

HCC' de Profilaksi, Erken Tanı, Tarama ve Tedavi Yaklaşımı

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Konuřmamda

❖ Erken Tanı...Tarama

- ✓ Kimi? Ne zaman? Ne sıklıkla?
- ✓ Hangi yöntemle?

❖ Tanısal Yaklaşım

❖ Tedavi Yaklaşımı

❖ Profilaksi

- ✓ Geliřmeyi önlemek
- ✓ Rekürensisi önlemek

✓ AASLD-2017

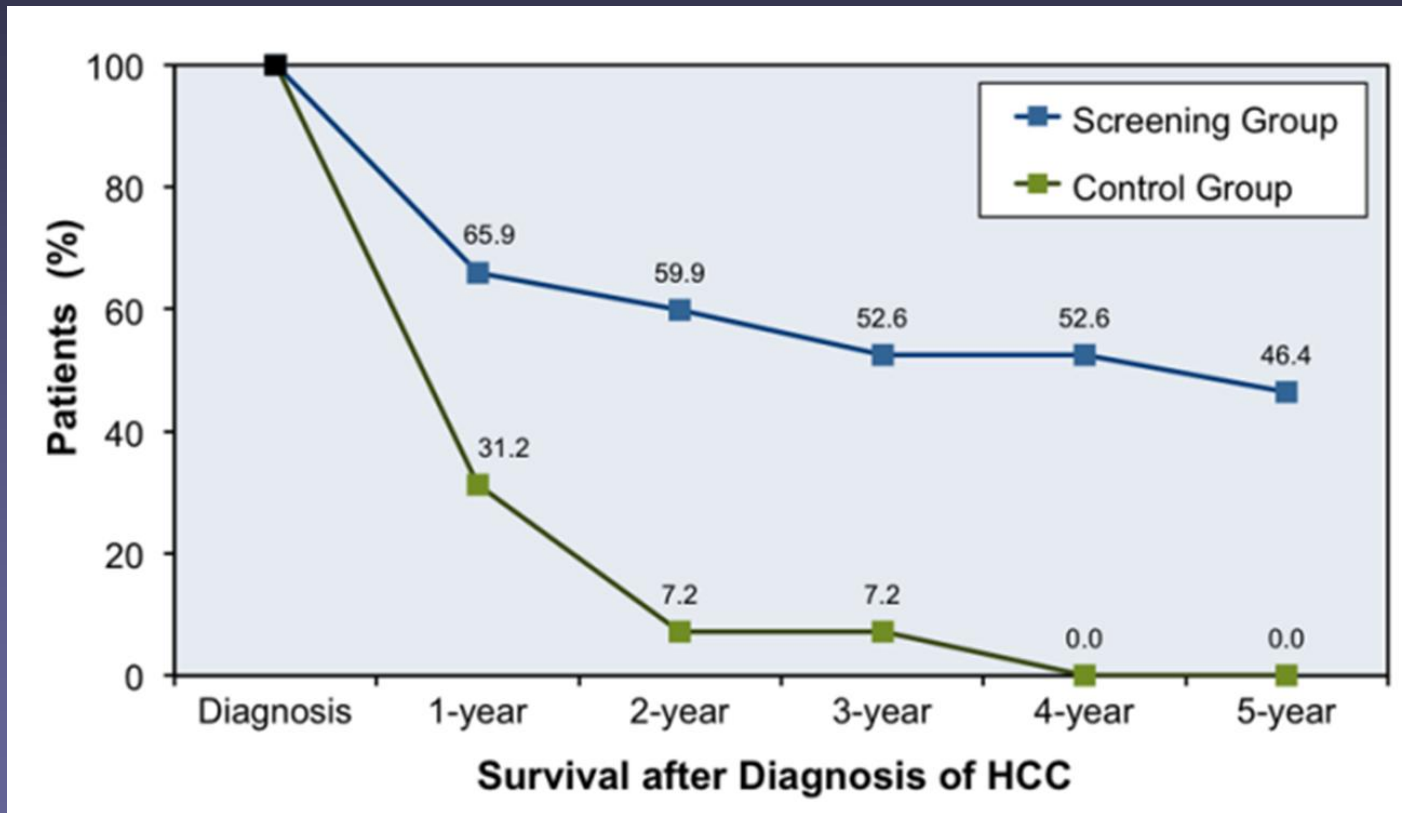
✓ APASL-2017

Erken Tanı için Tarama Şart

- ❖ Taramada temel amaç semptomlar çıkmadan vakaları yakalamak
- ❖ HCC erken yakalanması gereken bir kanser
 - ✓ Semptomatik vaka 5 yıllık yaşam (%0-10)
 - ✓ Asemptomatik vaka % 50 den fazla hatta kür var

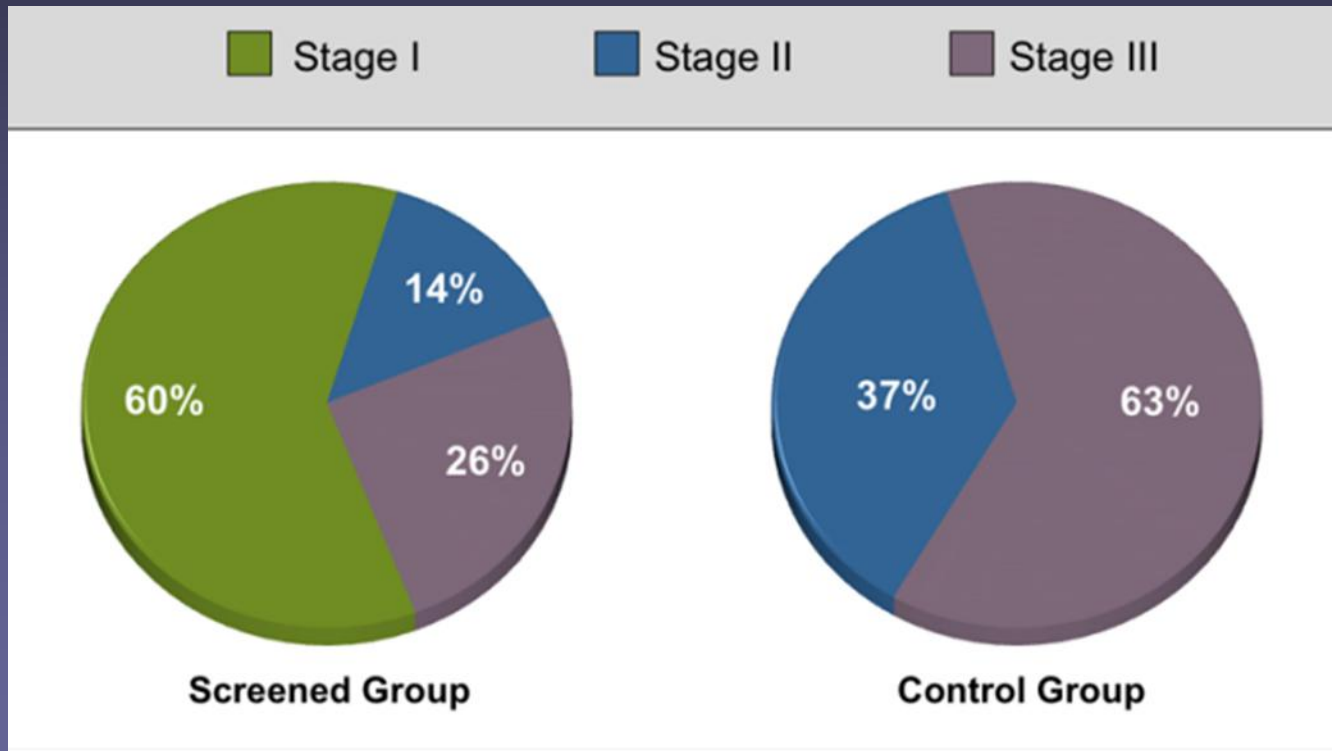
Tarama İşe Yarıyor mu?

- ❖ n=18000 hasta (çoğu HBV)
- ❖ RCT bir çalışma



Tarama İşe Yarıyor mu?

- ❖ n=18000 hasta (çoğu HBV)
- ❖ RCT bir çalışma



HCC-Tarama

Doğru Test

Uygun Hasta



HCC-Tarama

Dođru Test

- ✓ Yıllık maliyeti 50.000 dolardan az olacak
- ✓ Yaşanı 90-100 gün uzatacak (3 ay)

Uygun Hasta

- ❖ Yıllık HCC geliştirme riskine bakılarak karar verilmeli
 - ✓ HBV için %0,2' nin üzeri
 - ✓ Kronik HCV ve Siroz için yıllık HCC riski >%1,5

EASL, Journal of Hepatology 2012;56:908-943

AASLD, Hepatology;53,3,2011

HCC-Tarama

- ✓ HCV için $> \%1,5$
- ✓ HBV için $> \%0,2$
- ✓ Siroz için $> \%1,5$

❖ Uygun Hasta

❖ Yıllık HCC geliştirme riski

- ✓ 40 yaş altı HBV taşıyıcı $< \% 0,2$
- ✓ HBV 70 yaş üzeri $\% 1$
- ✓ HBV Sirotik hastada $\%2,5$
- ✓ Avrupalı hastalarda $\% 0,1-0,4$
- ✓ Anti-HBs geliştirmiş 40 yaş üzeri Asyalı hastada $\%0,2$
- ✓ OİH e bağlı siroz olan bireyde $\% 1,1$
- ✓ Siroz gelişmemiş kronik HCV de $< \% 1,5$

EASL, Journal of Hepatology 2012;56:908-943

AASLD, Hepatology;53,3,2011

Kimler Taranmalı?

✓ AASLD Guideline

- ❖ Yıllık HCC geliştirme riski HCV için %1,5 ve HBV için %0,2' nin üzerinde ise tarama önerilir

Table 3. Groups for whom HCC surveillance is recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Surveillance recommended		
Population group	Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)	Incidence of HCC
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/ year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/ year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

- ❖ Child C siroz transplantasyon listesinde değilse tarama yok

Kimler Taranmalı?

✓ EASL Guideline

Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.

1. Cirrhotic patients, Child-Pugh stage A and B*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

*Evidence 3A; strength B1;

**evidence 3D; strength B1;

***evidence 1B; strength A1 for Asian patients; evidence 3D; strength C1 for Western patients;

****evidence 3D; strength B1 for Asian patients; evidence 3D; strength B2 for Western patients.

Ne ile Tarayalım?

✓ USG

- ✓ Sensitivitesi %70 Sirozlu hastada erken evrede
- ✓ Sensitivitesi %90 Sirozlu hastada tüm evrelerde
- ✓ Spesifitesi %91 Sirozlu hastada tüm evrelerde

Ne ile Tarayalım?

✓ AFP

Yalancı pozitiflik çok yüksek !!!

❖ HALT-C

- HCC dışı AFP yüksekliği AFP > 20 ng/ml % 16,6

❖ HBV de HCC dışı AFP yükselmesi

- AFP > 20 ng/ml % 45,6

✓ HCC tanısı almış hastalarda AFP < 20 ng/ml % 44,5

J of Hepatol 2005; 43(3):434-441

Liver 1986;6(3)133-137

Am J Gastroenterol 2006;101:524-532

Ne ile Tarayalım ?

❖ AASLD

- 6 ayda bir USG ± AFP

❖ EASL

- 6 ayda bir USG

❖ APASL

- 6 ayda bir USG + AFP

Ne ile Tarayalım?

✓ AASLD

Table 1. Evidence profile for Q 1: Should adults with cirrhosis undergo surveillance for HCC, and if so, which surveillance test is best?

Outcomes	No. of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Early tumor detection rate	10 904 (38 observational studies)	⊕⊕○○ LOW	OR 2.11 (1.88 to 2.33)
Early tumor detection rate (defined early stage using BCLC or Milan criteria)	6348 (23 observational studies)	⊕⊕○○ LOW	OR 2.08 (1.80 to 2.37)
Early tumor detection rate (using BCLC to define early stage)	6573 (6 observational studies)	⊕⊕○○ LOW	OR 1.96 (1.41 to 2.73)
Curative treatment rate	24.374 (34 observational studies)	⊕⊕⊕○* MODERATE	OR 2.24 (1.99 to 2.52)
3-year survival rate*	10 850 (23 observational studies)	⊕⊕⊕○* MODERATE	OR 1.90 (1.67 to 2.17)
Early detection (ultrasound only)	(5 observational studies)	⊕⊕○○ LOW	OR 2.04 (1.55 to 2.68)
Early detection (ultrasound +/- AFP)	(14 observational studies)	⊕⊕○○ LOW	OR 2.16 (1.80 to 2.60)
Receipt of curative treatment (ultrasound only)	(8 observational studies)	⊕⊕○○ LOW	OR 2.23 (1.83 to 2.71)
Receipt of curative treatment (ultrasound +/- AFP)	(24 observational studies)	⊕⊕○○ LOW	OR 2.19 (1.89 to 2.53)

*Upgraded because of large effect size

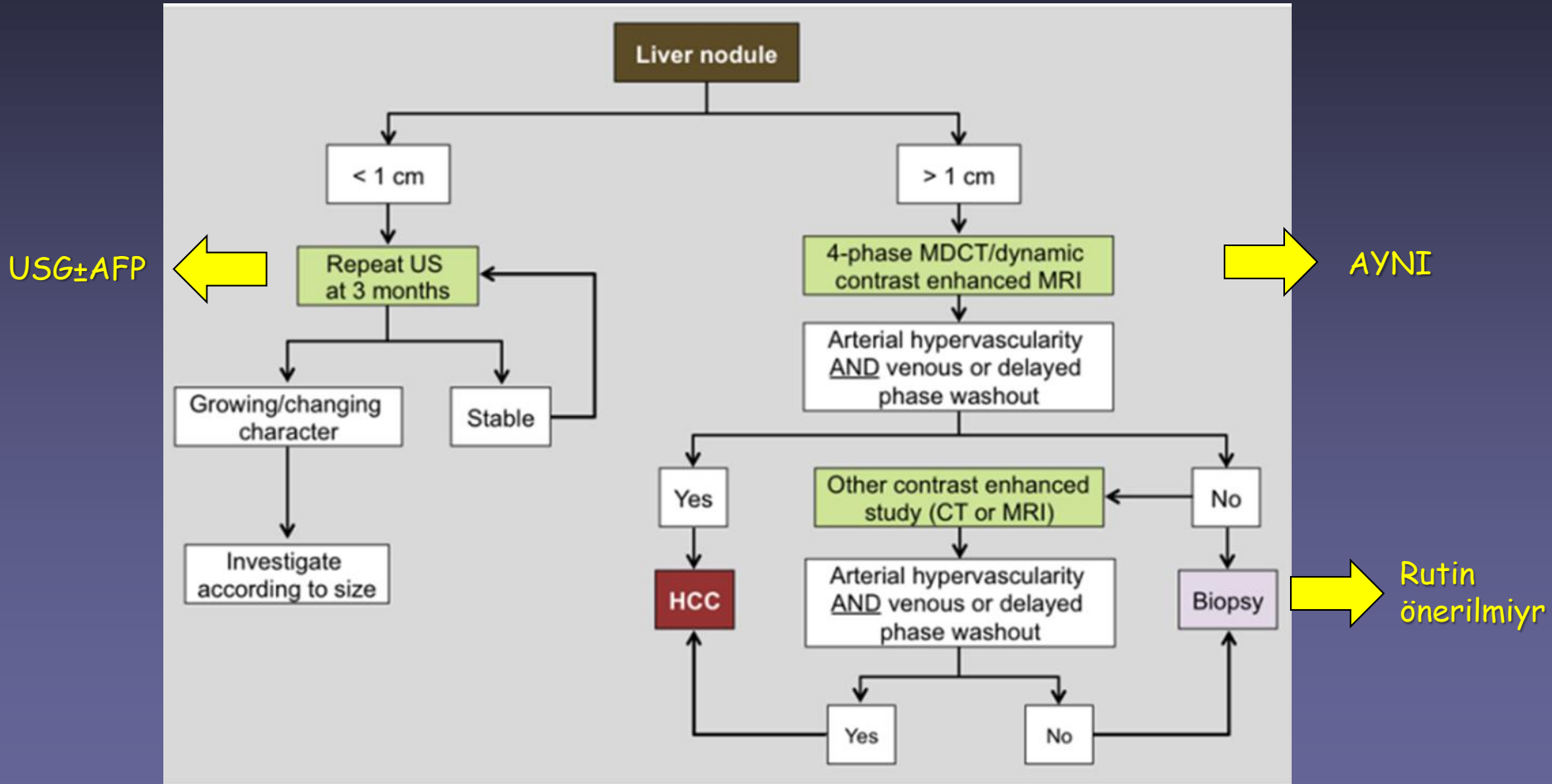
✓ 6 ayda bir USG ± AFP

AASLD, Hepatology;2017 Jan

Tanısal Yaklaşım

Tanışal Yaklaşımlar Farklı (Recall policy)

✓ AASLD



AASLD, *Hepatology*;53,3,2011

AASLD *Hepatology* Jan 2017

3. SHOULD ADULTS WITH CIRRHOSIS AND AN INDETERMINATE HEPATIC NODULE UNDERGO A BIOPSY, REPEATED IMAGING, OR ALTERNATIVE IMAGING FOR THE DIAGNOSTIC EVALUATION?

Recommendation

3A. AASLD suggests several options in patients with cirrhosis and an indeterminate nodule, including follow-up imaging, imaging with an alternative modality or alternative contrast agent, or biopsy, but cannot recommend one option over the other.

Quality/Certainty of Evidence: Very low

Strength of Recommendation: Conditional

3B. AASLD suggests against routine biopsy of every indeterminate nodule

Quality/Certainty of Evidence: very low

Strength of Recommendation: conditional

İndetermine Nodül

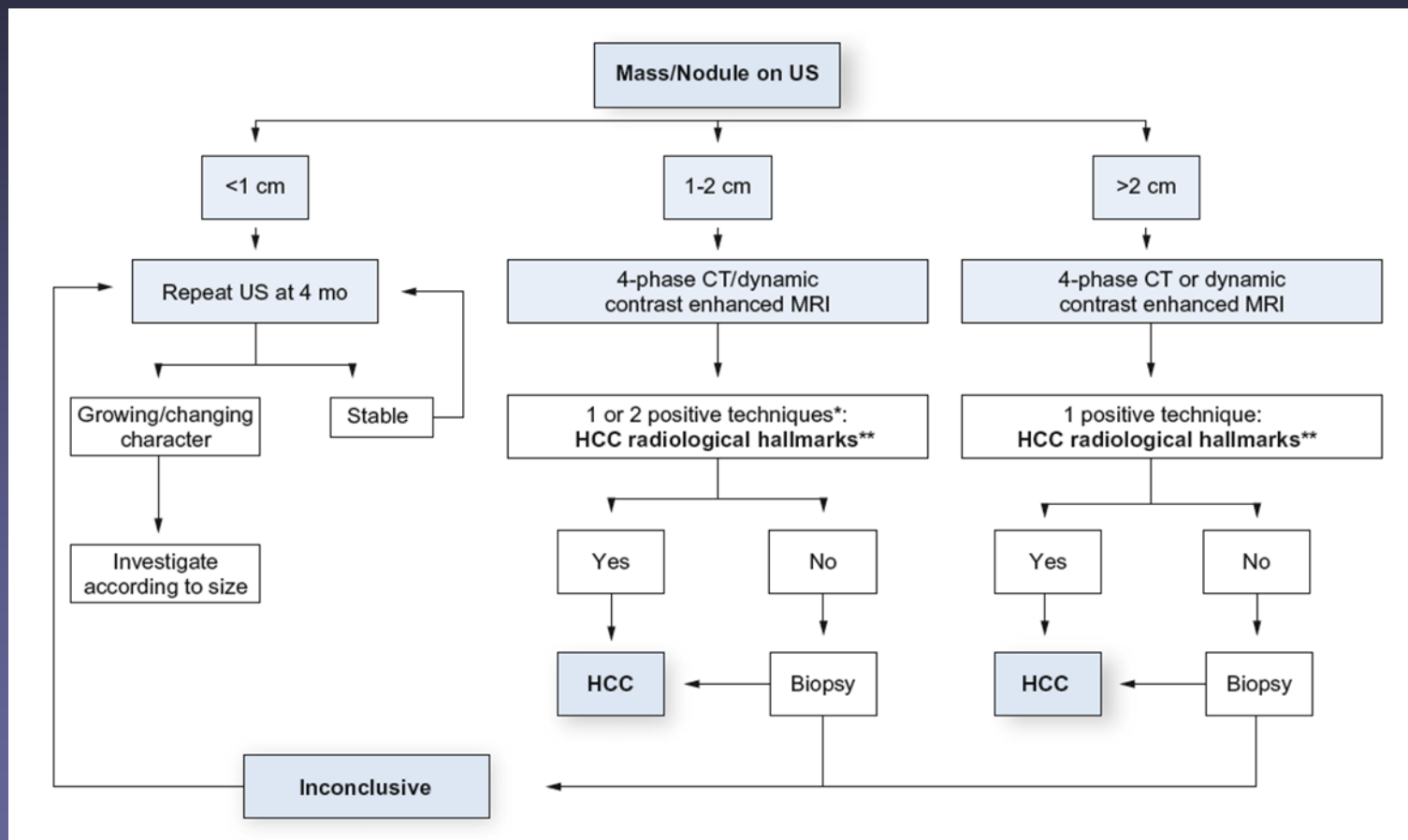
- ✓ Tipik tutulum paterni olmayan /
- ✓ 1 cm den küçük

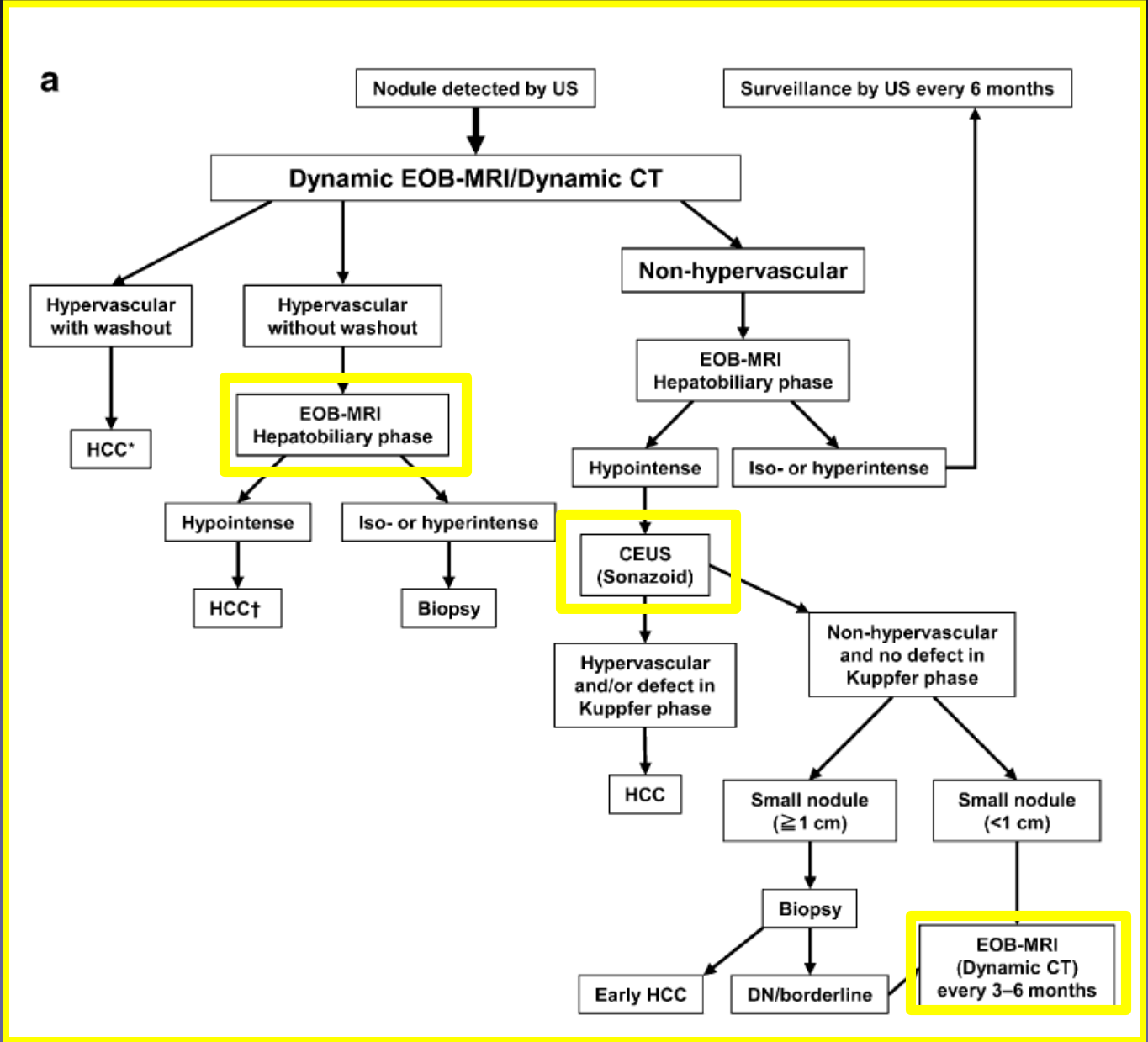
- ❖ 1-2 cm arası lezyonlarda HCC olasılığı %14-23
- ❖ <2cm lezyonlarda bx ile false negatiflik %30
- ❖ CT ve MR - Prob. benign HCC % 0
 - Intermediate prob. HCC %7
 - Prob. HCC %30

Radiology ACo. Liver Imaging Reporting and Data System. 2016. LIRADS. Forner A,. Hepatology. 2008;47(1):97-104. Khalili K, Hepatology.2011;54(6):2048-54.

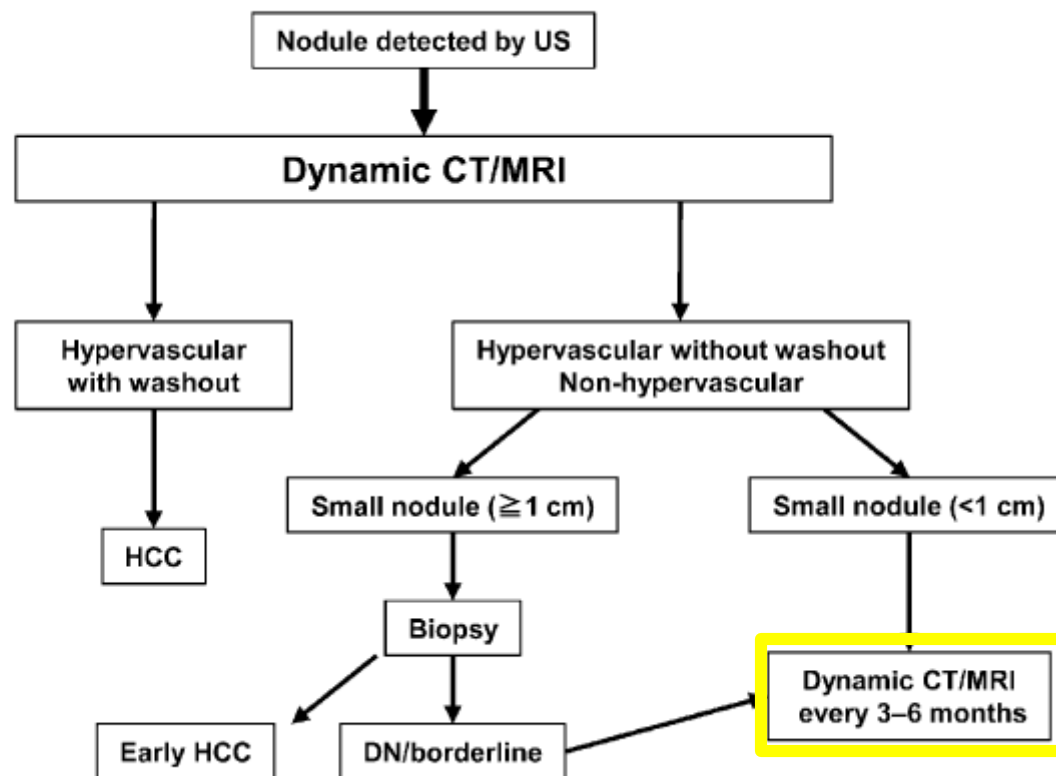
Tanışal Yaklaşımlar Farklı (Recall policy)

✓ EASL





b



Tanısıl Yaklaşımlar Farklı

❖ AASLD

- <1cm lezyonlar takip (USG±AFP)
- >1cm lezyonlar BT/MR
- Biyopsi her hastaya önerilmiyor

❖ EASL

- 1, 1-2, ve 2 cm e göre yaklaşım
- BT/MR ana yöntem
- Arada kalınca biyopsi

❖ APASL

- Boyuta bakmaksızın EOB-MR / BT
- Arada kalınan vaka hipervasküler ise Bx
- Arada kalınan vaka non-vasküler hipointense ise CEUS, Bx veya takip (BT/MR ile)

Tedavi Yaklaşımı

Clinical Practice Guidelines

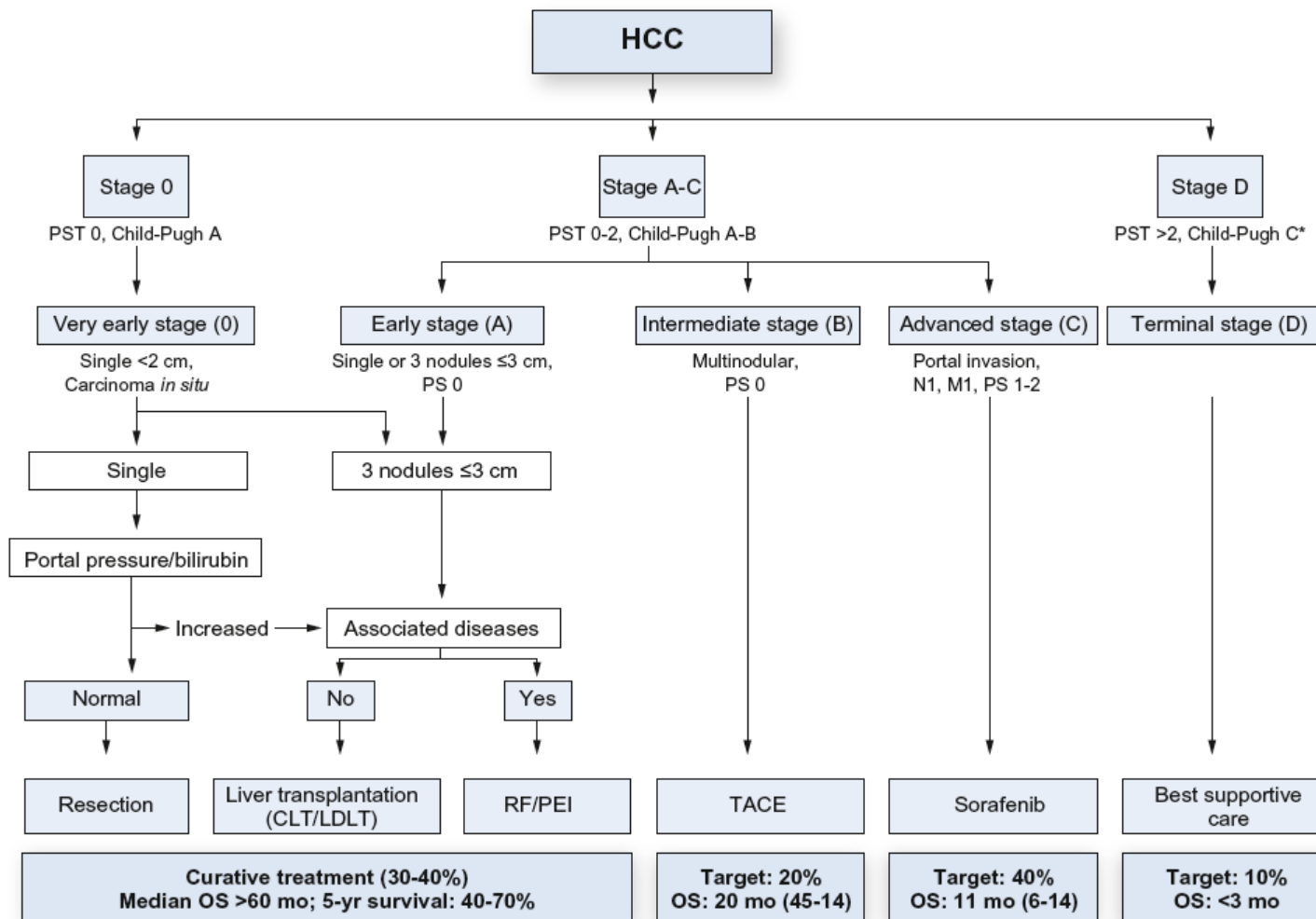
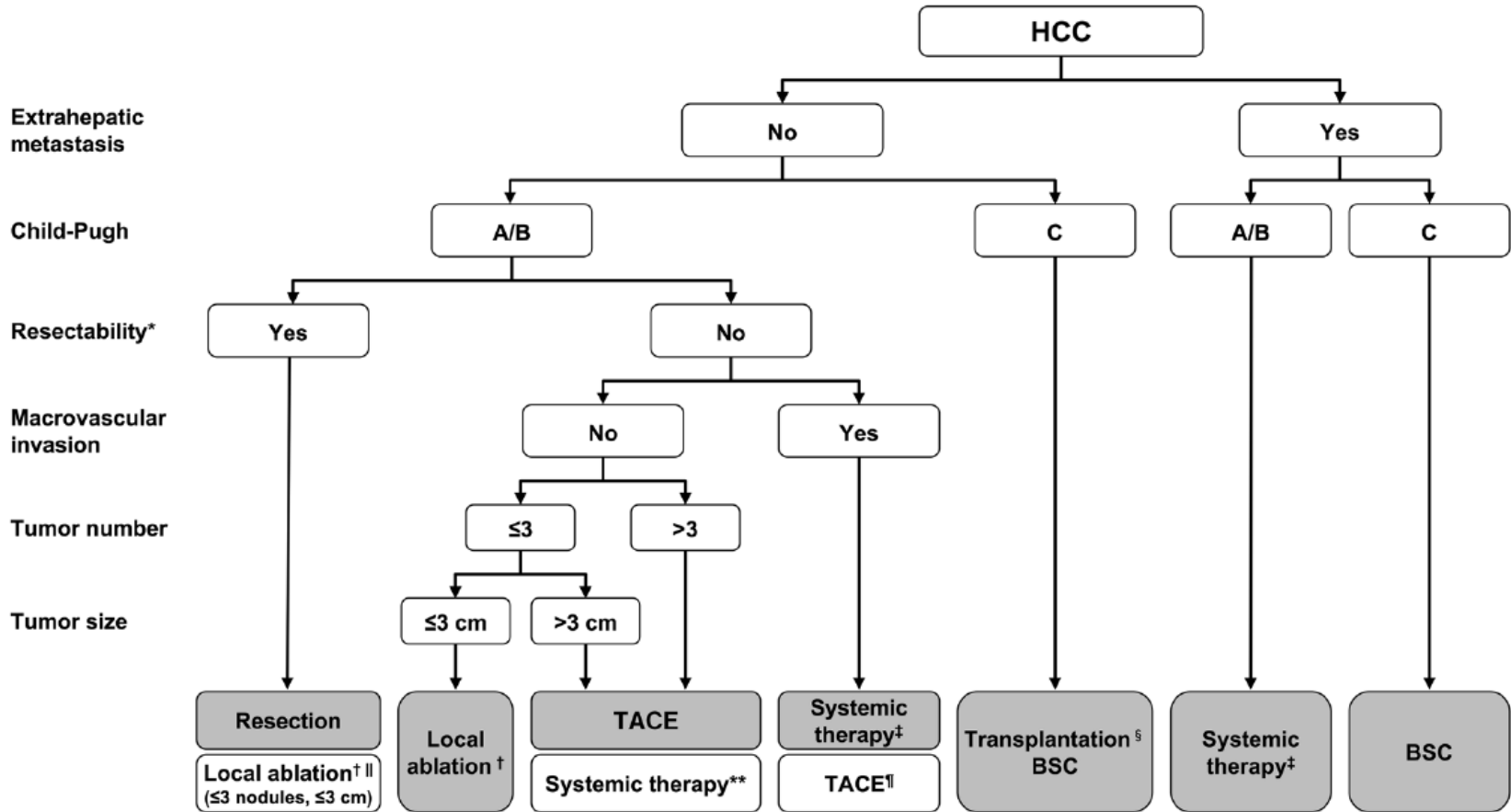


Fig. 3. Updated BCLC staging system and treatment strategy, 2011.

APASL



Standard treatments
 Treatments being widely performed in the field practice of the Asia-Pacific region

AASLD GUIDELINES FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

Julie Heimbach, MD, Laura M. Kulik, MD, Richard Finn, MD, Claude B. Sirlin, MD, Michael Abecassis,
MD, Lewis R. Roberts, MD, and Andrew Zhu, MD, PhD, M. Hassan Murad, Jorge Marrero, MD

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The guideline developers from the AASLD identified key questions that health care providers are faced with frequently in the evaluation and management of patients with HCC. These questions were:

1. Should adults with cirrhosis undergo surveillance for HCC? If, so which surveillance test is best?
2. Should adults with cirrhosis and suspected HCC undergo diagnostic evaluation with multiphasic CT or multiphasic MRI?
3. Should adults with cirrhosis and an indeterminate hepatic nodule undergo a biopsy, repeated imaging, or alternative imaging for the diagnostic evaluation?
4. Should adults with Child's class A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or locoregional therapy?
5. Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy or not?
6. Should adults with cirrhosis awaiting liver transplantation and HCC (T1) be treated or undergo observation?
7. Should adults with cirrhosis awaiting liver transplantation and HCC (Organ Procurement and Transplantation Network [OPTN] T2) undergo transplant alone or transplant with bridging therapy while waiting?
8. Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) be transplanted following downstaging to within Milan criteria?
9. Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?

Table 2. Clinical Questions Evaluated

Question	Population	Intervention	Comparison	Outcome	
1	Adults with cirrhosis	Surveillance for HCC	No surveillance	Survival	→ USG ± AFP
2	Adults with cirrhosis and suspected HCC	Diagnostic evaluation with multiphasic CT	Diagnostic evaluation with multiphasic MRI	Sensitivity and specificity	→ Eşit
3	Adults with cirrhosis and an indeterminate hepatic nodule	Biopsy	Repeated or alternative imaging	Sensitivity and specificity	→ Takip/alternatif
4	Adults with Child's class A cirrhosis and stage T1 or T2 HCC	Resection	Local-regional therapy	Survival, recurrence, morbidity	→ Rezeksiyon>LRT
5	Adults with cirrhosis and HCC successfully resected or ablated	Adjuvant therapy	No adjuvant therapy	Survival	→ Hayır
6	Adults with cirrhosis awaiting liver transplantation and T1 HCC	Local-regional therapy	Observation	Survival, progression to T3/waitlist dropout	→ Observation
7	Adults with cirrhosis awaiting liver transplantation and T2 HCC	Bridging therapy	Observation	Survival, progression to T3/waitlist dropout	→ Öneriliyor
8	Adults with cirrhosis awaiting liver transplantation and T3 HCC	Downstaging and transplant	No transplant	Posttransplant survival, recurrence	→ Öneriliyor
9	Adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation	Transarterial chemoembolization	Transarterial radioembolization or external radiation	Survival	→ LRT öneriliyor
10	Adults with Child's A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease	Systemic therapy	Local-regional therapy or no therapy	Survival	→ Sistemik Rx LRT ?

Önleme-Prevention

HCC' yi Önleyebilir miyiz? (Prevention)

❖ Primary prevention

- ✓ Yeni doğanları ve riskli grupları HBV için aşılama
- ✓ Viral hepatitler için bulaş yollarını engelleme

❖ Secondary prevention

- ✓ Antiviral tedavi

❖ Tertiary prevention

- ✓ Başarı ile tedavi edilmiş HCC vakasında rec engellemek

HCC' yi Önleyebilir miyiz?

✓ HBV-OAV Tedavi

Table 4
Prevention of HBV-related HCC by NUCs propensity score studies [29–31,22].

Author	Patients		Follow-up (yr)		HCC % at 5 yr		Relative risk	p Value
	NUC+	NUC–	NUC+	NUC–	NUC+	NUC–		
Wu et al (Taiwan)	21,595	21,595	3.4	5.2	7.3	22.7	0.31 (0.27–0.53)	<.001
Lim et al (Korea)	1792	1792	3.1	8.7	12.0 ^a	–	1.01 (0.80–1.27)	.95
					12.3			
Gordon et al (United States)	820	1851	5.2	5.2	2.4	2.5	0.39 (0.27–0.56)	<.001
Hosaka et al (Japan)	316	316	3.3	7.6	3.7	13.7	0.37 (0.15–0.91)	.03
Kumada et al (Japan)	117	117	12.3	11.6	2.7	11.3	0.28 (0.13–0.62)	.002

^a Entecavir vs Lamivudine.

✓ HCC riskini azaltıyor ancak elimine etmiyor

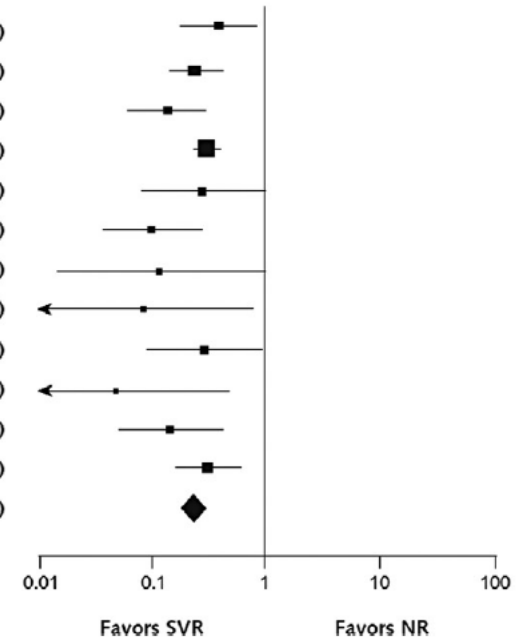
HCC' yi Önleyebilir miyiz?

✓ HCV-SVR

Study, Year (Reference)	log(Hazard Ratio)	SE	Total		Weight, %	Hazard Ratio IV, Random (95% CI)	Hazard Ratio IV, Random (95% CI)
			SVR	NR			
Asahina et al, 2010	-0.944	0.388	686	1356	9.2	0.39 (0.18-0.83)	
Hung et al, 2011	-1.423	0.273	1027	443	15.3	0.24 (0.14-0.41)	
Kawamura et al, 2010	-1.985	0.407	1081	977	8.5	0.14 (0.06-0.31)	
Kramer et al, 2011	-1.182	0.126	4292	10 276	31.2	0.31 (0.24-0.39)	
Kurokawa et al, 2009	-1.277	0.631	139	264	4.0	0.28 (0.08-0.96)	
Okanoue et al, 2002	-2.294	0.512	375	586	5.8	0.10 (0.04-0.28)	
Osaki et al, 2012	-2.130	1.053	185	197	1.5	0.12 (0.02-0.94)	
Pradat et al, 2007	-2.481	1.132	87	103	1.3	0.08 (0.01-0.77)	
Sinn et al, 2008	-1.246	0.596	296	194	4.4	0.29 (0.09-0.93)	
Takahashi et al, 2011	-3.022	1.163	89	114	1.3	0.05 (0.00-0.48)	
Tateyama et al, 2011	-1.968	0.537	139	234	5.3	0.14 (0.05-0.40)	
Yoshida et al, 1999	-1.164	0.324	789	1568	12.1	0.31 (0.17-0.59)	
Total			9185	16 312	100.0	0.24 (0.18-0.31)	

Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



Taiwandan SVR sağlanmış (ort 53 ay takip)
n=556 non-sirotik vs n=86 sirotik HCV hastası
HCC gelişme %0,68 vs %4,56

Sonuç Olarak

- ❖ Riskli hastalar mutlaka taranmalı
 - ✓ Yıllık HCC riski HBV %0,2 HCV ve sirotikler %1,5
- ❖ AASLD ve APASL 6 ayda bir USG+AFP. EASL USG
- ❖ Nodül tespit edildiğinde yaklaşımlar kılavuzlar arasında farklılıklar gösteriyor
 - ✓ AASLD 1cm, EASL <1, 1-2, >2 cm
 - ✓ AASLD ve EASL da 2. tercih CT ve MR
 - ✓ APASL vaskülariteye göre karar veriyor EOB-MR / BT ve 2. tercih olarak CEUS ve bx ve BT/MR ile takip

Sonuç Olarak

Önleme

- ❖ HBV için aşılama ve bulaş yollarını engelleme en iyi yöntem
- ❖ Antiviral tedavi HCC gelişmesini hem sirotiklerde hem de non-sirotiklerde azaltıyor
- ❖ HCC nüksünü ve mortaliteyi de azaltıyor
- ❖ HCC riskinin devam ettiği unutulmamalı... taramalar devam etmeli

Gelişebilecek Konular

- ❖ Yeni markerlar (proteomics ile)
- ❖ HCC gelişimini tahmin edecek risk skorlama sistemleri
- ❖ KVV sağlanmış HCV hastaları uzun dönem takipleri
- ❖ Non-viral nedenler ön plana çıkacak (2020)
 - ✓ NAFLD sonrası gelişen HCC
 - ✓ Diabet gibi risk faktörlerinin etkisi
 - ✓ Obezite ve metabolik sendrom