Hepatosellüler Karsinom (HCC)Tedavi Seçenekleri

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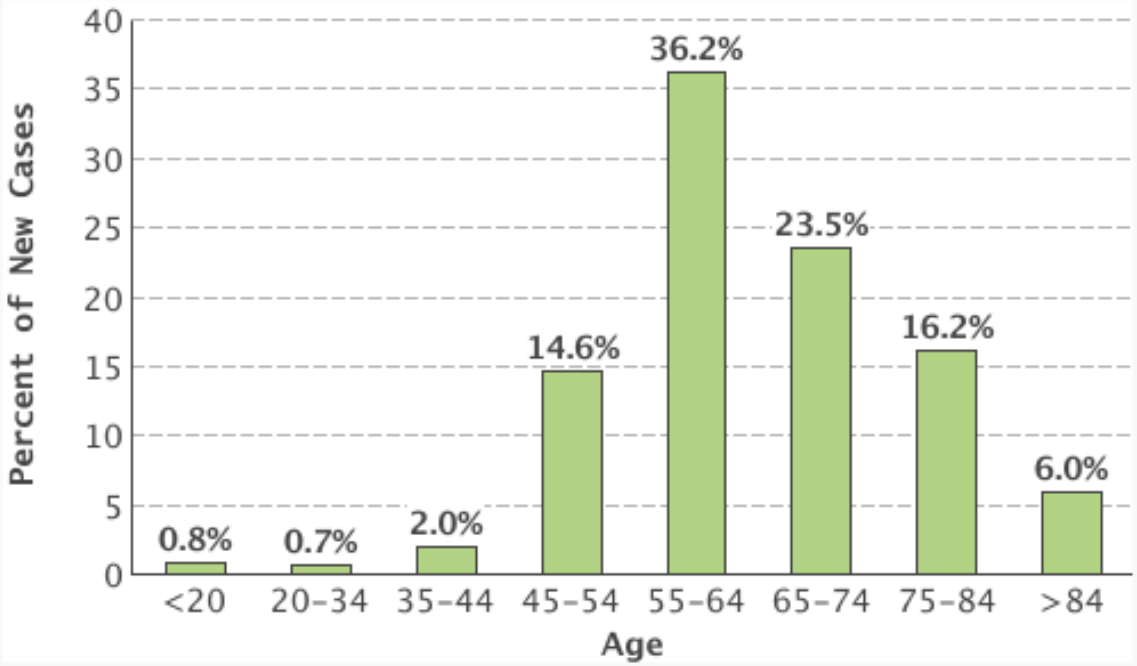
Tıbbi Onkoloji

Hepatosellüler Karsinom İnsidans ve Mortalite

Percent of New Cases by Age Group: Liver and Intrahepatic Bile Duct Cancer



Liver and intrahepatic bile duct cancer is most frequently diagnosed among people aged 55-64.

Median Age At Diagnosis
63

SEER 18 2009-2013, All Races, Both Sexes

Hepatosellüler Karsinom İnsidans ve Mortalite

SEER Stat Fact Sheets: Liver and Intrahepatic Bile Duct Cancer

Expand All | Collapse All

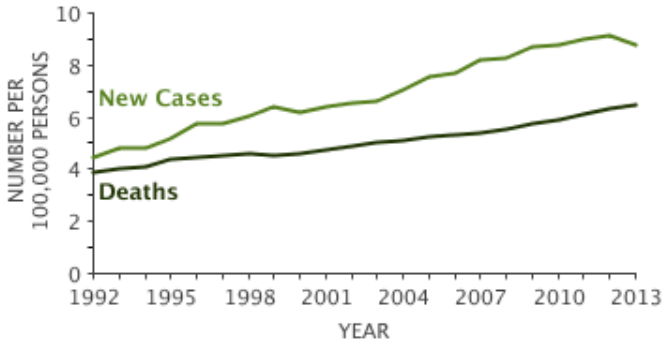
Lifetime risk estimates are not available with the current statistics release, but will be added later when population data for older age groups are available.

Statistics at a Glance

Show Less –

At a Glance

Estimated New Cases in 2016	39,230
% of All New Cancer Cases	2.3%
Estimated Deaths in 2016	27,170
% of All Cancer Deaths	4.6%



Percent Surviving 5 Years

17.5%

2006–2012

Number of New Cases and Deaths per 100,000: The number of new cases of liver and intrahepatic bile duct cancer was 8.4 per 100,000 men and women per year. The number of deaths was 6.1 per 100,000 men and women per year. These rates are age-adjusted and based on 2009–2013 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 0.9 percent of men and women will be diagnosed with liver and intrahepatic bile duct cancer at some point during their lifetime, based on 2010–2012 data.

Prevalence of This Cancer: In 2013, there were an estimated 54,954 people living with liver and intrahepatic bile duct cancer in the United States.

Hepatosellüler Karsinom İnsidans ve Mortalite

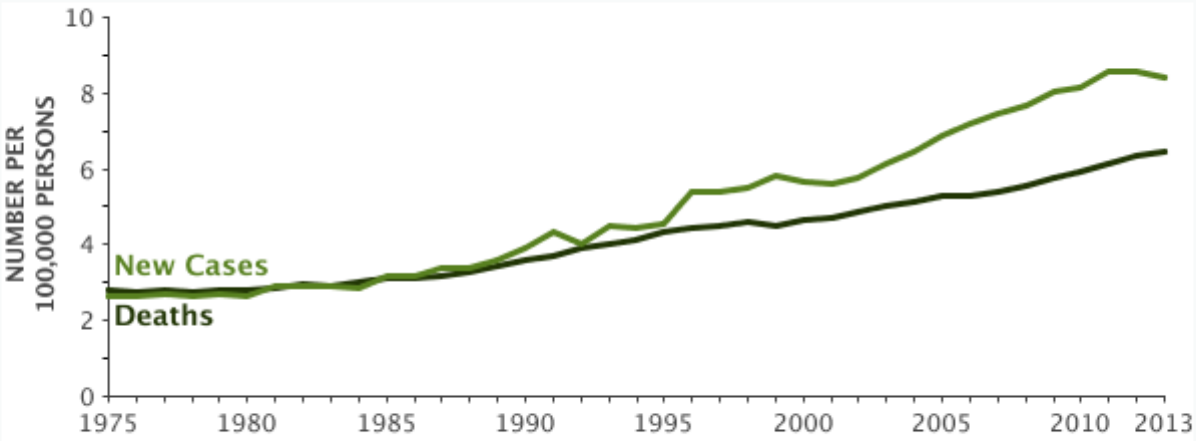
Changes Over Time

Keeping track of the number of new cases, deaths, and survival over time (trends) can help scientists understand whether progress is being made and where additional research is needed to address challenges, such as improving screening or finding better treatments.

Using statistical models for analysis, rates for new liver and intrahepatic bile duct cancer cases have been rising on average 3.0% each year over the last 10 years. Death rates have been rising on average 2.7% each year over 2004–2013. 5-year survival trends are shown below the figure.

New Cases, Deaths and 5-Year Relative Survival

View Data Table

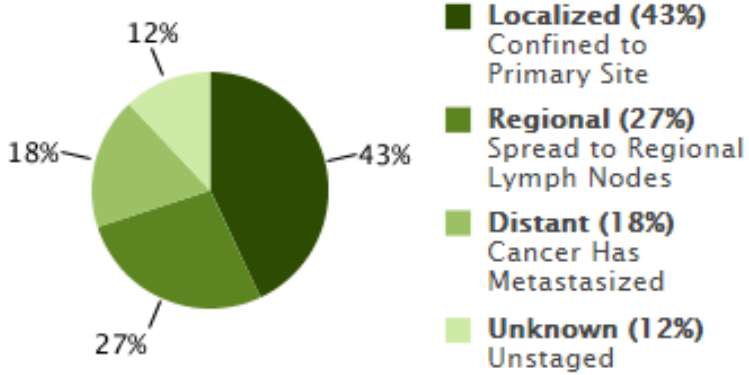


Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	3.0%	3.2%	7.0%	5.3%	5.7%	11.7%	14.5%	18.5%

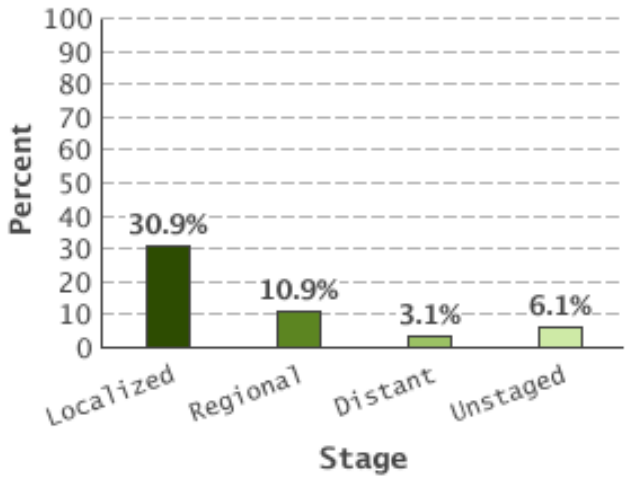
Hepatosellüler Karsinom İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Liver and Intrahepatic Bile Duct Cancer

Percent of Cases by Stage



5-Year Relative Survival



SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

Hepatosellüler Karsinom İnsidans ve Mortalite

HEPATOCELLULAR CARCINOMA

- 3RD cause of cancer-related death worldwide
- Cirrhosis:
  - primary pre-malignant condition
  - Cirrhosis 7th cause of death worldwide
- Cirrhosis from all causes can lead to HCC
  - Viral hepatitis
  - Alcohol
  - NAFLD: non-alcoholic fatty liver disease

Hepatosellüler Karsinom İnsidans ve Mortalite

HEPATOCELLULAR CARCINOMA

ETIOLOGY

- HCV is primary etiology in U.S., Europe, Japan
- Notes on minor etiologies:
  - NASH: risk for HCC with or without cirrhosis
  - Aflatoxin B: *cofactor* with HBV which increases risk
  - Steroids: androgens and OCPs- weak association based on case series and reports

Hepatosellüler Karsinom İnsidans ve Mortalite

HEPATOCELLULAR CARCINOMA

ETIOLOGY

- Notes on minor etiologies *cont'd:*
  - Hemochromatosis
  - α1 antitrypsin deficiency
  - Wilson's disease
  - PCT (*porphyria cutanea tarda*)
  - Primary biliary cirrhosis
  - Autoimmune hepatitis
- ALCOHOL is both a primary factor as well as a co-factor with HCV

Hepatosellüler Karsinom Yüksek Risk Grubu İçin Tarama

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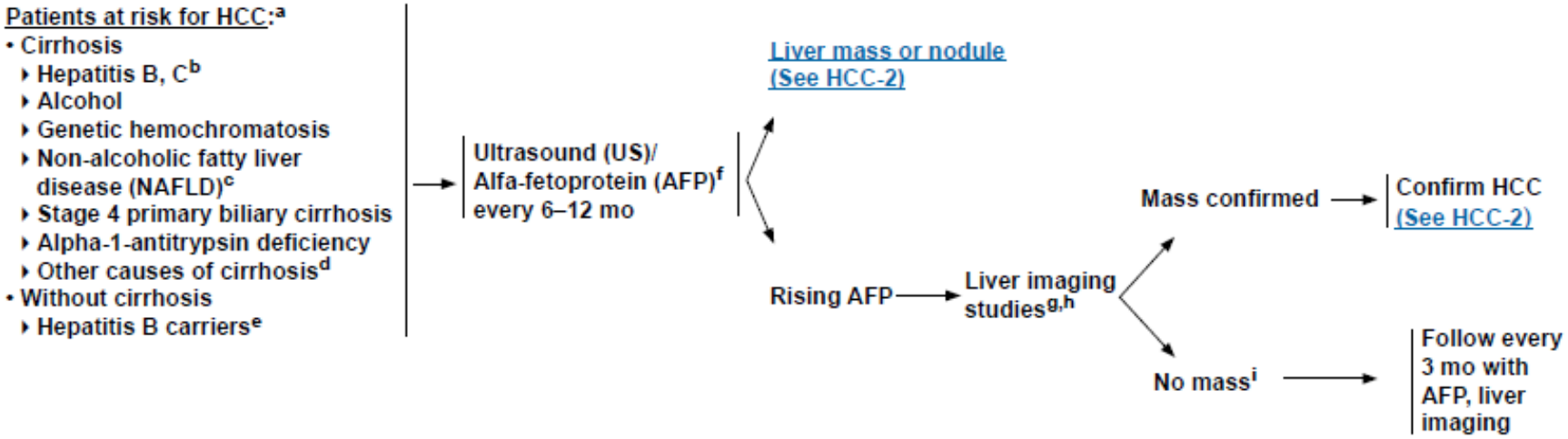
HEPATOCELLULAR CARCINOMA (HCC)
SCREENING



Hepatosellüler Karsinom Tanı ve Takip

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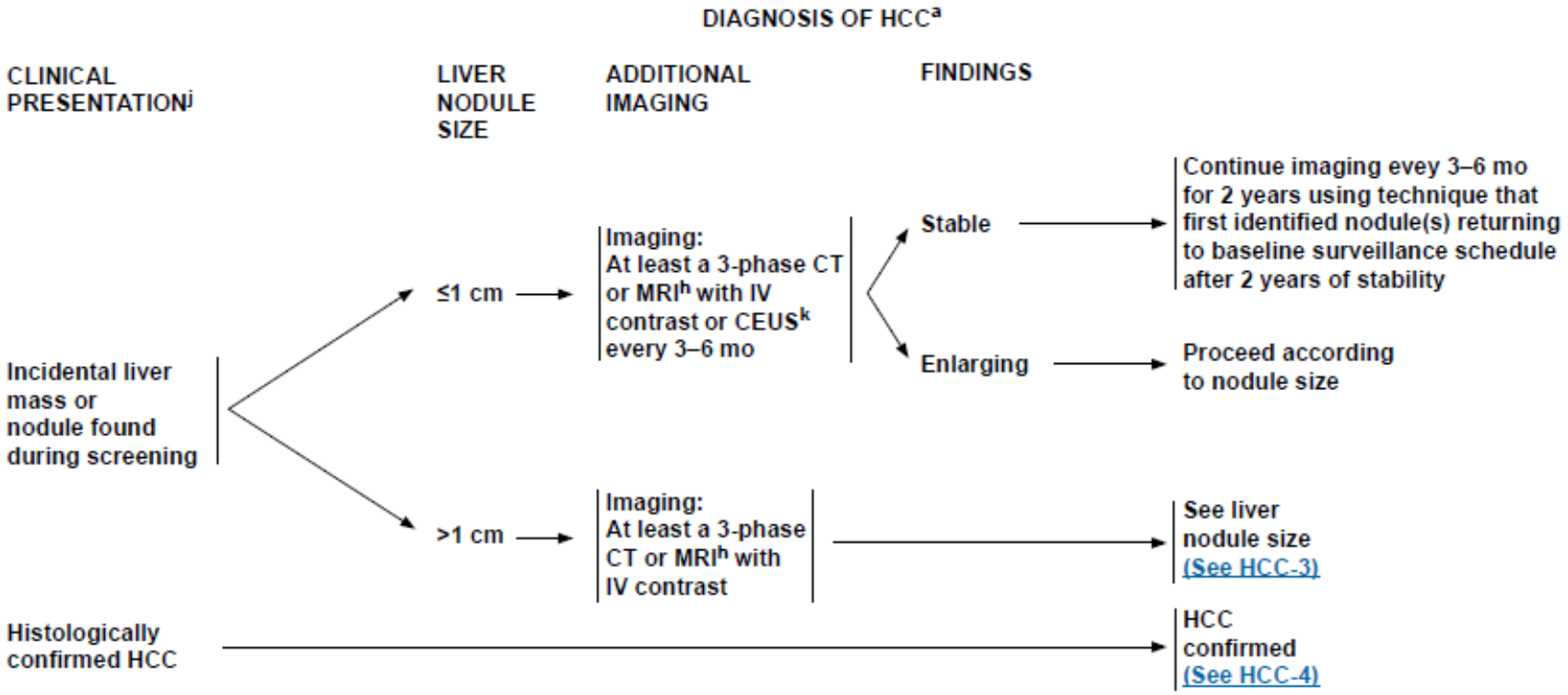
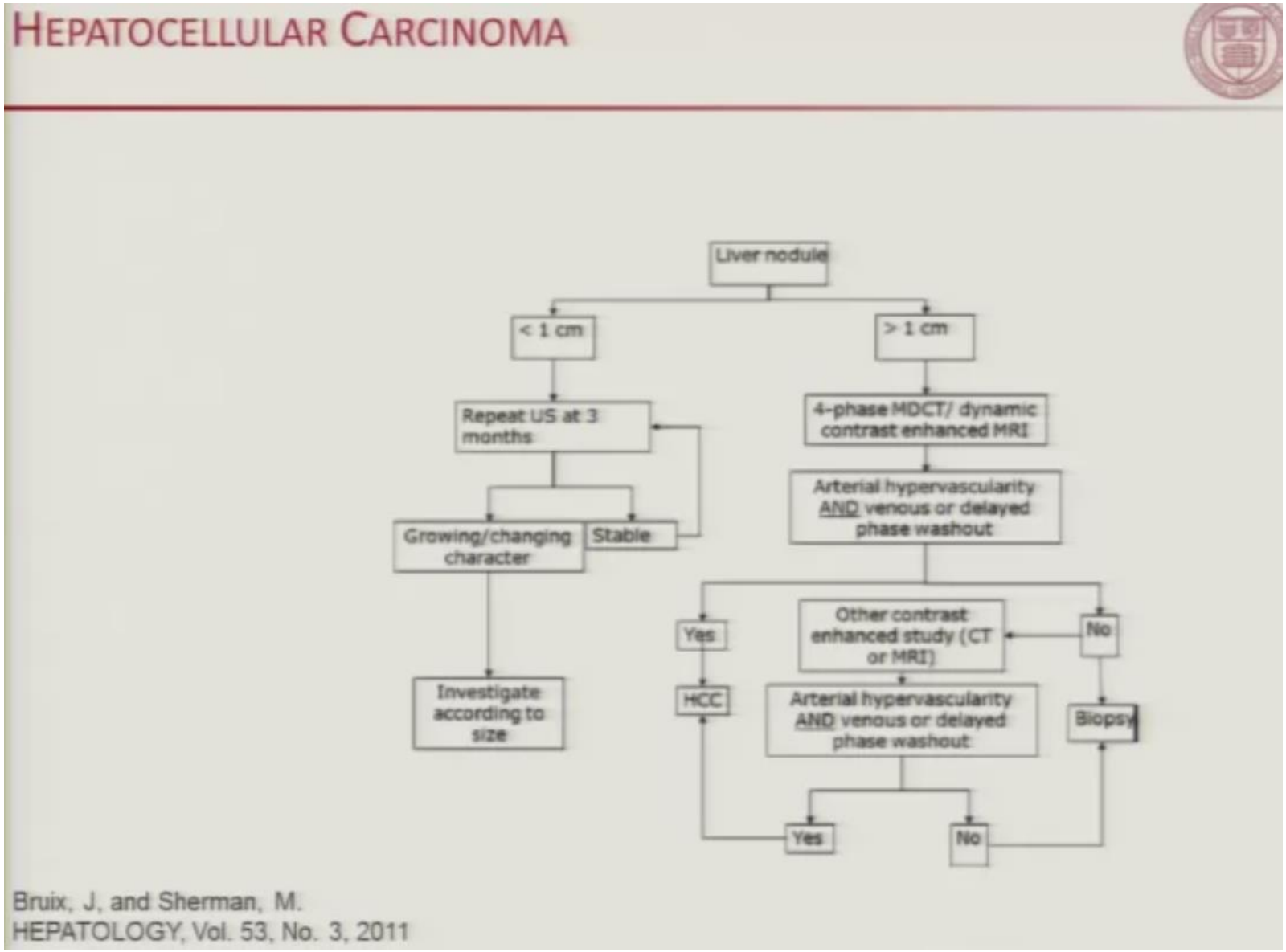


Hepatosellüler Karsinom Tanı ve Dışlama Algoritması



Hepatosellüler Karsinom Tanı ve Dışlama Algoritması

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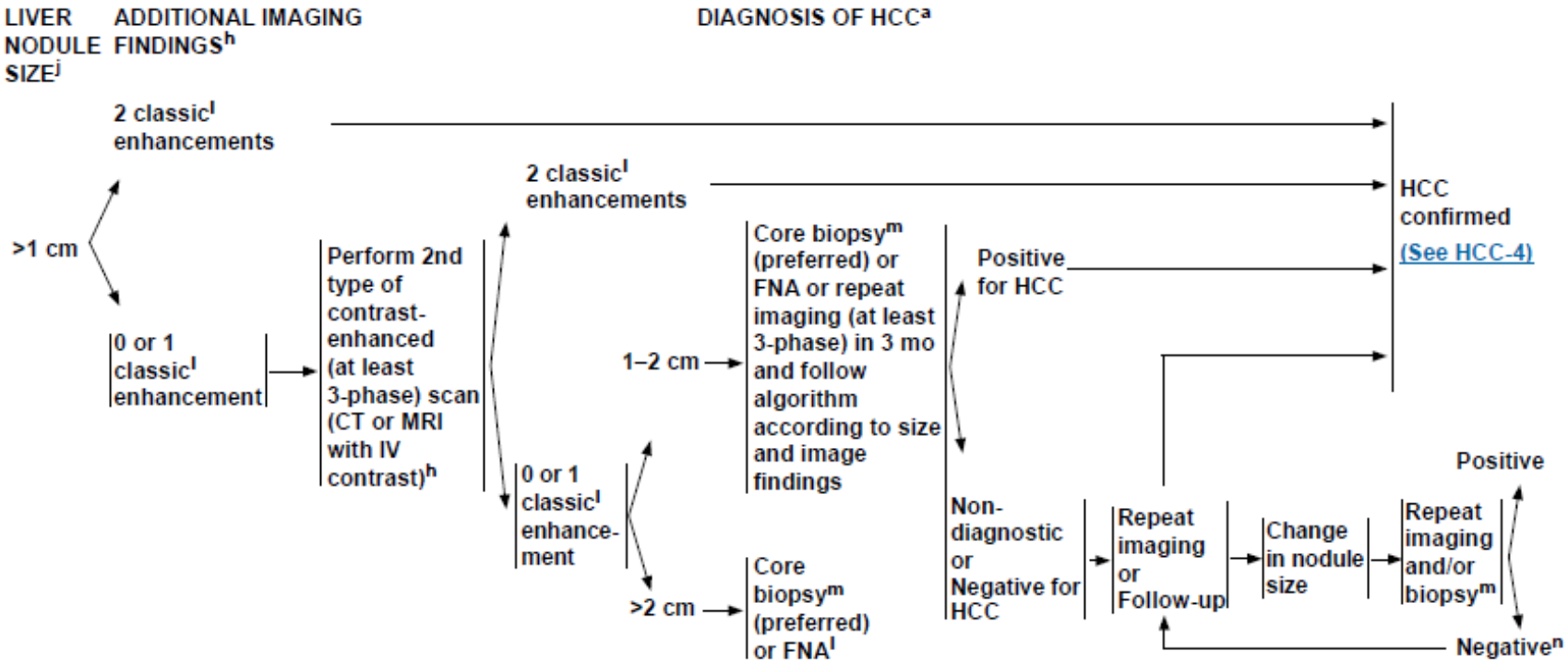


Hepatosellüler Karsinom Evreleme

Hepatocellular Carcinoma

Staging

- Several staging systems:
  - Child-Pugh/MELD: liver function only
  - TNM: surgical staging system
  - Okuda: liver function + tumor burden
  - CLIP: LFT+ AFP+ vascular invasion+ tumor morphology
    - Validated for palliative/TACE settings
  - BCLC: Barcelona Clinic Liver Cancer Group
    - PS is dominant in prognosis and decision-making along with other factors above
    - Useful for RFA outcome predictions

Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA

SURVIVAL

Table 4 Survival of patients in different stages, according to the different staging systems: CLIP, Okuda, and Child-Pugh classifications (n=257 patients)

Classification system	No (%)	Median (95% CI) survival (months)*	One year survival (%)	Three year survival (%)	Five year survival (%)
CLIP					
0	62 (24.1)	—	92	67	67
1	65 (25.3)	32.6 (19–46)	80	37	17
2	48 (18.7)	12.7 (9–17)	52	20	0
3	45 (17.5)	7.0 (5–9)	37	0	0
4	27 (10.5)	3.2 (2.6–3.8)	4	0	0
5	7 (2.7)	3.2 (2.9–3.5)	0	0	0
6	3 (1.2)	1.0 (0–2.4)	0	0	0
Okuda					
1	132 (51.3)	36.3 (32–40)	82	50	35
2	111 (43.2)	7.0 (5–9)	36	9	0
3	14 (5.5)	3.5 (2.7–4.2)	14	0	0
Child-Pugh					
A	191 (74.3)	27.9 (19–37)	67	38	29
B	49 (19.1)	8.5 (4–13)	37	5	0
C	17 (6.6)	3.5 (0–7.7)	18	0	0

*Median survival could not be calculated for the CLIP stage 0 as the last cumulative survival in this group was 67%. Median survival is the first observed time when cumulative survival is 50% or less.

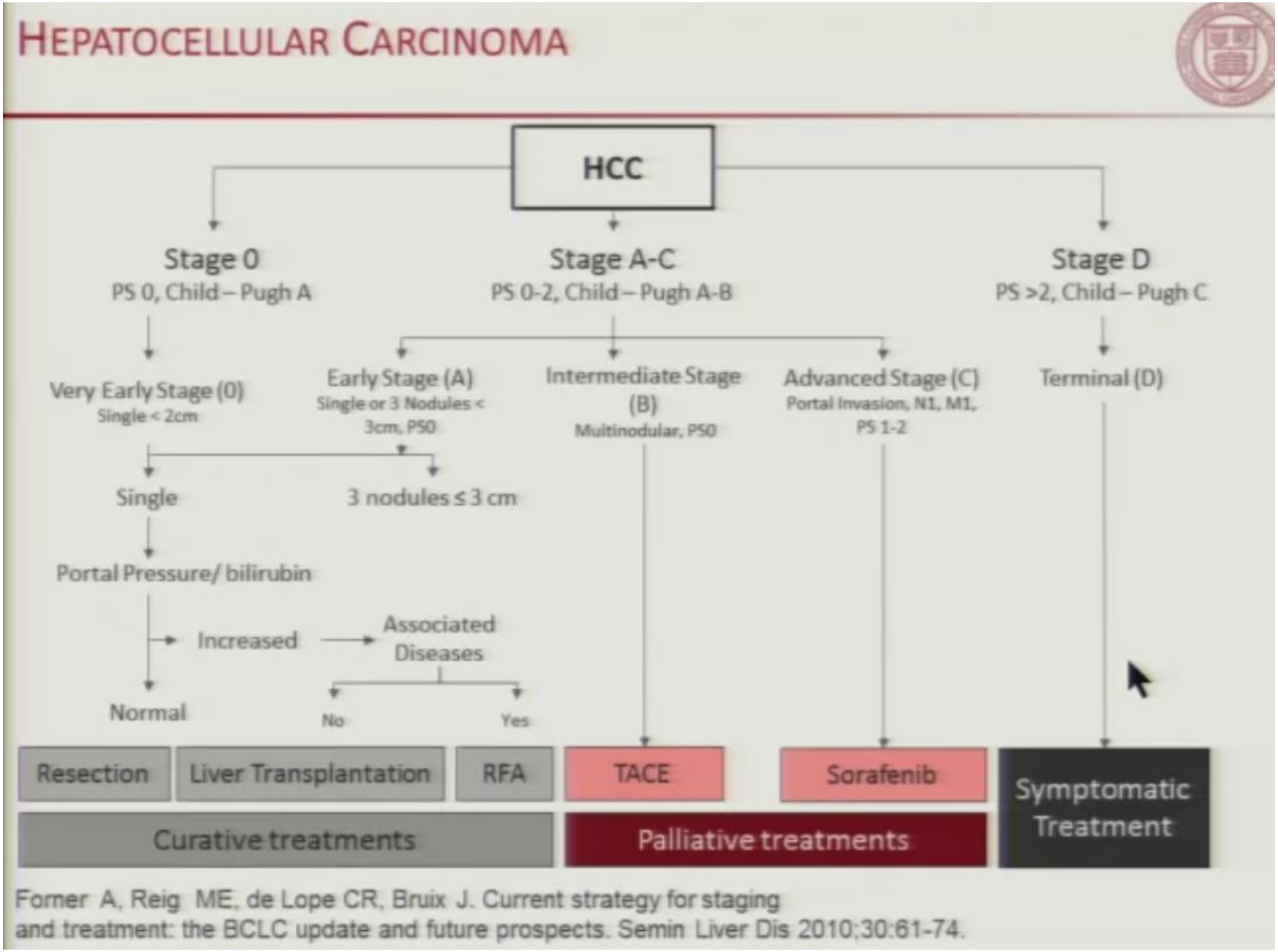
Levy et al. Gut 2002;50:881-885

Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA OS

- BCLC
  - STAGE A: 50-75% OS at 5yrs
  - STAGE B: 50% OS at 3 yrs
  - STAGE C: 10% OS at 3 yrs
  - STAGE D: no long-term survivors

Hepatosellüler Karsinom Tedavi Algoritması



Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA OS

- BCLC
  - STAGE A: 50-75% OS at 5yrs
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  - STAGE C: 10% OS at 3 yrs
  - STAGE D: no long-term survivors

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

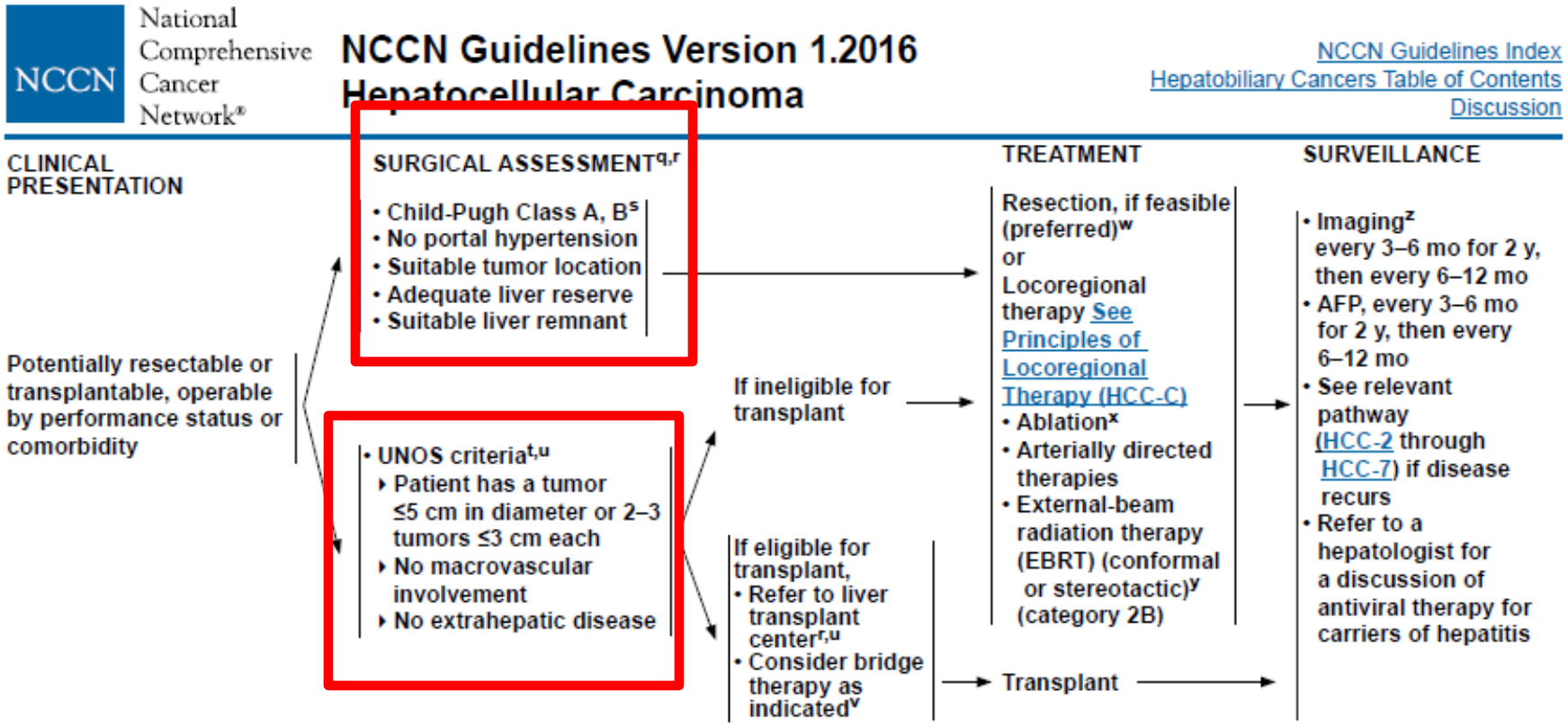
- Practical categories:
  - Resection transplant
  - Unresectable disease
  - Inoperable patient
  - Metastatic

Hepatosellüler Karsinom Tedavi

Hepatocellular Carcinoma

- Resectable disease:
  - CP-A
  - CP-B w/o portal HTN
  - Solitary mass w/o vascular invasion
  - Sufficient liver reserve
- Multifocality
  - Lower survival but may still be resectable
- LN metastases:
  - Rare [<10%]
  - Contraindication to resection for all except fibrolamellar histology

Hepatosellüler Karsinom Tedavi Cerrahi-Transpalantasyon



Hepatosellüler Karsinom Tedavi Cerrahi-Transpalantasyon

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PRINCIPLES OF SURGERY

- Patients must be medically fit for a major operation.
- Hepatic resection is indicated as a potentially curative option in the following circumstances:
  - Adequate liver function (generally Child-Pugh Class A without portal hypertension, but small series show feasibility of limited resections in patients with mild portal hypertension)[1]
  - Solitary mass without major vascular invasion
  - Adequate future liver remnant (FLR) (at least 20% without cirrhosis and at least 30%–40% with Child-Pugh Class A cirrhosis, adequate vascular and biliary inflow/outflow)
- Hepatic resection is controversial in the following circumstances, but can be considered:
  - Limited and resectable multifocal disease
  - Major vascular invasion
- For patients with chronic liver disease being considered for major resection, preoperative portal vein embolization should be considered.[2]
- Patients meeting the UNOS criteria ([single lesion ≤5 cm, or 2 or 3 lesions ≤3 cm] http://www.unos.org) should be considered for transplantation (cadaveric or living donation). More controversial are those patients whose tumor characteristics are marginally outside of the UNOS guidelines and may be considered at some institutions for transplantation.[3] Furthermore, patients with tumor characteristics beyond Milan criteria that are downstaged to within criteria can also be considered for transplantation.[4]
- The Model for End-stage Liver Disease (MELD) score is used by UNOS to assess the severity of liver disease and prioritize the allocation of the liver transplants.[3] MELD score can be determined using the MELD calculator (http://optn.transplant.hrsa.gov/resources/MeldPeldCalculator.asp?index=98). Additional MELD "exception points" may be granted to patients with HCC eligible for liver transplant.[5]
- Patients with Child-Pugh Class A liver function, who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA

- Transplant
  - Milan criteria:
    - Established 1996
    - solitary HCC < 5 cm or with up to three nodules less than 3 cm
    - 75% survival at 5 years
  - Expanded criteria [UCSF]:Yao et al.
    - 30- 90% survival at 5 years
- Liver transplant:
  - 1st line therapy for advanced cirrhosis

Hepatosellüler Karsinom Evreleme

HEPATOCELLULAR CARCINOMA

Expansion criteria of OLT

UCSF criteria (2001)[7]

OLT if:

- 1 tumor ≤6.5 cm
- up to 3 tumors, none larger than 4.5 cm and sum of diameter no larger than 8 cm

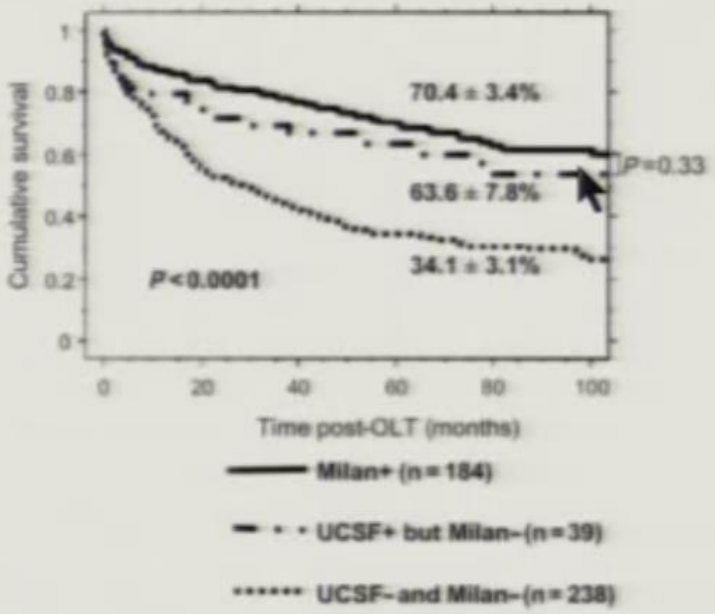
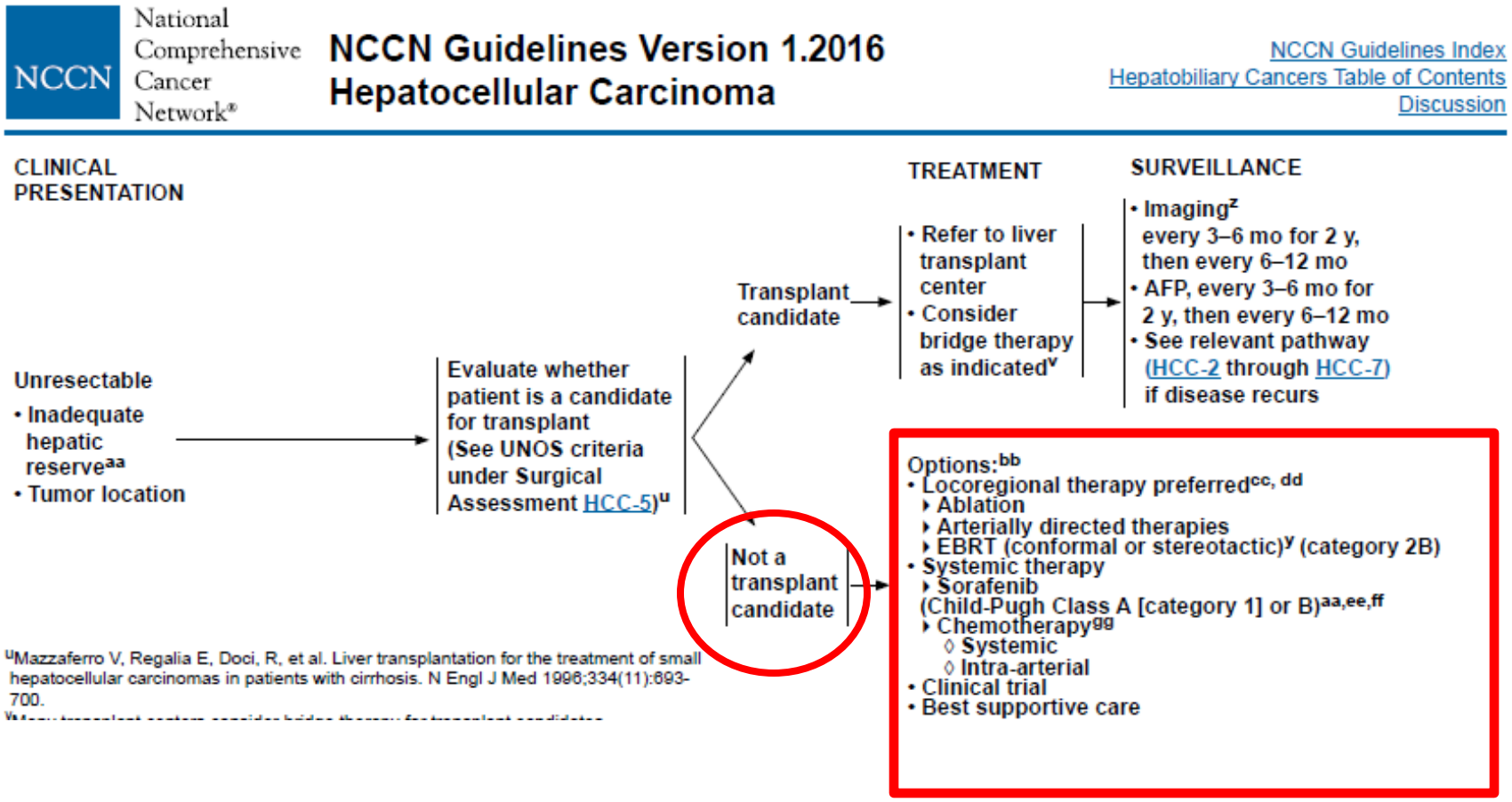


Figure 4. The 5-yr overall survival of patients according to UCSF and Milan criteria assessed on pathological reports.

Yao et al. Predicted 70-75% 5yr. OS based on a posteriori analysis

Hepatosellüler Karsinom Tedavi



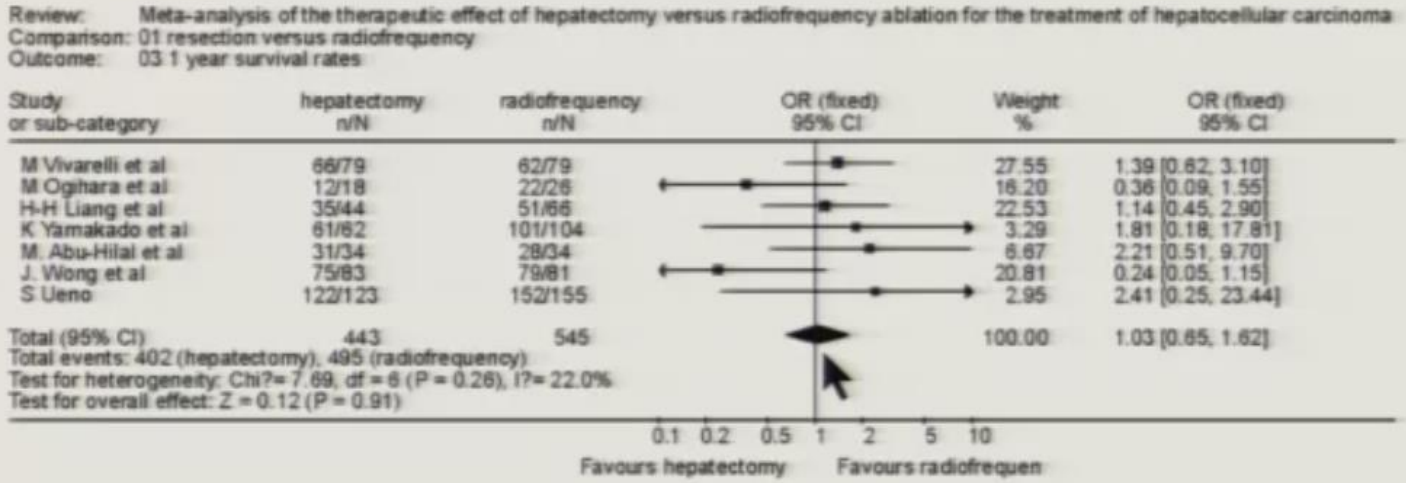
Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

- Radiofrequency Ablation [RFA]:
  - few randomized controlled trials (RCTs) comparing RFA with other interventions
  - ~ 80% complete ablation most series
  - reserved for unresectable disease

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA



Surg Laparosc Endosc Percutan Tech. 2010 Jun;20(3):130-40.
Meta-analysis of the therapeutic effect of hepatectomy versus radiofrequency ablation for the treatment of hepatocellular carcinoma

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

- Transarterial chemoembolization
  - majority of the blood supply to an HCC is derived from the hepatic artery rather than the portal vein
    - bland particle embolization
      - [gelatin sponge, polyvinyl alcohol (PVA)]
    - transarterial chemoembolization (TACE) without or with lipiodol
      - lipodiol: oily contrast agent that is thought to promote intratumoral chemotherapy retention
    - transarterial chemotherapy alone or with lipiodol

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

- Contraindications to TACE:
  - Thrombus in the main portal vein and portal vein obstruction
  - Encephalopathy
  - Biliary obstruction
  - Child-Pugh C cirrhosis
- Relative contraindications:
  - transaminitis
  - elevated bilirubin
  - renal insufficiency
  - large tumor burden

Hepatosellüler Karsinom Tedavi

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PRINCIPLES OF LOCOREGIONAL THERAPY

All patients with HCC should be evaluated for potential curative therapies (resection, transplantation, and for small lesions, ablative strategies). Locoregional therapy should be considered in patients who are not candidates for surgical curative treatments, or as a part of a strategy to bridge patients for other curative therapies. These are broadly categorized into ablation and arterially directed therapies.

Ablation (radiofrequency, cryoablation, percutaneous alcohol injection, microwave):

- All tumors should be amenable to ablation such that the tumor and, in the case of thermal ablation, a margin of normal tissue is treated. A margin is not expected following percutaneous ethanol injection.
- Tumors should be in a location accessible for percutaneous/laparoscopic/open approaches for ablation.
- Caution should be exercised when ablating lesions near major vessels, major bile ducts, diaphragm, and other intra-abdominal organs.
- Ablation alone may be curative in treating tumors ≤3 cm. In well-selected patients with small properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Lesions 3 to 5 cm may be treated to prolong survival using arterially directed therapies, or with combination of an arterially directed therapy and ablation as long as tumor location is accessible for ablation.[1,2,3]
- Unresectable/inoperable lesions >5 cm should be considered for treatment using arterially directed or systemic therapy.[4-6]
- Sorafenib should not be used as adjuvant therapy post-ablation.[7]

Arterially Directed Therapies:

- All tumors irrespective of location may be amenable to arterially directed therapies provided that the arterial blood supply to the tumor may be isolated without excessive non-target treatment.
- Arterially directed therapies include transarterial bland embolization (TAE),[5,6,8] chemoembolization (transarterial chemoembolization [TACE][9] and TACE with drug-eluting beads [DEB-TACE][6,10]), and radioembolization (RE) with yttrium-90 microspheres.[11,12]
- All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental injections can be performed.[13] RE with yttrium-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin over 2 mg/dL.[12]
- Arterially directed therapies are relatively contraindicated in patients with main portal vein thrombosis and Child-Pugh Class C.
- The angiographic endpoint of embolization may be chosen by the treating physician.
- Sorafenib may be appropriate following arterially directed therapies in patients with adequate liver function once bilirubin returns to baseline if there is evidence of residual/recurrent tumor not amenable to additional local therapies. The safety and efficacy of the use of sorafenib concomitantly with arterially directed therapies has not been associated with significant benefit in two randomized trials; other randomized phase III trials are ongong to further investigate combination approaches.[14,15,16]

Hepatosellüler Karsinom Tedavi

- Hepatokarsinogenezde çok sayıda mekanizma rol almaktadır.[1,2]
  - Hepatosit transformasyonu inflamasyon, rejenerasyon, hiperplazi, siroz ve genetik veya epigenetik değişiklikler kapsamında ortaya çıkabilmektedir.
- HSK'da sıklıkla mekanizmasında bozulma gözlenen hücresel sinyal yolakları arasında aşağıdakiler yer almaktadır:[1,2]
  - VEGF/VEGFR2 → tümör neoanjiyogenezi
  - RTK/Ras/Raf/MEK/ERK → tümör hücresi proliferasyonu
  - RTK/PI3K/Akt/mTOR → tümör hücresi sağkalımı
  - Wnt/β-katenin → HSK tümör hücrelerinde farklılaşmanın azalması

→ Moleküler tedaviye ilişkin temel yolaklar ve hedefler

Hepatosellüler Karsinom Tedavi

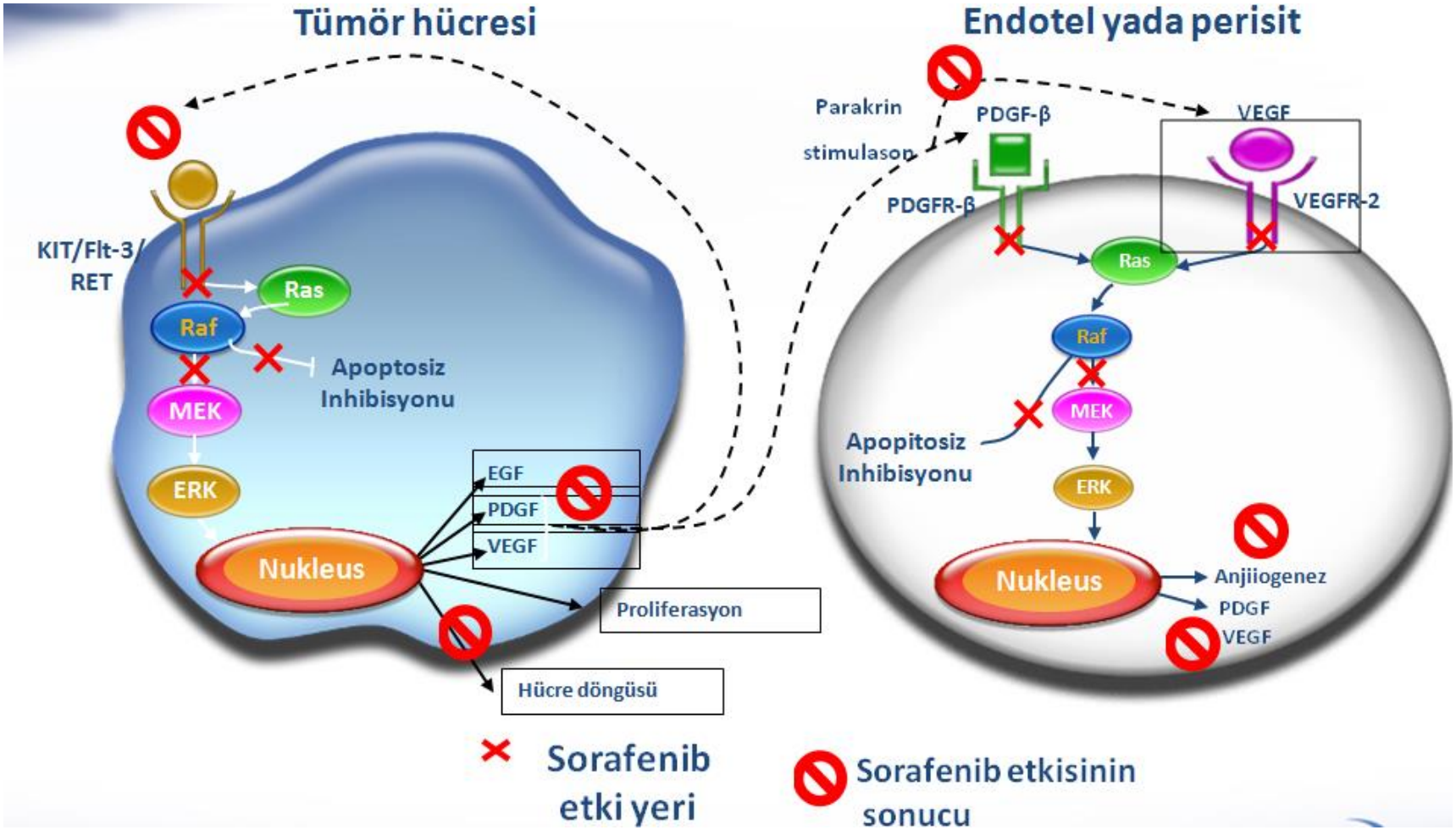
CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

Hepatosellüler Karsinom Tedavi



Hepatosellüler Karsinom Tedavi

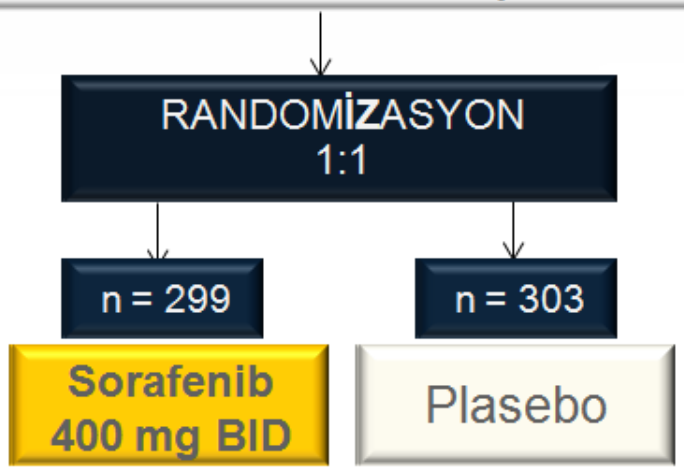
SHARP[1]

Dahil edilme kriterleri

• İleri evre HSK, ECOG PS 0–2, Child-Pugh A, daha önce sistemik tedavi almamış

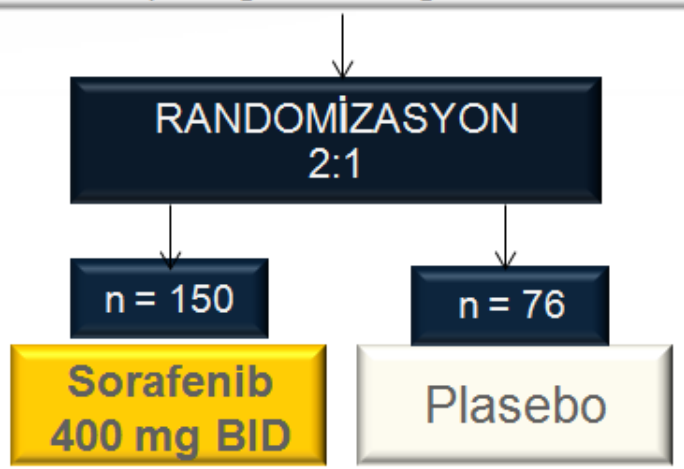
Katmanlandırma

• MVY ve/veya EHY, ECOG PS (0 vs. 1–2), coğrafik bölge



1º Sonlanım: OS, TTSP
2º Sonlanım: TTP, HKO, güvenlilik

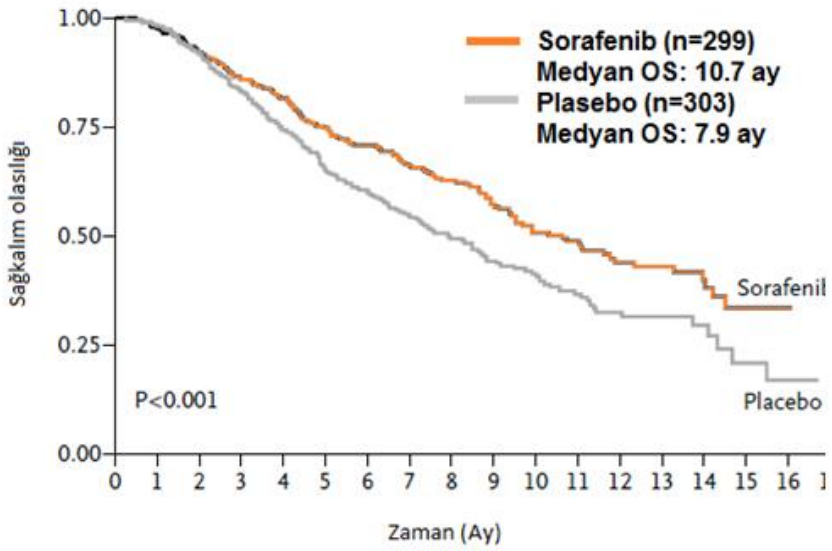
Asya–Pasifik[2]



Sonlanım: OS, TTSP, TTP, HKO, güvenlilik

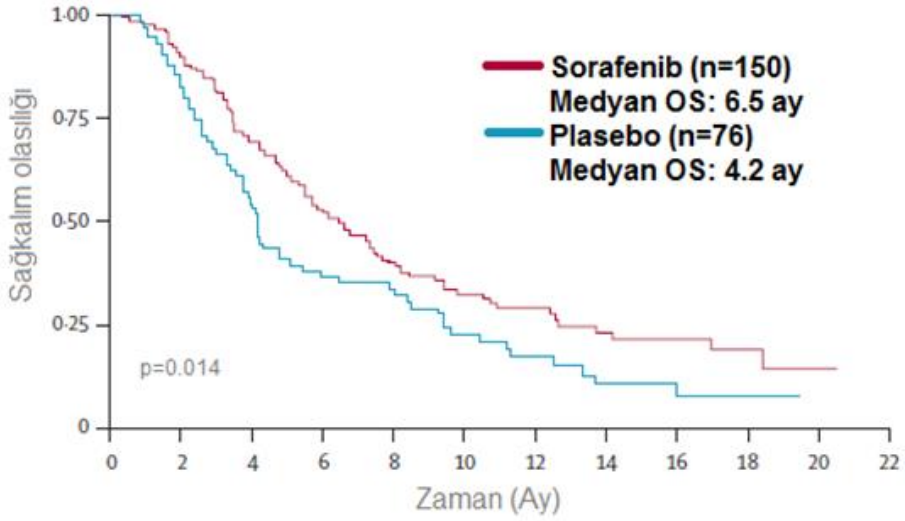
Hepatosellüler Karsinom Tedavi

SHARP[1]



HR=0.69

Asya–Pasifik[2]



HR=0.68

Hepatosellüler Karsinom Tedavi

Advers olay	Derecesine göre insidansı (%)			
	SHARP (N=297)[3]		Asya-Pasifik (N=149)[2]	
	Herhangi derece	Derece 3/4	Herhangi derece	Derece 3/4
Diyare	39	8	25.5	6
Bitkinlik	22	4	20.1	3.4
El-ayak deri reaksiyonu	21	8	45	10.7
Döküntü/deskuamasyon	16	1	20.1	<1
Anoreksi	14	<1	12.8	0
Karaciğer disfonksiyonu	<1	<1	<1	NR
Bulantı	11	<1	11.4	<1
Hipertansiyon	5	2	18.8	2

Hepatosellüler Karsinom Tedavi

ORIGINAL PAPER

First interim analysis of the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) non-interventional study

R. Lencioni,[1] M. Kudo,[2] S.-L. Ye,[3] J.-P. Bronowicki,[4] X.-P. Chen,[5] L. Dagher,[6] J. Furuse,[7] J. F. Geschwind,[8] L. L. de Guevara,[9] C. Papandreou,[10] A. J. Sanyal,[11] T. Takayama,[12] S. K. Yoon,[13] K. Nakajima,[14] F. Cihon,[15] S. Heldner,[16] J. A. Marrero[17]

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

ORIGINAL PAPER

GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with : second interim analysis

udo,[2] S.-L. Ye,[3] J.-P. Bronowicki,[4] X.-P. Chen,[5] L. Dagher,[6] J. Furuse,[7] L. Ladrón de Guevara,[9] C. Papandreou,[10] T. Takayama,[11] S. K. Yoon,[12] K. hr,[14] S. Heldner,[15] A. J. Sanyal[16]

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Future ONCOLOGY

RESEARCH ARTICLE

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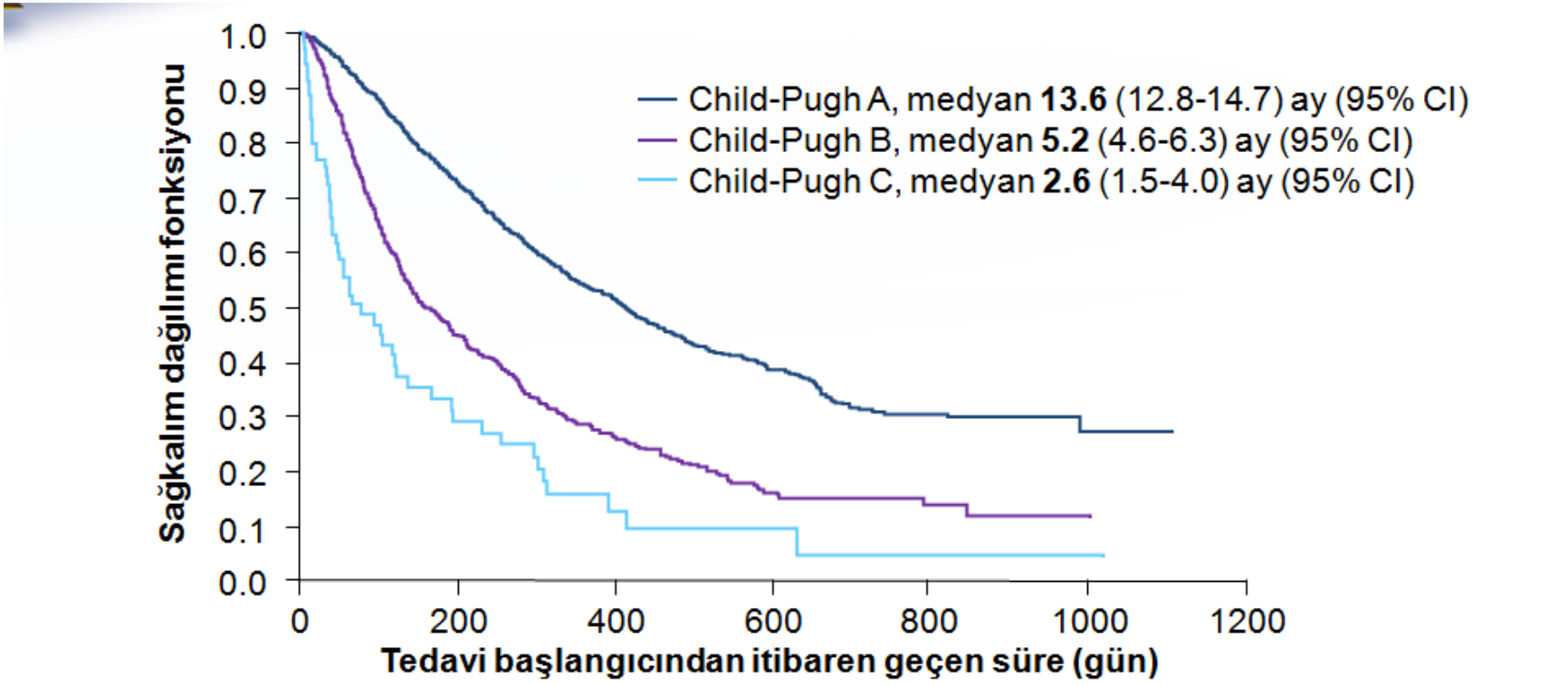
Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study

Bruno Daniele[a,1], Adina Croitoru[2], Christos Papandreou[3], Jean-Pierre Bronowicki[4], Philippe Mathurin[5], Fatima Serejo[6], Per Stål[7], Juan Turnes[8], Vlad Ratziu[9] & György Bodoky[10]

- **G**lobal **I**nvestigation of therapeutic **DE**cisions in hepatocellular carcinoma **[HCC] and O**f its treatment with sorafe**N**ib
- Sorafenib kullanan HSK hastalarında büyük ölçekli, global, prospektif, gözlemsel, çalışma
- Hasta sayısı 3371, 39 ülke, 5 kıta
- Primer amaç: klinik pratikte sorafenib kullanımının güvenliliğini değerlendirmek
- Sekonder amaçlar: sorafenib için etkililik, dozlama ve pratikte uygulama paternlerini

Hepatosellüler Karsinom Tedavi



3213 hastanın analizi

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

- NEXAVAR
  - SHARP trial:
  - pivotal, placebo-controlled trial
  - CP-A only
  - 7.9 v 10.7 mo
- Sorafenib prolonged overall survival versus placebo in advanced HCC
  - Median OS- 46 weeks v 34 weeks
  - HR 0.69, P=0.00058
  - 44% increase in overall Survival
- Sorafenib prolonged time to progression versus Placebo
  - Median TTP 24 weeks v 12 weeks
  - HR 0.58, P=0.000007
  - 73% prolongation in time to progression
- Sorafenib was well-tolerated with manageable side effects

Hepatosellüler Karsinom Tedavi

HEPATOCELLULAR CARCINOMA

- NEXAVAR
- post- SHARP:
  - 2009 retrospective analysis
    - evaluation of outcomes based on CP class
    - no OS benefit for CP-C
  - GIDEON trial
    - 2011 ASCO
    - prospective database
    - shorter OS: 5 versus 10.5 months
    - higher AE rate w/ CP-B vs CP-A

Hepatosellüler Karsinom Tedavi

- **Cerrahi**
- **Transplantasyon**

  Tek lezyon≤5cm, yada 3 ≤ lezyon ve toplam boyut ≤ 8 cm
- **Unresektable Hastalık**

  Lokoragional tedavi seçenekler; RFA, Radyoembolizasyon, TACE
- **Metastatik hastalık**

  Child A, ChildB8 Sorafenib

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