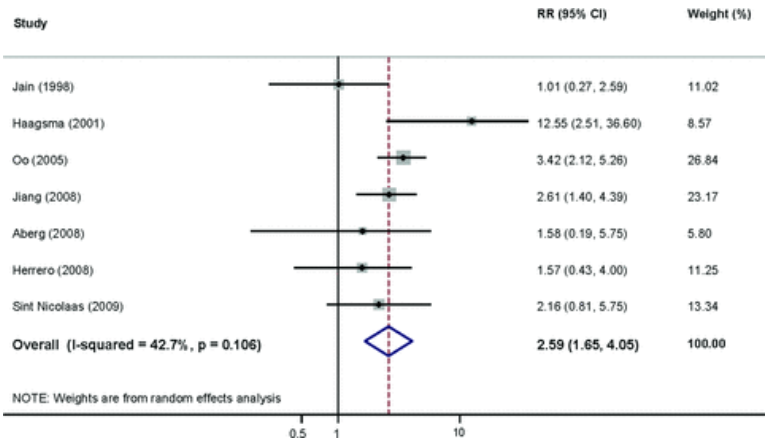
Patients with post-LT malignancy (except non-melanoma skin cancer) have worse survival





Taborelli et al. Int J Cancer 2019

Post-LT patients have higher risk of colon cancer



Incidence rate 119 per 100,000 person-years post-LT vs. 77.9 in age-matched controls

Majority CRC cases occur in patients with PSC and IBD

Although higher risk in non-PSC patients, unclear if warrants increased CRC screening intensity

Post-transplant lymphoproliferative disorder

- Standardized incidence ratio of PTLD in post-LT patients versus general population is ~7-8
  - However incidence lower than other solid organ transplants given less immunosuppression
- Incidence greatest in first 12-18 months
  - Risk factors include recipient age < 18 years, degree of immunosuppression, and EBV mismatch (donor positive – recipient negative)
- Clinical symptoms range from infectious mononucleosis to systemic, high-grade monoclonal lymphoma
  - Elevated LDH and rising EBV titers can help with diagnosis in some patients
  - Definitive diagnosis is typically made by biopsy
- First step is reduction of immunosuppression (typically by ~25-60%)
  - Can produce tumor responses in ~50% of patients within 2-4 weeks, particularly if early
- Other therapies: Rituximab (2nd line), chemotherapy, radiation, and surgery

Cancer Prevention/Surveillance Recommendations

- Recommendations for smoking cessation and limiting alcohol intake
- Routine use of sunscreen and dermatologic exams with low threshold to biopsy suspicious lesions
- Adherence to other age-appropriate screening recommendations
  - Cervical cancer via pelvic exam and PAP, breast cancer via mammography
  - Patients with PSC and IBD should undergo annual colonoscopy; otherwise recommendations per average-risk population (e.g. q10 years in absence of family hx)
  - Consider lung cancer screening in those with sufficient smoking history (~30 pack year history)
  - Can consider prostate cancer screening
  - Can consider head-neck exams by ENT if smoking history and history of alcohol-related liver disease

Management of patients with post-LT malignancy

- Can consider sirolimus or everolimus-based regimen for patients at high risk of HCC recurrence
- Minimize immunosuppression as tolerated
- Surgery or locoregional treatment (e.g. radiation) for oligometastatic disease
- Checkpoint inhibitors are high risk and should be avoided if possible
  - Graft loss observed in ~1/3 of patients
- Multidisciplinary management is key to optimize outcomes

Summary

- HCC incidence and mortality increasing in the United States
  - Increasingly common populations are post-SVR and NASH cirrhosis
- Diagnosis is often made radiographically without need for biopsy
- Curative treatments available for early HCC
  - Surgical resection treatment of choice in patients without cirrhosis or without portal HTN
  - Transplant cure for cirrhosis and HCC, with eligibility expanded to UNOS-downstaging criteria
- Advances in treatment options for locoregional and systemic HCC
- Malignancy common cause of post-transplant mortality
  - Surveillance for recurrence of HCC important
  - Non-melanoma skin cancer most common malignancy so sunscreen/skin exams critical
  - High level of suspicion for PTLD particularly if early post-LT and EBV mismatch
  - Cornerstone of treatment is minimizing immunosuppression
  - Should be cautious re: checkpoint inhibitors (immunotherapy) in post-transplant patients