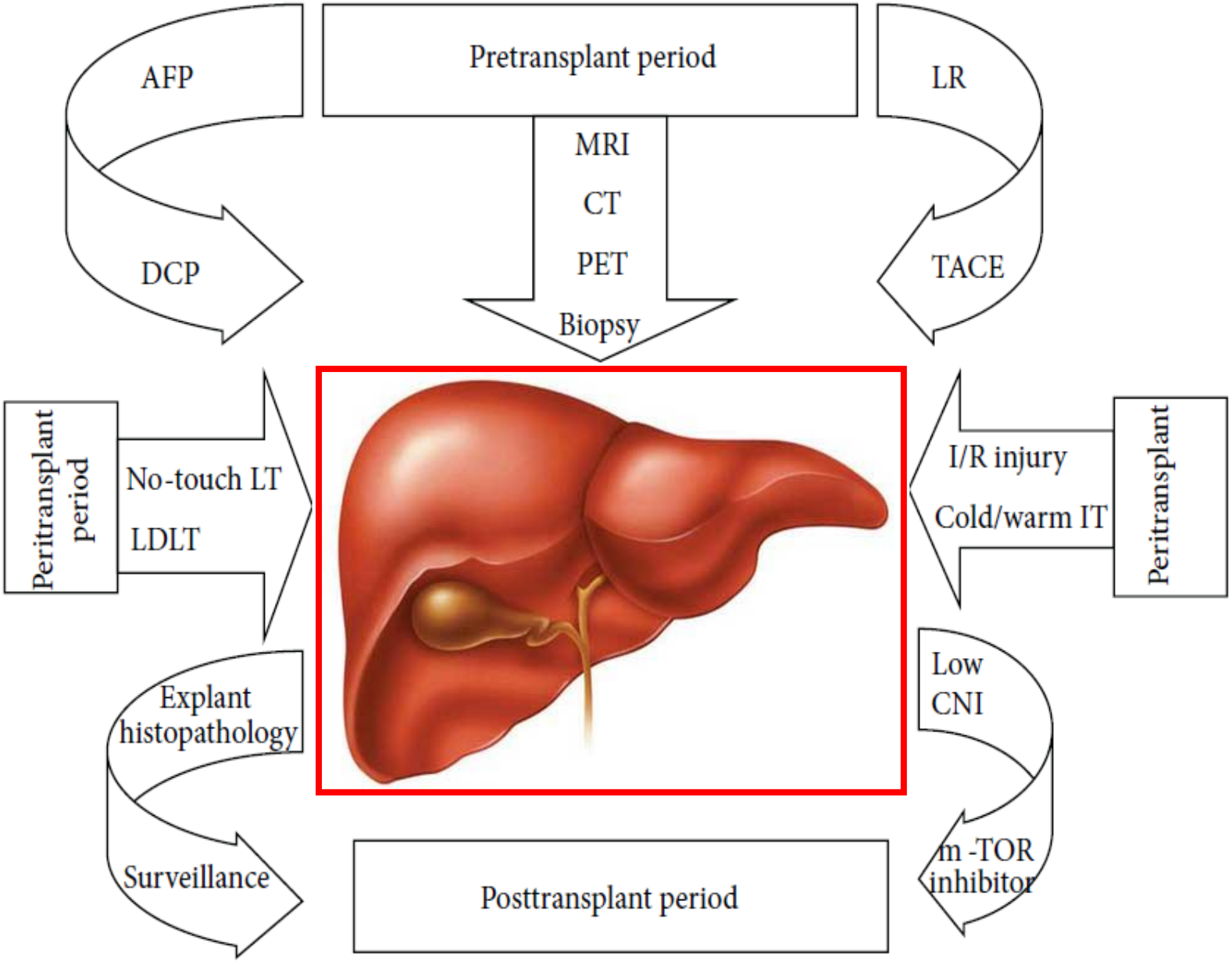
HEPATOSELLÜLER KARSİNOMDA KARACİĞER NAKLİ SINIRLARI NEDİR, NEREDE DURMALIYIM?

MILAN KRİTERLERİNİ AŞMAYALIM!

TARKAN ÜNEK
DOKUZ EYLÜL ÜNİVERSİTESİ TIP FAKÜLTESİ
GENEL CERRAHİ ANABİLİM DALI
HEPATOPANKREATOBİLİER CERRAHİ VE KARACİĞER TRANSPLANTASYONU BİRİMİ

HCC – KARACİĞER TRANSPLANTASYONU



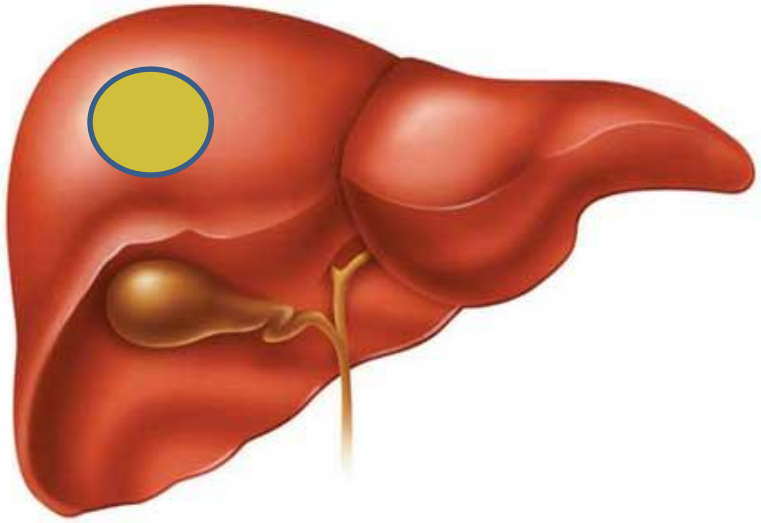
NEDEN KRİTERLERE GEREKSİNİM VAR?

- Graft kısıtlılığı
- Graftların uygun kullanımı
- KT'ndan yarar görecek HCC hastaları?
- Donör güvenliği
- Maliyet

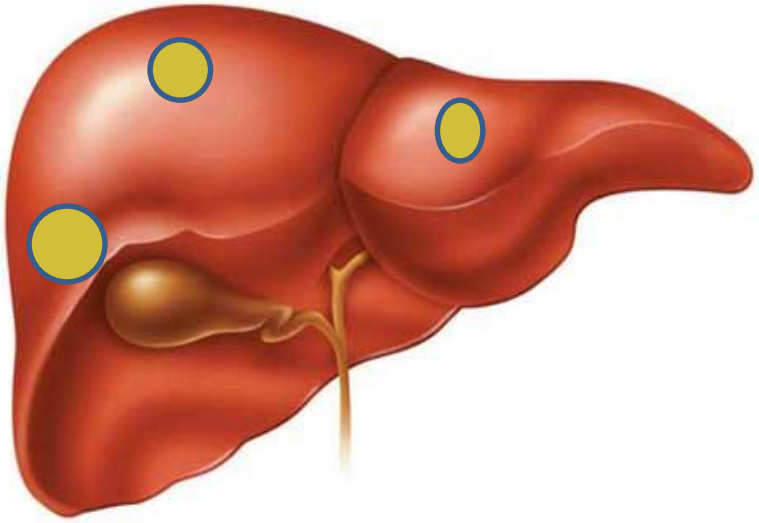
MILAN KRİTERLERİ

Vasküler invazyon ve uzak metastaz olmamalı

Tek tümör varsa, çapı < 5 cm



Çoğul tümör varsa en çok 3 tane, bu tümörlerin her biri < 3 cm



Mazzafero V, et al. N Engl J Med 1996

MILAN KRİTERLERİ

LIVER TRANSPLANTATION FOR THE TREATMENT OF SMALL HEPATOCELLULAR CARCINOMAS IN PATIENTS WITH CIRRHOSIS

VINCENZO MAZZAFERRO, M.D., ENRICO REGALIA, M.D., ROBERTO DOCI, M.D., SALVATORE ANDREOLA, M.D., ANDREA PULVIRENTI, M.D., FEDERICO BOZZETTI, M.D., FABRIZIO MONTALTO, M.D., MARIO AMMATUNA, M.D., ALBERTO MORABITO, PH.D., AND LEANDRO GENNARI, M.D., PH.D.

Abstract *Background.* The role of orthotopic liver transplantation in the treatment of patients with cirrhosis and hepatocellular carcinoma is controversial, and determining which patients are likely to have a good outcome after liver transplantation is difficult.

Methods. We studied 48 patients with cirrhosis who had small, unresectable hepatocellular carcinomas and who underwent liver transplantation. In 94 percent of the patients, the cirrhosis was related to infection with hepatitis B virus, hepatitis C virus, or both. The presence of tumor was confirmed by biopsy or serum alpha-fetoprotein assay. The criteria for eligibility for transplantation were the presence of a tumor 5 cm or less in diameter in patients with single hepatocellular carcinomas and no more than three tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors. Twenty-eight patients with sufficient hepatic function underwent treatment for the tumor, mainly chemoembolization, before transplantation. After liver transplantation, the patients were followed prospectively for a median of 26 months (range, 9 to 54). No anticancer treatment was given after transplantation.

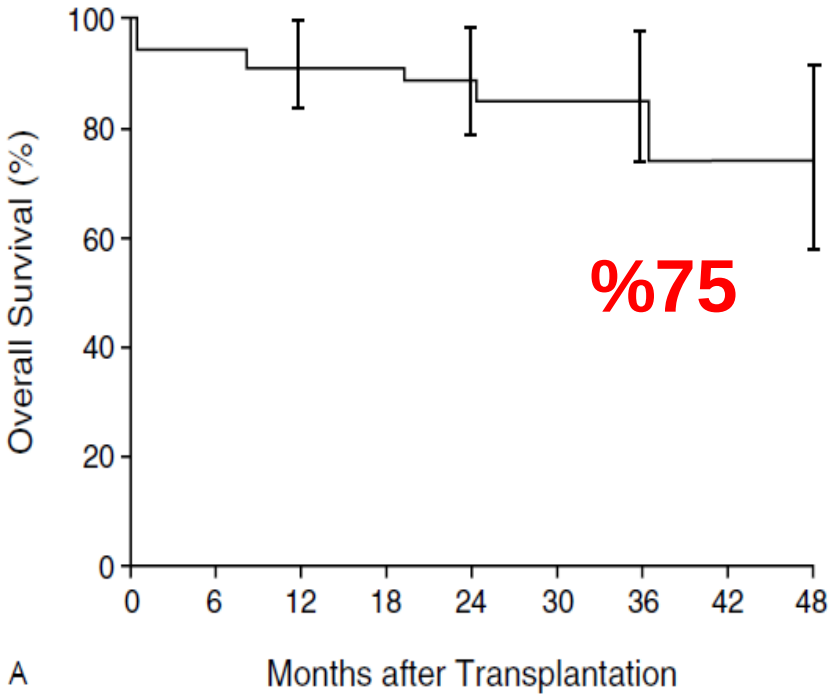
Results. The overall mortality rate was 17 percent. After four years, the actuarial survival rate was 75 percent and the rate of recurrence-free survival was 83 percent. Hepatocellular carcinoma recurred in four patients (8 percent). The overall and recurrence-free survival rates at four years among the 35 patients (73 percent of the total) who met the predetermined criteria for the selection of small hepatocellular carcinomas at pathological review of the explanted liver were 85 percent and 92 percent, respectively, whereas the rates in the 13 patients (27 percent) whose tumors exceeded these limits were 50 percent and 59 percent, respectively ($P=0.01$ for overall survival; $P=0.002$ for recurrence-free survival). In this group of 48 patients with early-stage tumors, tumor–node–metastasis status, the number of tumors, the serum alpha-fetoprotein concentration, treatment received before transplantation, and 10 other variables were not significantly correlated with survival.

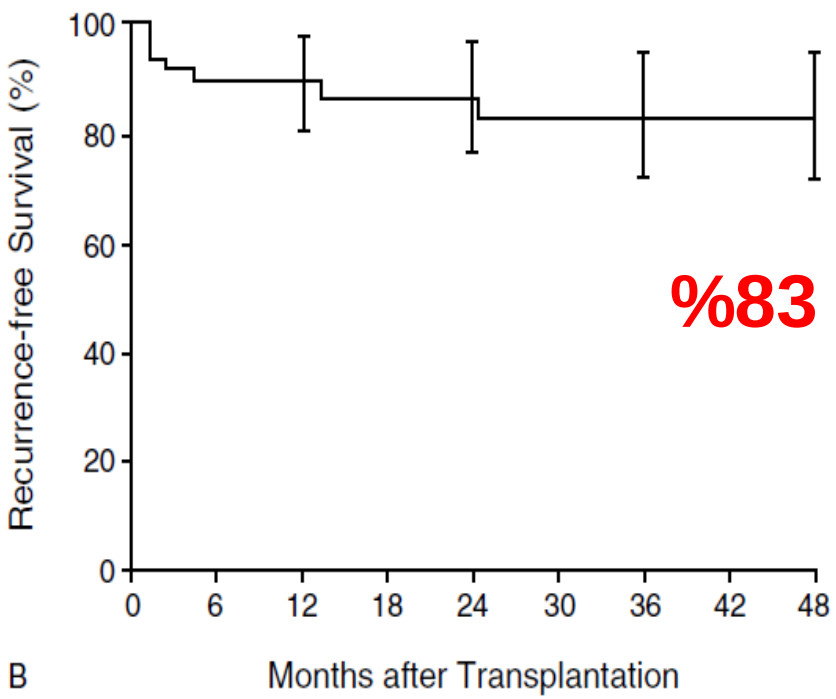
Conclusions. Liver transplantation is an effective treatment for small, unresectable hepatocellular carcinomas in patients with cirrhosis. (N Engl J Med 1996;334:693-9.)

Mazzafero V, et al. N Engl J Med 1996

- **48 KN alıcısı**
- **Preoperatif görüntüleme yöntemleriyle hasta seçimi**
- **5 cm'den küçük tek tümör ya da**
- **3 cm'den küçük en fazla 3 tümör**
- **Ekstrahepatik hastalık ya da vasküler invazyon yok**

MILAN KRİTERLERİ





Mazzafero V, et al. N Engl J Med 1996

Lancet Oncol. 2012 January ; 13(1): e11–e22. doi:10.1016/S1470-2045(11)70175-9.

Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report

Pierre-Alain Clavien, MD,
Department of Surgery, Swiss HPB and Transplant Centers, University Hospital Zurich, Zurich, Switzerland

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Department of Surgery, Swiss HPB and Transplant Centers, University Hospital Zurich, Zurich, Switzerland

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Gregory J Gores, MD,
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Bernard Langer, MD, and
Department of Surgery, University of Toronto, Toronto, ON, Canada

Arnaud Perrier, MD on behalf of the OLT for HCC Consensus Group
Department of Internal Medicine, University Hospital of Geneva, Geneva, Switzerland

2012 uluslararası konsensus panelinde, Milan Kriterleri HCC hastalarında KT endikasyonu konulmasında altın standart yöntem olarak kabul edilmiştir

MILAN KRİTERLERİ

- **Milan +** → **Rekürrens %10-16**
  En önemli ölüm nedeni

Plessier A, et al. Liver Transplant 2004
Escartin A, et al. Transplant Proc 2007

- **Sadece morfolojik kriterler yeterli mi?**

- **Ayrıca, Milan Kriterleri'nin çok katı olduğu ve KT'ndan yarar görebileceği halde bazı HCC olgularını dışladığı görüşü mevcuttur**

Koschny R, et al. Clin Transplant 2009

- **Milan dışı kriterler KT bekleme listesini** ↑

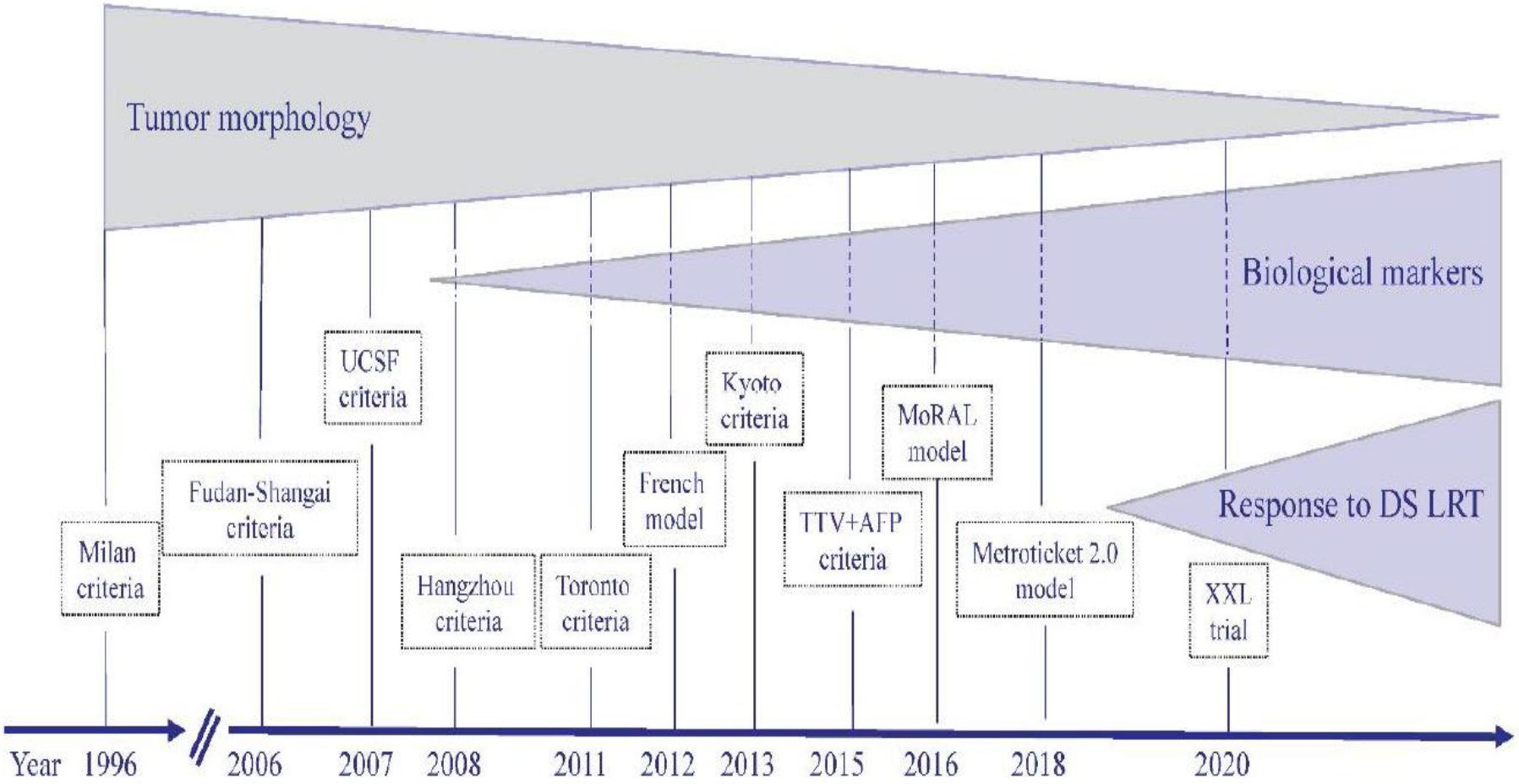
MILAN DIŞI KRİTERLERLE İLGİLİ SORULAR

1. **Milan dışı hastalarda KT düşünmek için tümör yükünün üst sınırı nedir?**

2. **KT sonrası kabul edilebilir genel sağkalım süresi nedir?**

3. **KT yapılacak hastaları daha iyi seçebilmek için tümör yüküne ek olarak kullanılabilecek tümör biyolojisini gösteren belirteçler nelerdir?**

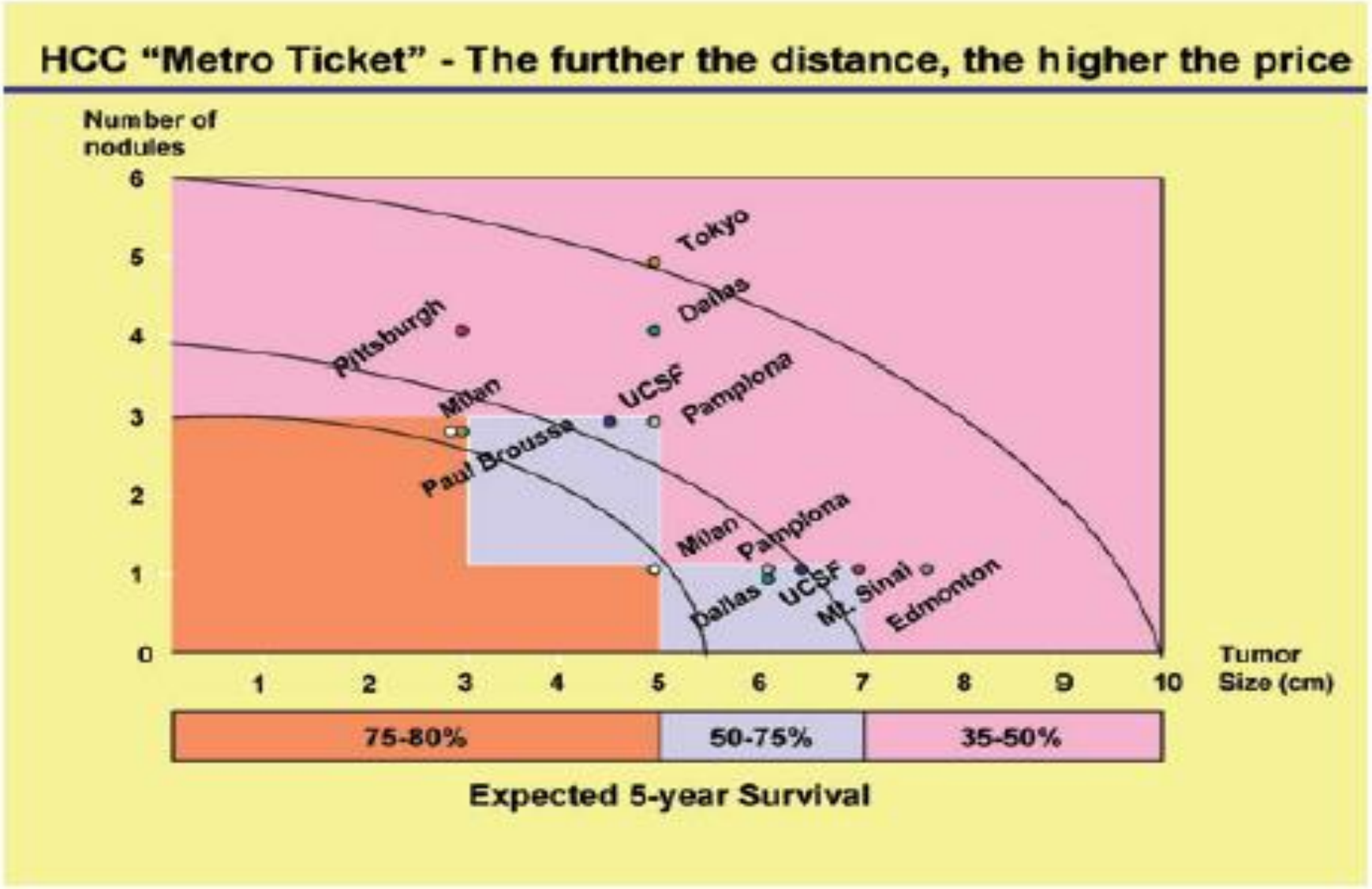
HEPATOSELLÜLER KARSİNOMDA KARACİĞER TRANSPLANTASYON KRİTERLERİ



HEPATOSELLÜLER KARSİNOMDA KARACİĞER TRANSPLANTASYON KRİTERLERİ

Kriter	Yıl	Tümör Sayısı	Ek	Sağkalım
Milan	1996	Çapı 5 cm ve altında tek tümör ya da herbirinin çapı 3 cm ve altında olan en çok 3 tümör	Major vasküler invazyon ve metataz yok	4 yıl %75
University of California San Francisco	2001	Çapı 6.5 cm ve altında tek tümör ya da en büyük çapı 4.5 cm ve altında olan ve total tümör boyutu 8 cm ve altında olan en çok 3 tümör	Major vasküler invazyon ve metastaz yok	5 yıl %75.2
University of Tokyo	2007	Çapı 5 cm ve altında en çok 5 tümör	Major vasküler invazyon ve metastaz yok	3 yıl %82, 5 yıl %75
Baskent University (Haberal) Ankara	2007	Kısıtlama yok	Major vasküler invazyon ve metastaz yok	5 yıl %50.3
Asan Medical Center	2008	Çapı 5 cm ve altında en çok 6 tümör	Major vasküler invazyon ve metastaz yok	3 yıl %88, 5 yıl %82
Hangzhou	2008	Boyut kısıtlaması olmadan en çok 8 tümör	8 cm'den büyük tümörlerde biyopside histopatolojik derece I/II ve AFP<400 ng/mL	5 yıl %72
Chang Gung	2008	Çapı 6.5 cm ve altında tek tümör ya da en büyük çapı 4.5 cm ve altında olan en çok 3 tümör		3 yıl %96, 5 yıl %90
University of Hong Kong	2008	Çapı 6.5 cm ve altında tek tümör ya da en büyük çapı 4.5 cm ve altında olan en çok 3 tümör		3 yıl %78, 5 yıl %66
Up to seven	2009	En büyük tümörün cm olarak boyutu ve tümör sayısı toplamı 7 ve altında		5 yıl %71.2
Total tumor and AFP	2009	Total tümör hacmi≤115 cm^3 ve AFP≤400 ng/mL	Makrovasküler invazyon ve metastaz olmamalı	5 yıl %76.4
Kyushu	2009	Çapı 5 cm ve altında tümörler (Sayı kısıtlaması yok)	PIVKA II≤300 mAU/mL	3 yıl %86, 5 yıl %83
Kyoto	2010	Çapı 5 cm ve altında en çok 10 tümör	PIVKA II≤400 mAU/mL	5 yıl %87
Toronto	2011	Kısıtlama yok	Karaciğer transplantasyonu öncesi biyopside kötü diferansiyasyon olmamalı, metastaz olmamlı	5 yıl %72
Extended Toronto	2016	Kısıtlama yok	Karaciğer transplantasyonu öncesi biyopside kötü diferansiyasyon olmamalı, metastaz ve tümöre bağlı semptomlar olmamalı	5 yıl %68
Japanese National Expanded Criteria	2019	Çapı 5 cm ve altında en çok 5 tümör	AFP<500 ng/mL	5 yıl %75.8

"METRO TICKET" MODEL



HİSTOPATOLOJİK ÖZELLİKLERİ ELE ALAN KRİTERLER

- **Milan dışı hastalarda MVİ ↑**

Rudnick SR, et al. Expert Rev Gastroenterol Hepatol 2018

- **Milan + → %11**
- **Milan - → %42**

EKSPLANT PATOLOJİSİ

Mazzaferro V, et al. Lancet Oncol 2009

- **MVİ – Büyük nodül ve multinodüler HCC**
- **MVİ + → Rekürrens %68**

- **Biyopsi – Tümör yayılımı, doğru örnek alınmasında sorunlar**

HİSTOPATOLOJİK ÖZELLİKLERİ ELE ALAN KRİTERLER

- MVİ ?– Noninvaziv yöntemler
- 18F-FDG PET-BT
- Gadoxetic acid MRG

Yaprak O, et al. World J Gastrointest Oncol 2018
Choi SH, et al. Ann Surg Oncol 2015

- 18F-FDG PET-BT → **Glikolitik enzim aktivitesi**
  HCC büyüme hızı
- Kötü diferansiye HCC → 18F-FDG PET-BT uptake ↑
- SUVmax T / SUVmax L ≥ 1.2 → MVİ oranı ↑

Ahn SY, et al. Abdom Imaging 2015

J Hepatobiliary Pancreat Sci (2017) 24:49–57
DOI: 10.1002/jhbp.412

ORIGINAL ARTICLE

Significance of preoperative fluorodeoxyglucose-positron emission tomography in prediction of tumor recurrence after liver transplantation for hepatocellular carcinoma patients: a Japanese multicenter study

Yasutsugu Takada · Toshimi Kaido · Ken Shirabe · Hiroaki Nagano · Hiroto Egawa · Yasuhiko Sugawara · Akinobu Taketomi · Takeshi Takahara · Go Wakabayashi · Chikashi Nakanishi · Naoki Kawagishi · Akira Kenjo · Mitsukazu Gotoh · Yoshikazu Toyoki · Kenichi Hakamada · Masayuki Ohtsuka · Nobuhisa Akamatsu · Norihiro Kokudo · Kazuhisa Takeda · Itaru Endo · Hiroyuki Takamura · Hideaki Okajima · Hiroshi Wada · Shoji Kubo · Kaoru Kuramitsu · Yonson Ku · Kohei Ishiyama · Hideki Ohdan · Eitaro Ito · Yoshihiko Maehara · Masaki Honda · Yukihiro Inomata · Hiroyuki Furukawa · Shinji Uemoto · Hiroki Yamaue · Masaru Miyazaki · Tadahiro Takada · on behalf of the LTx-PET study group of the Japanese Society of Hepato-Biliary-Pancreatic Surgery and the Japanese Liver Transplantation Society

- **Milan -** → **18F-FDG PET-BT – AFP < 115 ng/mL** → **5 yıllık rekürrens %19**

Original Clinical Science—Liver

Clinical Impact of ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma

Seung Duk Lee, MD,[1] Seong Hoon Kim, MD, PhD,[1] Seok-Ki Kim, MD, PhD,[2] Young-Kyu Kim, MD,[3] and Sang-Jae Park, MD, PhD[1]

(*Transplantation* 2015;99: 2142–2149)

- **18F-FDG PET-BT –**

- **5 yıllık hastalıksız sağkalım Milan - %73.3**
  UCSF - %72.8

SERUM BİYOBELİRTEÇLERİ ÖLÇÜMÜNE DAYANAN KRİTERLER

- **HCC'nin Biyolojik Karakteristikleri ile İlgili Belirteçler**
  - AFP
  - DCP
- **Sistemik Konakçı İnflamatuvar Yanıtını Yansıtan Belirteçler**
  - Nötrofil/Lenfosit
  - Trombosit/lenfosit
- **Moleküler Biyobelirteçler**
  - Genetik mutasyonlar
  - Enzimler
  - MicroRNA

Toniutto P, et al. Journal of Clinical Medicine 2021

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

- AFP → Diferansiasyon, Vasküler invazyon
- Optimal AFP ölçüm zamanı?
- Aralıklı AFP ölçümü
- AFP>15 ng/mL/ay vs AFP≤15 ng/mL/ay

↓

Bekleme listesinde kayıp ↑
Sağkalım ↓

Lai Q, et al. Liver Transplant 2014

- Evre düşürme sonrası AFP ↑ → Kötü prognoz

Toniutto P, et al. Journal of Clinical Medicine 2021

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

Liver Transplantation for Hepatocellular Carcinoma: Hangzhou Experiences

Shu-Sen Zheng, Xiao Xu, Jian Wu, Jun Chen, Wei-Lin Wang, Min Zhang, Ting-Bo Liang, and Li-Ming Wu

(*Transplantation* 2008;85: 1726–1732)

- **Portal ven invazyonu –**
- **HCC≤8 cm ya da HCC>8 cm AFP<400 ng/mL ve histolojik grade I-II**
- **5 yıllık sağkalım %70.7**
- **5 yıllık rekürrenssiz sağkalım %62.4**
- **1, 3 yıllık sağkalım Milan + ile aynı**

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

HEPATOBILIARY MALIGNANCIES

Total Tumor Volume and Alpha-Fetoprotein for Selection of Transplant Candidates With Hepatocellular Carcinoma: A Prospective Validation

Christian Toso,[1] Glenda Meeberg,[2] Roberto Hernandez-Alejandro,[3] Jean-François Dufour,[4] Paul Marotta,[3] Pietro Majno,[1] and Norman M. Kneteman[2]

(HEPATOLOGY 2015;62:158-165)

- 6000 hastalık kohort
- 195 hasta Milan +, 23 hasta Milan – ve TTV/AFP +
- TTV≤115 cm^3 ve AFP≤400 ng/mL
- 4 yıllık sağkalım %74.6
- 4 yıllık rekürrenssiz sağkalım %68

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

Gastroenterology 2018;154:128–139

CLINICAL—LIVER

Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma

Vincenzo Mazzaferro,[1] Carlo Sposito,[1] Jian Zhou,[2,3] Antonio D. Pinna,[4] Luciano De Carlis,[5] Jia Fan,[2,3] Matteo Cescon,[4] Stefano Di Sandro,[5] He Yi-feng,[2,3] Andrea Lauterio,[5] Marco Bongini,[1] and Alessandro Cucchetti[4]

- Tümör sayısı ve boyutu toplamı ve log_{10}AFP
- AFP<200 ng/mL tümör sayısı ve boyutu toplamı<7
- MVI –
- 5 yıllık sağkalım %74.9
- 5 yıllık rekürrenssiz sağkalım %77.9

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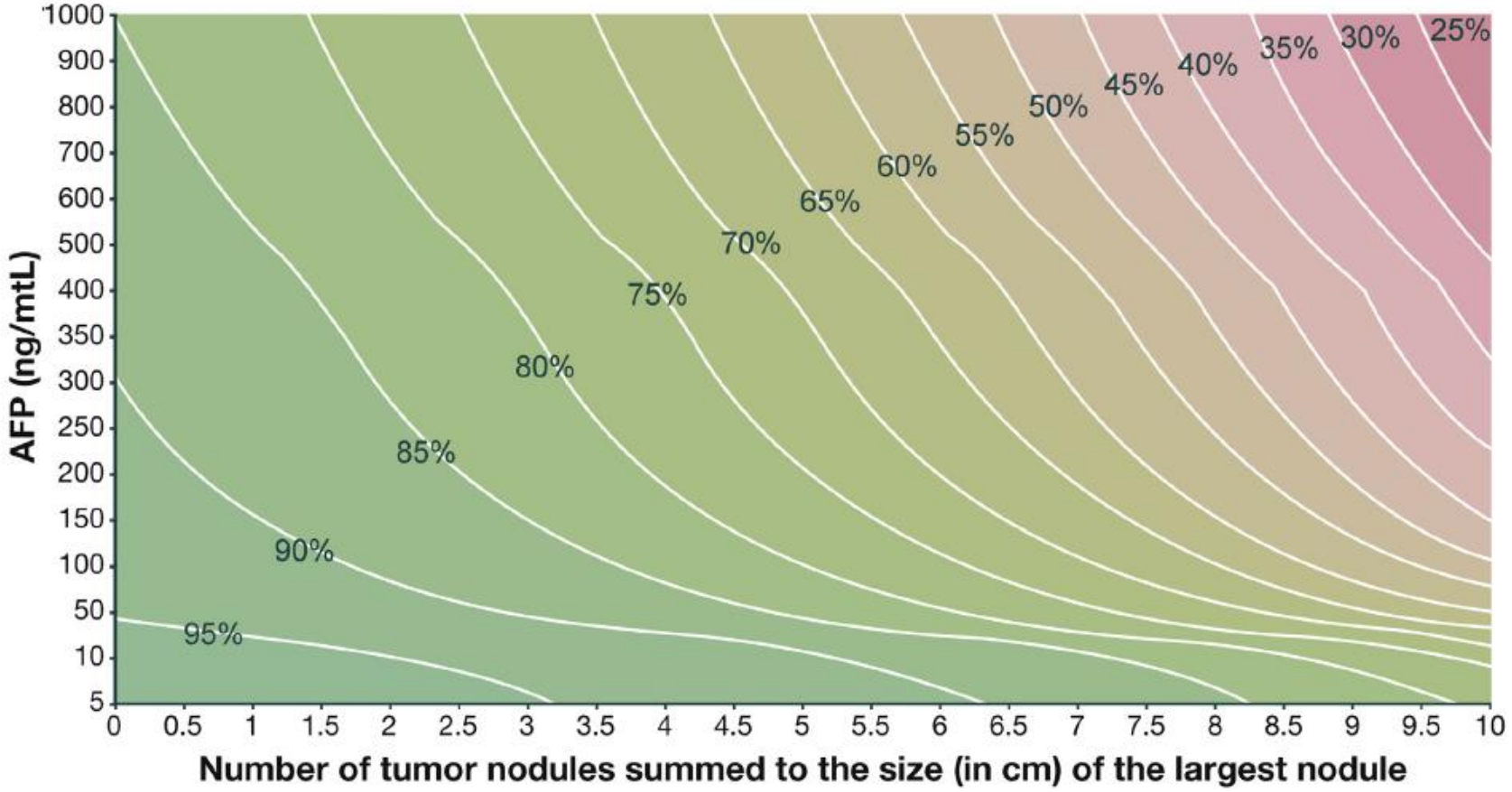

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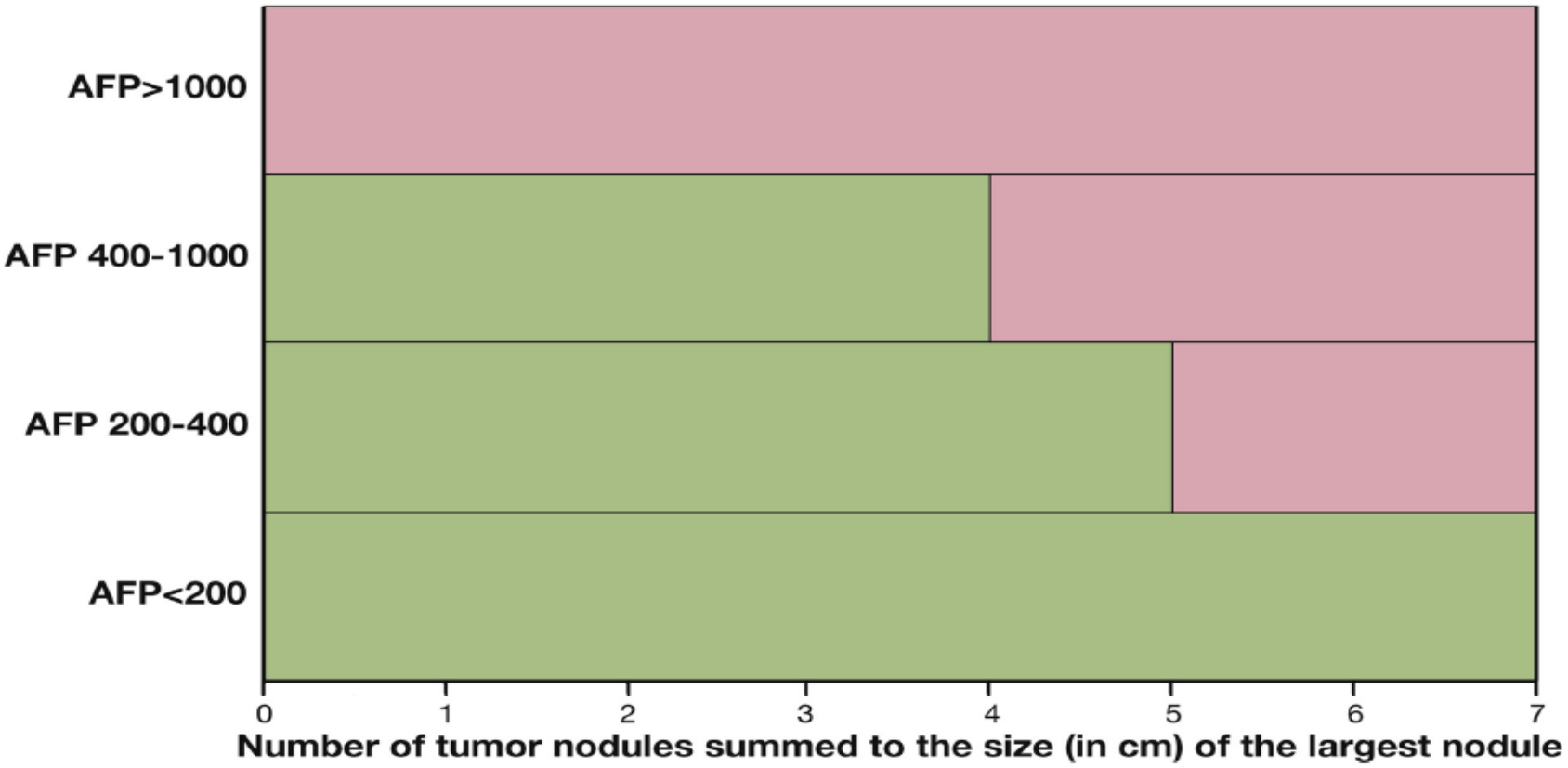

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Gastroenterology 2018;154:128–139

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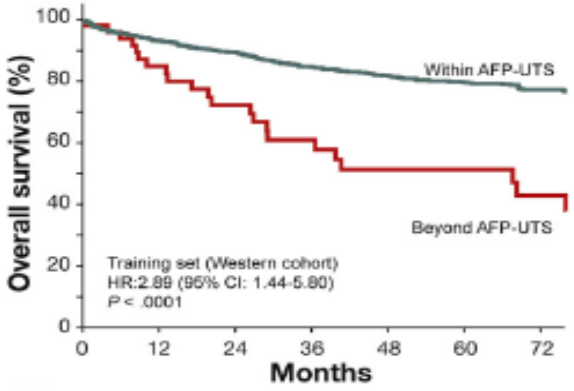
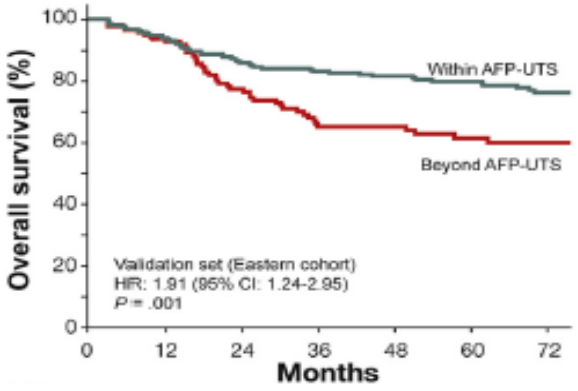
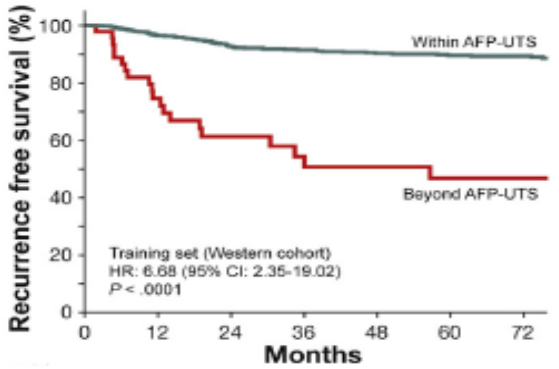
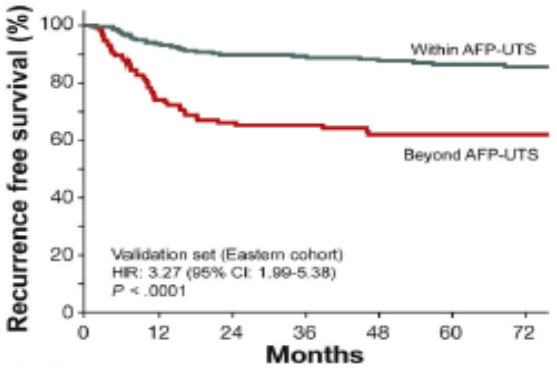








MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

Normal AFP
Yüksek DCP

→ **Kötü Diferansiasyon**
MVİ

Okuda H, et al. J Gastroenterol Hepatol 2001
Hong YM, et al. Tumour Biol 2017

Kyoto Kriterleri

→ **≤5 cm**
10 nodül
DCP≤400 mAU/mL

Kaido T, et al. Surgery 2013
Takada Y, et al. Dig Dis 2007
Fujiki M, et al. Am J Transplant 2009

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

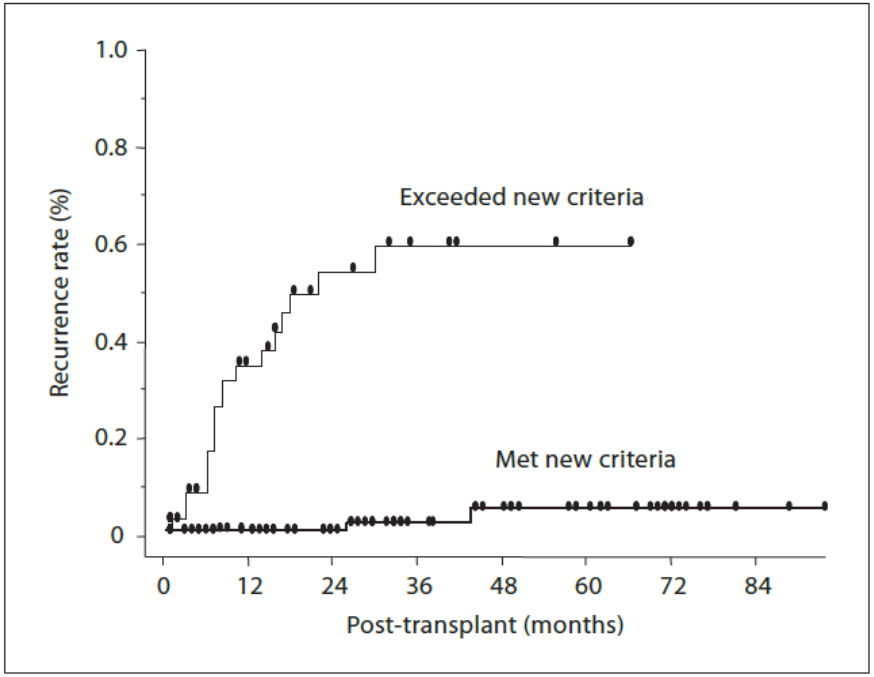
Digestive Diseases

Dig Dis 2007;25:299–302
DOI: 10.1159/000106908

Living Donor Liver Transplantation for Patients with HCC Exceeding the Milan Criteria: A Proposal of Expanded Criteria

Yasutsugu Takada[a] Takashi Ito[a] Mikiko Ueda[a] Seisuke Sakamoto[a]
Hironori Haga[b] Yoji Maetani[c] Kohei Ogawa[a] Yasuhiro Ogura[a]
Fumitaka Oike[a] Hiroto Egawa[a] Shinji Uemoto[a]

- 1999-2007
- Milan +: 74, Milan -: 62
- Kyoto Kriteri +: 33
- Rekürrens:
- Milan +: %7
- Kyoto +: %10



MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

Extended Indication for Living Donor Liver Transplantation in Patients With Hepatocellular Carcinoma

Yuji Soejima,[1,4] Akinobu Taketomi,[1] Tomoharu Yoshizumi,[1] Hideaki Uchiyama,[1] Shinich Aishima,[2] Takahiro Terashi,[2] Mitsuo Shimada,[3] and Yoshihiko Maehara[1]

(*Transplantation* 2007;83: 893–899)

- **Herhangi bir sayıda <5 cm**
- **DCP<300 mAU/mL**

- **Canlı verici kullanılan KT'nda HCC rekürrensini saptamada > Kyoto ve UCSF Kriterleri**

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

ORIGINAL ARTICLE

Serum Tumor Markers Provide Refined Prognostication in Selecting Liver Transplantation Candidate for Hepatocellular Carcinoma Patients Beyond the Milan Criteria

Jeong-Hoon Lee, MD, PhD, Yuri Cho, MD,*† Hwi Young Kim, MD, PhD,‡ Eun Ju Cho, MD, PhD,* Dong Hyeon Lee, MD,* Su Jong Yu, MD, PhD,* Jae Woo Lee, MD,* Nam-Joon Yi, MD, PhD,‡ Kwang-Woong Lee, MD, PhD,‡ Seoung Hoon Kim, MD, PhD,§ Jong Man Kim, MD, PhD,¶ Jae-Won Joh, MD, PhD,¶ Lewis W. Teperman, MD, PhD,|| James S. Park, MD, PhD,|| Yoon Jun Kim, MD, PhD,* Kyung-Suk Suh, MD, PhD,‡ and Jung-Hwan Yoon, MD, PhD**

(*Ann Surg* 2016;263:842–850)

- **HBV ağırlıklı hastalar**
- **Canlı vericili KT**
- **AFP ve DCP, HCC rekürrensinde etkili**

- **MoRAL ≤ 314.8, Milan – Genel Sağkalım %82.1**
  Rekürrenssiz Sağkalım %66.3

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

ORIGINAL ARTICLE

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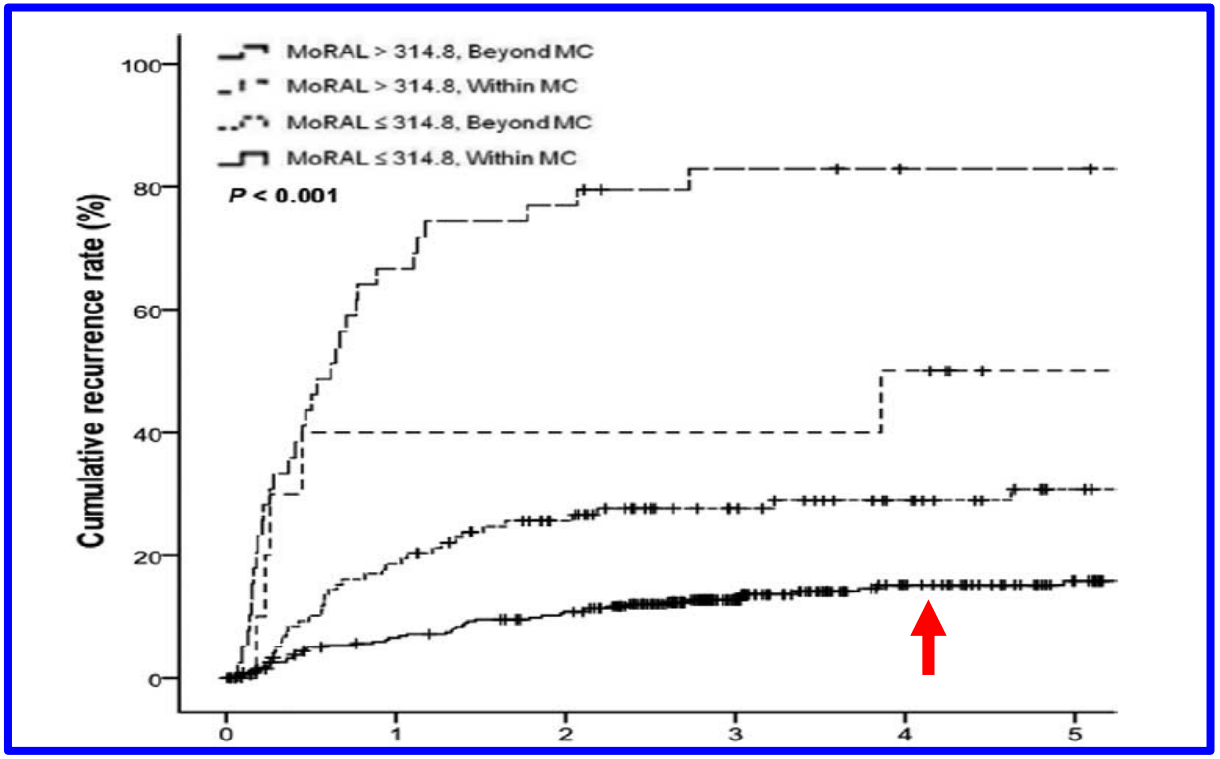

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

- **Milan – hastalarda LRT'lere yanıt HCC agresifliğini ve rekürrensini belirlemede akılcı bir yaklaşım**

Toniutto P, et al. Hepatoma Res 2020

- **LRT → Bekleme listesinden çıkarılma riskini ↓**

KT'na Köprü Tedavi

- **LRT'ye karşın 6 ay içinde progresyon → Kötü prognoz**

Lai Q, et al. Liver Transplant 2013
Otto G, et al. Liver Transplant 2006

- **LRT'ye yanıt → Tümörün biyolojik davranışı ile ilgili**

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

- **LRT sonrası kabul edilebilir sonuçlar sağlamada uygun kriterlere (Milan) ulaşmak için tümör yükünün azaltılması**

DownstagingTedavi

Rudnick SR, et al. Expert Rev Gastroenterol Hepatol 2018

- **TAKE**
- **TARE**
- **Neoadjuvan tedaviler**
  - **Tirozin kinaz inhibitörleri**
  - **Checkpoint inhibitörleri**

Sonbol MB, et al. JAMA Oncol 2020

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investi

N Engl J Med 2020;382:1894-905

BACKGROUND

The combination of atezolizumab and bevacizumab showed encouraging antitumor activity and safety in a phase 1b trial involving patients with unresectable hepatocellular carcinoma.

METHODS

In a global, open-label, phase 3 trial, patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib until unacceptable toxic effects occurred or there was a loss of clinical benefit. The coprimary end points were overall survival and progression-free survival in the intention-to-treat population, as assessed at an independent review facility according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).

RESULTS

The intention-to-treat population included 336 patients in the atezolizumab–bevacizumab group and 165 patients in the sorafenib group. At the time of the primary analysis (August 29, 2019), the hazard ratio for death with atezolizumab–bevacizumab as compared with sorafenib was 0.58 (95% confidence interval [CI], 0.42 to 0.79; P<0.001). Overall survival at 12 months was 67.2% (95% CI, 61.3 to 73.1) with atezolizumab–bevacizumab and 54.6% (95% CI, 45.2 to 64.0) with sorafenib. Median progression-free survival was 6.8 months (95% CI, 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6) in the respective groups (hazard ratio for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001). Grade 3 or 4 adverse events occurred in 56.5% of 329 patients who received at least one dose of atezolizumab–bevacizumab and in 55.1% of 156 patients who received at least one dose of sorafenib. Grade 3 or 4 hypertension occurred in 15.2% of patients in the atezolizumab–bevacizumab group; however, other high-grade toxic effects were infrequent.

CONCLUSIONS

In patients with unresectable hepatocellular carcinoma, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival outcomes than sorafenib. (Funded by F. Hoffmann–La Roche/Genentech; ClinicalTrials.gov number, NCT03434379.)

MORFOLOJİK ÖLÇÜMLERE SERUM AFP VE/VEYA DCP EKLENMESİNE DAYALI KRİTERLER

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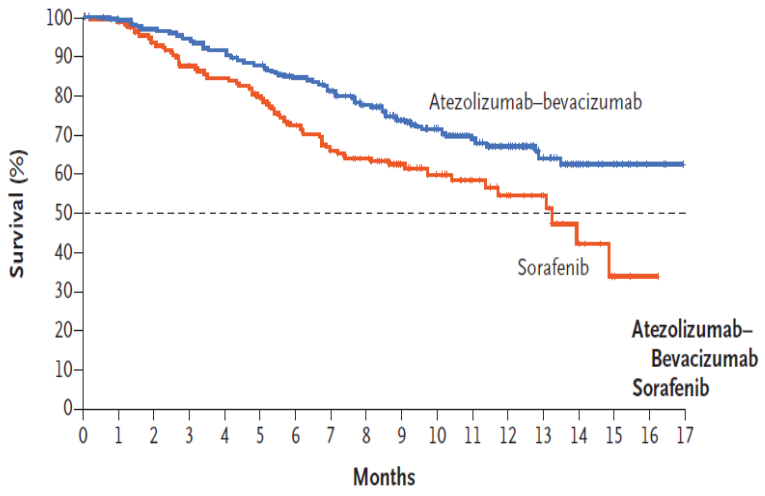
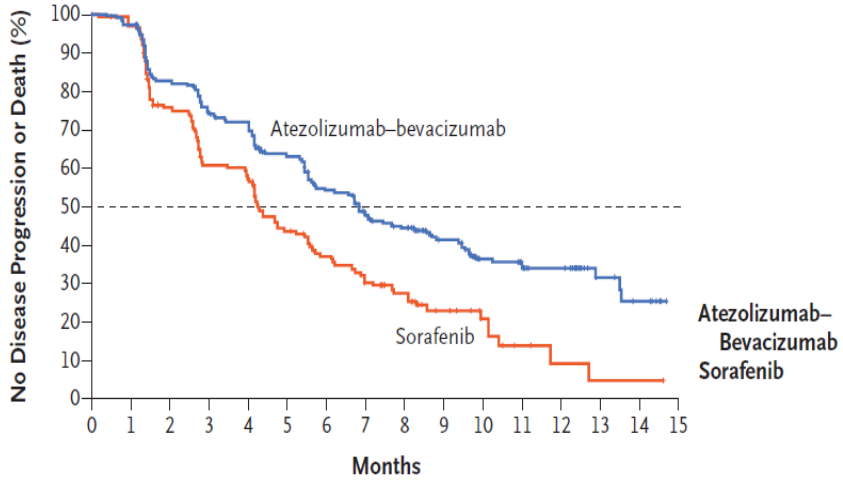
N Engl J Med 2020;382:1894-905

Overall Survival



Survival without Disease Progression



HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

mRECIST

- **Tam yanıt (CR)**
- **Parsiyel yanıt (PR)**
- **Stabil hastalık (SD)**
- **Progressif hastalık (PD)**

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

Hepatocellular Carcinoma:
CT for Tumor Response after Transarterial Chemoembolization in Patients Exceeding Milan Criteria—— Selection Parameter for Liver Transplantation[1]

Irene Bargellini, MD
Claudio Vignali, MD
Roberto Cioni, MD
Pasquale Petruzzi, MD
Antonio Cicorelli, MD
Daniela Campani, MD
Paolo De Simone, MD
Franco Filipponi, MD
Carlo Bartolozzi, MD

- **Milan -, TAKE sonrası KT**
- **33 hasta**
- **5 yıllık sağkalım**
  - **CR %94.4**
  - **PR %45.4**
  - **SD %50**

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

HEPATOLOGY

AASLD

HEPATOLOGY, VOL. 71, NO. 3, 2020

National Experience on Down-Staging of Hepatocellular Carcinoma Before Liver Transplant: Influence of Tumor Burden, Alpha-Fetoprotein, and Wait Time

Neil Mehta [1], Jennifer L. Dodge,[2] Joshua D. Grab,[2] and Francis Y. Yao[1,2]

- **UNOS Veritabanı, Retrospektif çalışma**
- **3819 hasta**
- **Milan +, UNOS-DS**
- **KT sonrası 3 yıllık sağkalım**
  - **Milan + %83.2**
  - **UNOS-DS %79.1**
- **3 yıllık rekürrens: Milan + %6.9, UNOS-DS %12.8**
- **UNOS-DS – KT sonrası rekürrenste AFP≥100 ng/mL**

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

Vincenzo Mazzaferro, Davide Citterio, Sherrie Bhoori, Marco Bongini, Rosalba Miceli, Luciano De Carlis, Michele Colledan, Mauro Salizzoni, Renato Romagnoli, Barbara Antonelli, Marco Vivarelli, Giuseppe Tisone, Massimo Rossi, Salvatore Gruttadauria, Stefano Di Sandro, Riccardo De Carlis, Maria Grazia Lucà, Massimo De Giorgio, Stefano Mirabella, Luca Belli, Stefano Fagiuoli, Silvia Martini, Massimo Iavarone, Gianluca Svegliati Baroni, Mario Angelico, Stefano Ginanni Corradini, Riccardo Volpes, Luigi Mariani, Enrico Regalia, Maria Flores, Michele Droz dit Busset, Carlo Sposito

Lancet Oncol 2020; 21: 947–56

- **74 hasta, randomize kontrollü**
- **Makrovasküler invazyon -, metastaz-**
- **5 yıllık yaşam beklentisi en az %50 olan hastalar**
- **CTP 5-7**
- **LRT / Sistemik tedavi**
- **3 ay izlem (Sorafenib tedavisine devam)**
- **mRECIST – CR / PR AFP izlemi**
- **KT vs. LRT / Sistemik tedavi**

HCC'NİN KÖPRÜ YA DA DOWNSTAGING TEDAVİLERİNE YANITI TEMELİNDE KRİTERLER

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Lancet Oncol 2020; 21: 947–56

- **Droup-out: 29/74 %39.1**
- **KT: 23**
- **LRT/Sistemik tedavi: 22**

Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial

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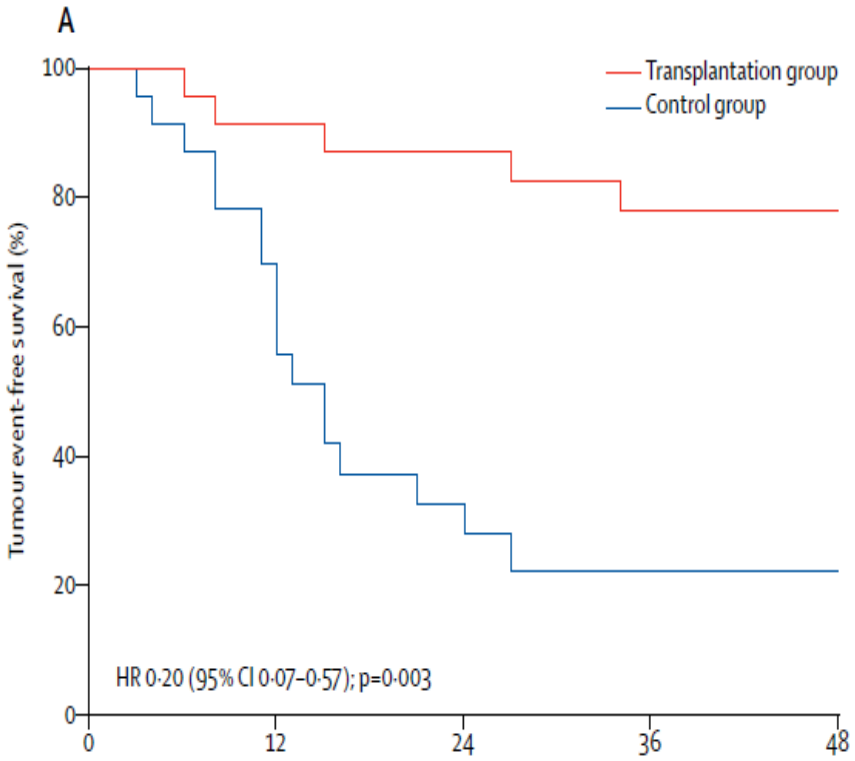

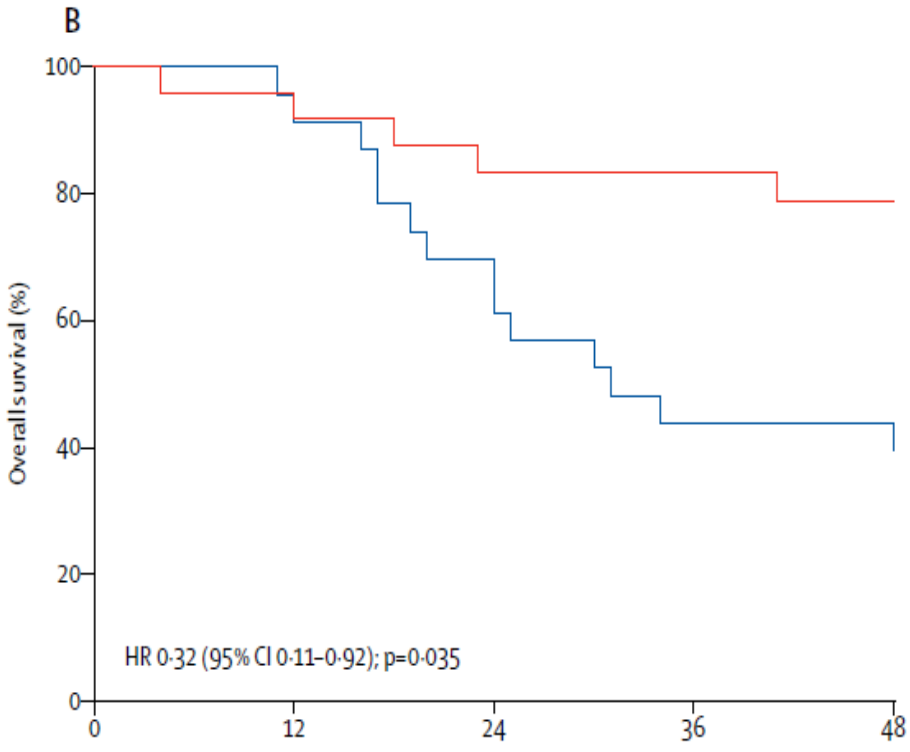

%76.8 vs. %18.3

%77.5 vs. %31.2

LIVER TRANSPLANTATION 18:1226-1236, 2012

ORIGINAL ARTICLE

Living Donor Liver Transplantation Versus Deceased Donor Liver Transplantation for Hepatocellular Carcinoma: A Meta-Analysis

Wenhua Liang,[1*] Linwei Wu,[1*] Xiaoting Ling,[1*] Paul M. Schroder,[2] Weiqiang Ju,[1] Dongping Wang,[1] Yushu Shang,[1] Yuan Kong,[1] Zhiyong Guo,[1] and Xiaoshun He[1]

[1]*Organ Transplant Center, First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; and*
[2]*Department of Medical Microbiology and Immunology, University of Toledo College of Medicine, Toledo, OH*

Because of the severe organ shortage, living donor liver transplantation (LDLT) offers a timely alternative to deceased donor liver transplantation (DDLT) for patients with hepatocellular carcinoma (HCC). However, the higher recurrence rate of HCC after LDLT and the indication criteria remain controversial. By conducting a quantitative meta-analysis, we sought to compare the survival outcomes and recurrence rates with LDLT and DDLT for patients with HCC. Comparative studies of LDLT and DDLT for HCC, which were identified by a comprehensive literature search, were included in this study. The evaluated outcomes included patient survival, recurrence-free survival (RFS), and recurrence rates at defined time points. Seven studies with a total of 1310 participants were included in this study. For LDLT and DDLT recipients, we found comparable patient survival rates [1 year, odds ratio (OR) = 1.03, 95% confidence interval (CI) = 0.62-1.73; 3 years, OR = 1.07, 95% CI = 0.77-1.48; and 5 years, OR = 0.64, 95% CI = 0.33-1.24] and RFS rates (1 year, OR = 0.86, 95% CI = 0.54-1.38; 3 years, OR = 1.04, 95% CI = 0.69-1.58; and 5 years, OR = 1.11, 95% CI = 0.70-1.77). Moreover, we found no significant differences in the 1-, 3-, or 5-year recurrence rates between LDLT and DDLT recipients (1 year, OR = 1.55, 95% CI = 0.36-6.58; 3 years, OR = 2.57, 95% CI = 0.53-12.41; and 5 years, OR = 1.21, 95% CI = 0.44-3.32). A subgroup analysis revealed similar outcomes for patients with HCC meeting the Milan criteria. These findings demonstrate that for HCC patients (especially those within the Milan criteria), LDLT represents an acceptable option that does not compromise patient survival or increase HCC recurrence in comparison with DDLT. *Liver Transpl 18:1226-1236, 2012.*

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i37.4206

World J Gastroenterol 2011 October 7; 17(37): 4206-4212
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Comparison of Milan and UCSF criteria for liver transplantation to treat hepatocellular carcinoma

Tarkan Unek, Sedat Karademir, Naciye Cigdem Arslan, Tufan Egeli, Gulsen Atasoy, Ozgul Sagol, Funda Obuz, Mesut Akarsu, Ibrahim Astarcioglu

Table 3 Follow-up data for patients who underwent orthotopic liver transplantation for hepatocellular carcinoma *n* (%)

Variables	Milan +	Milan -/UCSF +	UCSF -
No. of patients	34	7	15
Post-operative death	2 (5.9)	-	1 (4.5)
Death	5 (14.7)	2 (28.6)	11 (73.3)
HCC recurrence	2 (5.8)	1 (14.3)	6 (40.0)
Median follow-up	51.5 (1:124)	32 (1:66)	14 (3:66)

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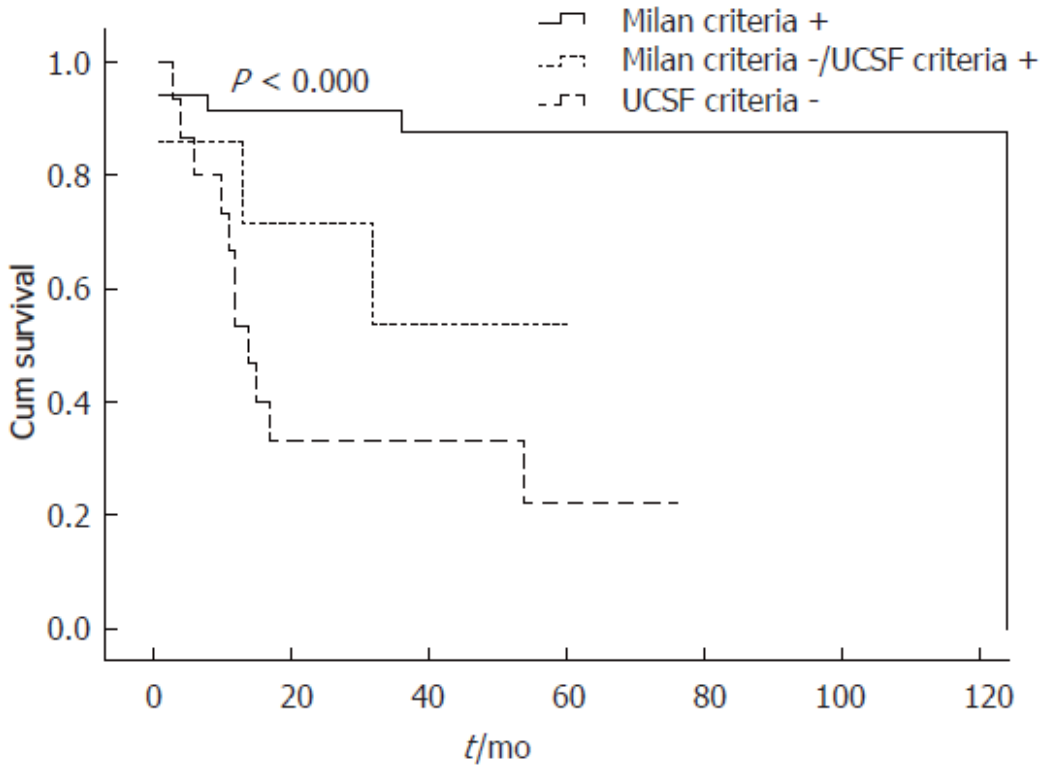
Genel Sağkalım



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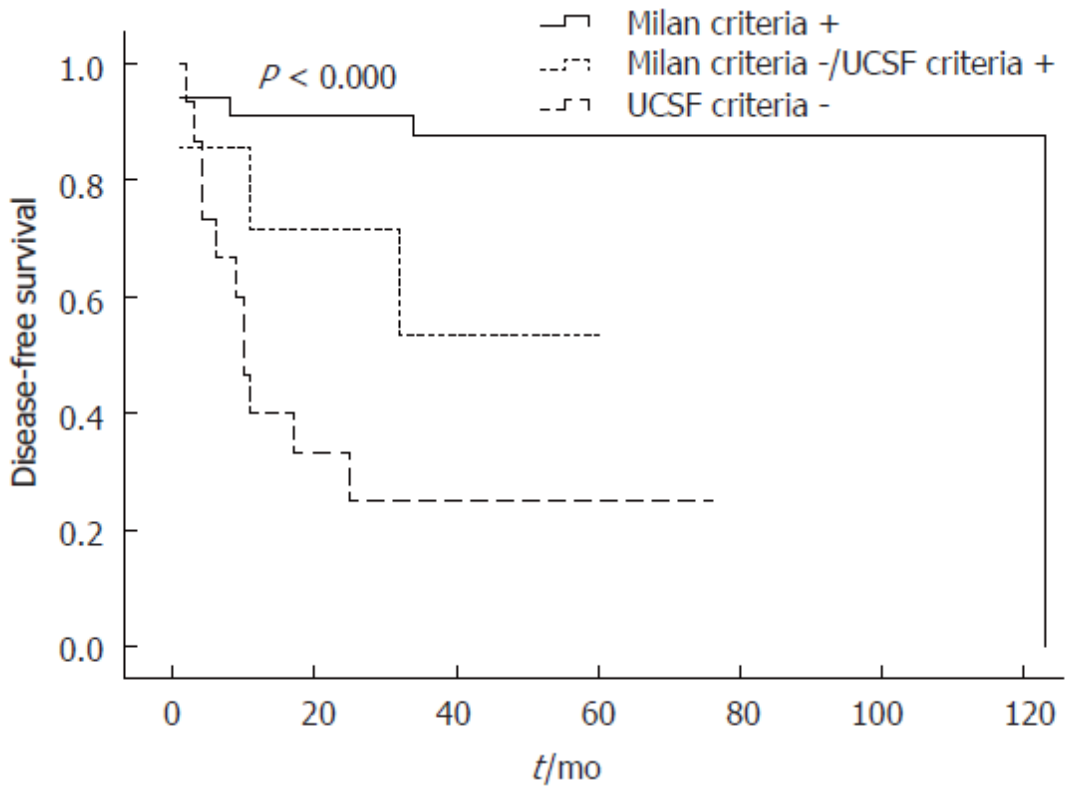
Hastalıksız Sağkalım



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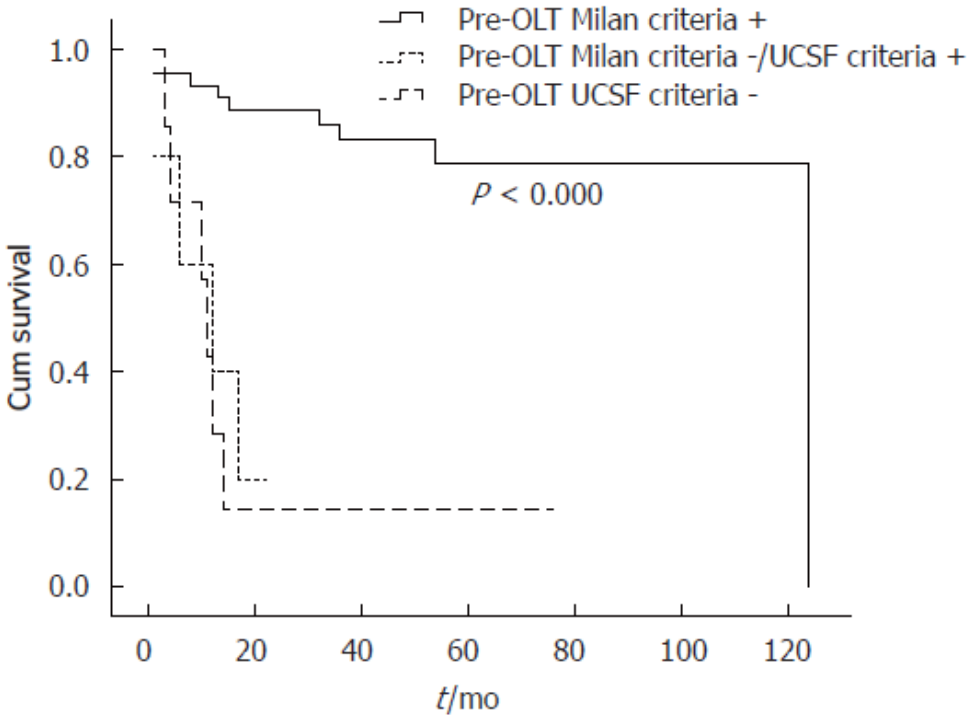
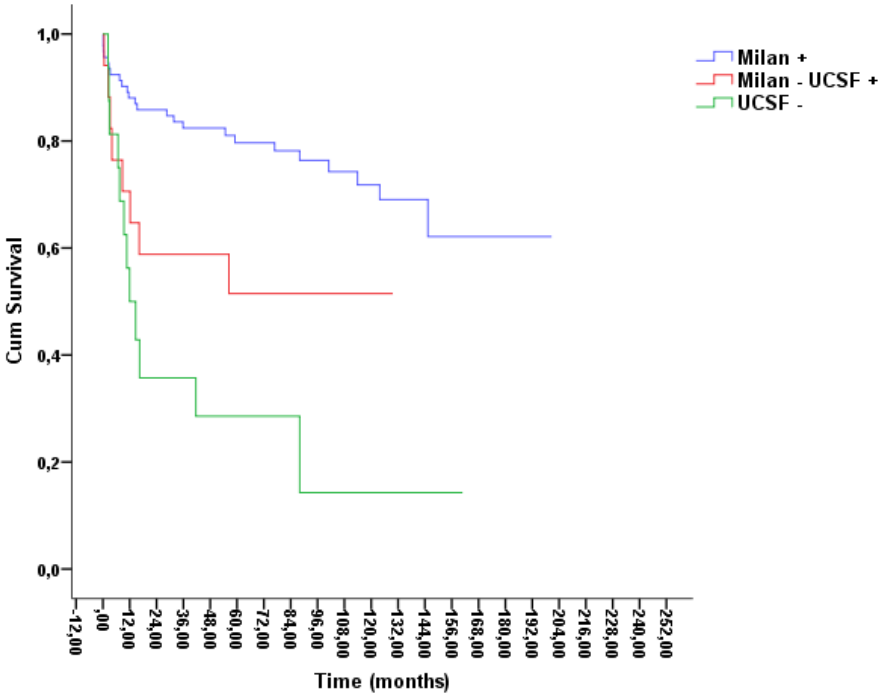
KT Öncesi Radyolojik Görüntülemeye Göre Sağkalım



Dokuz Eylül Üniversitesi Deneyimi

Milan ve UCSF Kriterlerine Göre Overall Sağkalım



p=0.000

Milan + (92 hasta)
3-yıl %82.4
5-yıl %79.7
10-yıl %71.8
15-yıl %62.1
Ortalama Sağkalım: 149.31±8.97 yıl

Milan – UCSF + (17 hasta)
3-yıl %58.8
5-yıl %51.5
10-yıl %51.5
Ortalama Sağkalım: 73.64±14.50 yıl

UCSF - (15 hasta)
3-yıl %35.7
5-yıl %28.6
10-yıl %14.3
Ortalama Sağkalım: 44.14±8.36 yıl

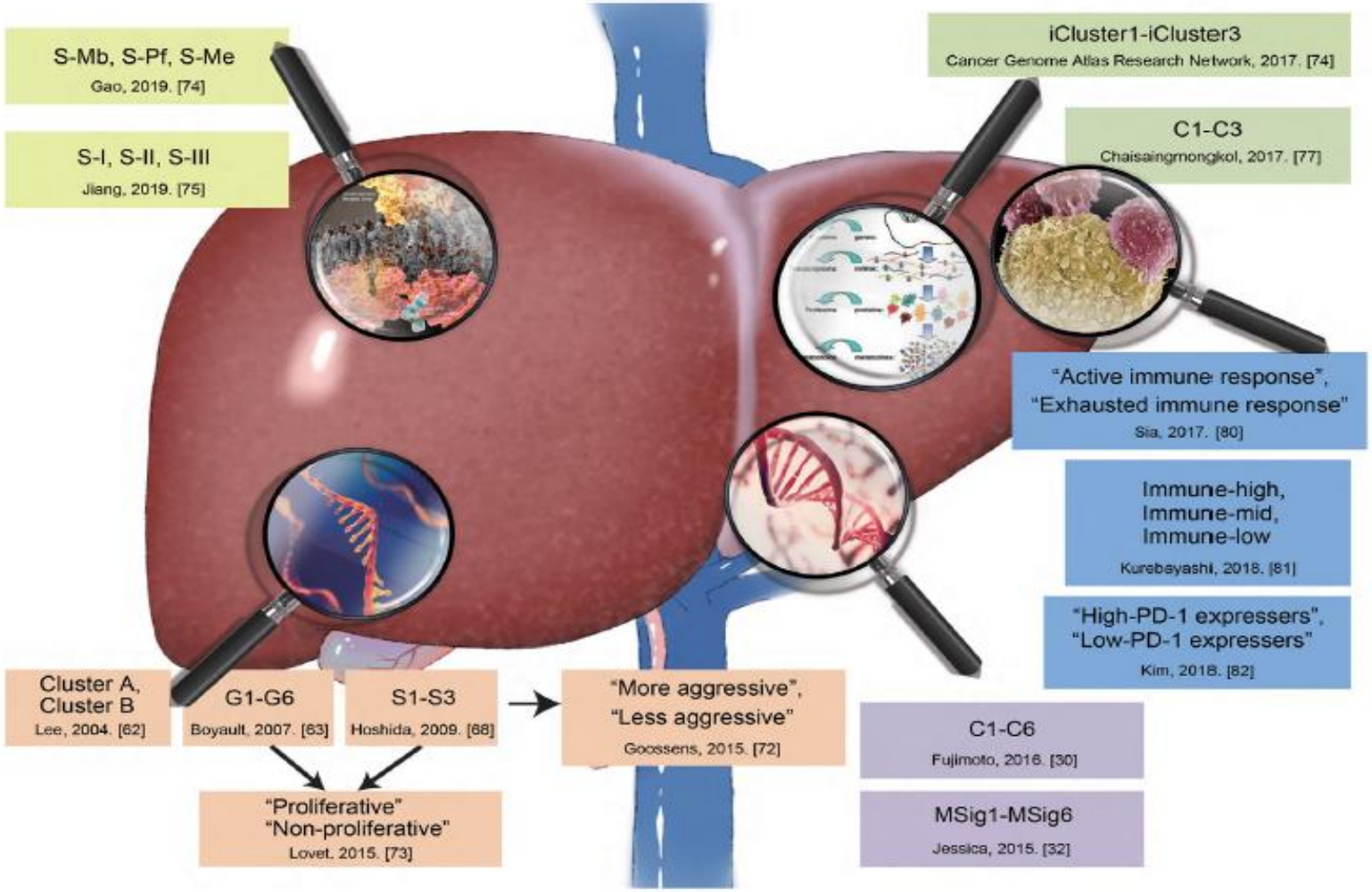
DOI: 10.1002/cac2.12115

REVIEW

CANCER COMMUNICATIONS Open Access

Molecular subtyping of hepatocellular carcinoma: A step toward precision medicine

Yichao Wu[1,2,3,#] | Zhikun Liu[1,2,3,#] | Xiao Xu[1,2,3]



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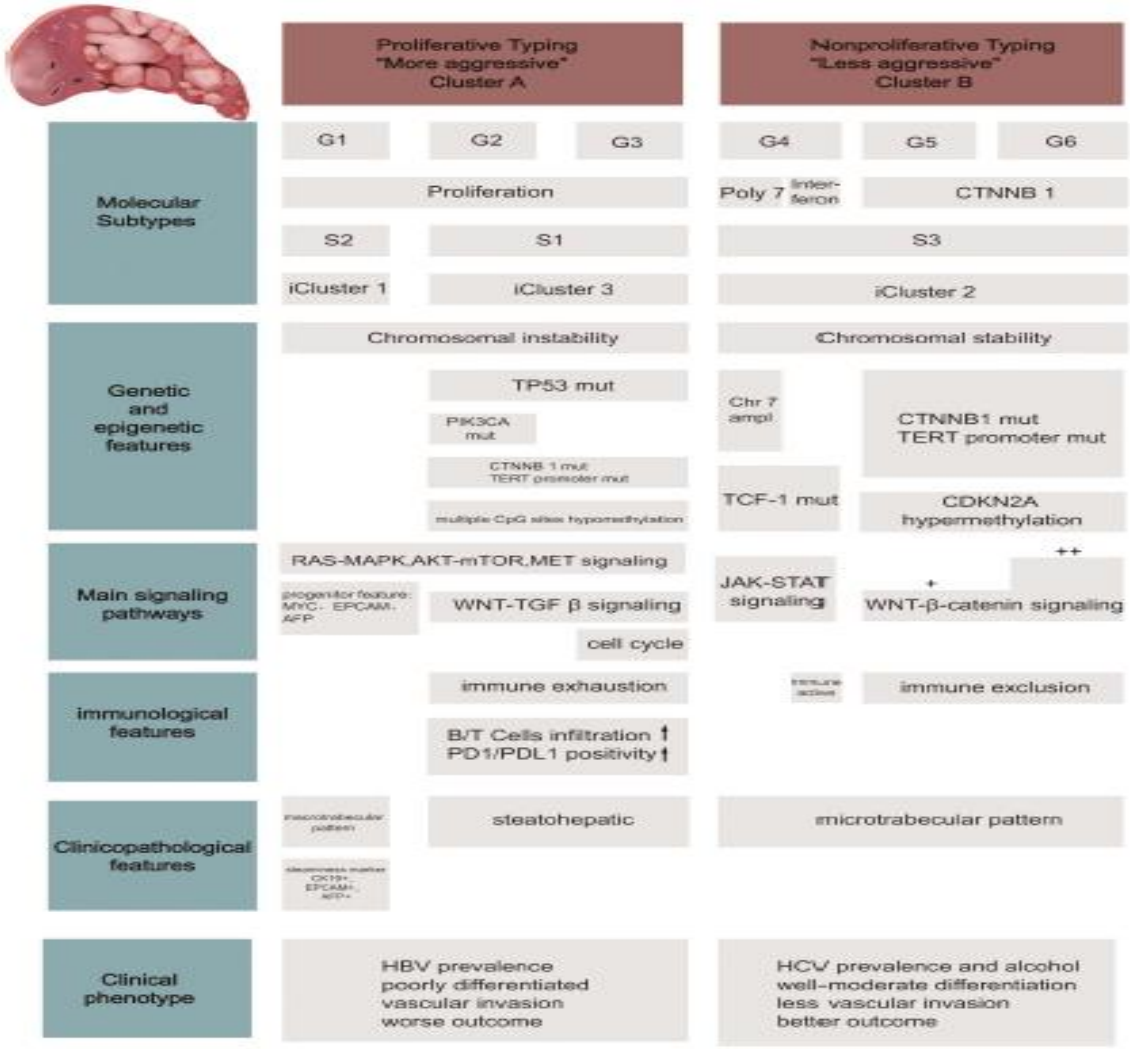


SONUÇ VE ÖNERİLER

- **Ülkemizde ve birçok ülkede kadaverik karaciğer graftı dağıtımında Milan Kriterleri geçerli**
- **Canlı vericili KT için Milan Kriterleri çok sınırlayıcı**
- **Kriterler genişledikçe bekleme listesinde artış kaçınılmaz – Hasta seçimi?**
- **Kriterler genişlediğinde canlı vericilerin kullanımında artış – Verici komplikasyonları**
- **Tümör biyolojisini ortaya koyan daha iyi kriterlere gereksinim var**

TEŞEKKÜR EDERİM

SORU

- **52 yaşında erkek hasta**
- **HBV'ye bağlı siroz**
- **CTP: 9, MELD-Na: 15**
- **Total Bilirubin: 2.2 mg/dL**
- **Tümör çapları 4.5, 3.5 ve 1.5 cm olan 3 HCC**
- **18F–FDG PET-BT: Tutulum yok**

- **Downstaging ? / Karaciğer transplantasyonu ?**

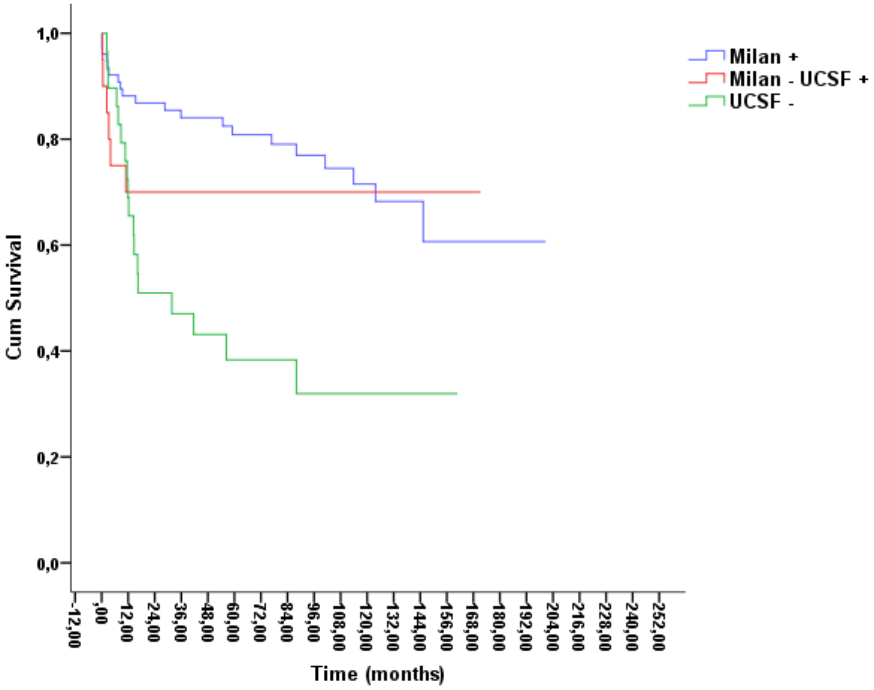
Dokuz Eylül Üniversitesi Deneyimi

Radyolojik ve Patolojik Milan ve UCSF Kriterlerindeki Kaymalar

Rad. Milan+ (92)	→	**Pat.**	**Milan+**	**75**
			Milan- UCSF+	**10**
			UCSF-	**7**
Rad. Milan- UCSF+ (17)	→	**Pat.**	**Milan+**	**1**
			Milan- UCSF+	**8**
			UCSF-	**8**
Rad. UCSF- (16)	→	**Pat.**	**Milan+**	**1**
			Milan- UCSF+	**1**
			UCSF-	**14**

Dokuz Eylül Üniversitesi Deneyimi

Patolojik Milan ve UCSF Kriterlerine Göre Overall Sağkalım



p=0.001

Milan + (76hasta)
3-yıl %85.5
5-yıl %80.8
10-yıl %71.5
15-yıl %60.7
Ortalama Sağkalım: 149.25±9.74 yıl

Milan – UCSF + (20 hasta)
3-yıl %70
5-yıl %70
10-yıl %70
Ortalama Sağkalım: 120.89±17.18 yıl

UCSF - (29 hasta)
3-yıl %47
5-yıl %38.3
10-yıl %31.9
Ortalama Sağkalım: 67.48±13.22 yıl