HCC'de Karaciğer Nakli Sınırları Nedir, Nerede Durmalıyım? Milanı Aşabiliriz!

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Karaciğer Nakli Enstitüsü - Malatya

Sunum Planı

- Birinci bölüm
  - HCC için Karaciğer Nakli ve Milan kriterleri
  - Genişletilmiş kriterler

- İkinci bölüm
  - HCC için Karaciğer Naklinde Malatya deneyimi
  - Kriterlerin Malatya kohortuna uygulanarak karşılaştırılması

- Son bölüm
  - İleri evre HCC için Karaciğer Nakli
  - Çıkarımlarımız

HCC için Karaciğer Nakli

- **Karaciğer nakli (KN), hem altta yatan sirozu hem de tümörü uzaklaştırdığı için, HCC'de etkin bir küratif tedavi yöntemidir**

- **HCC için KN'de iki temel hedef**

  1. **Uzun greft ve hasta sağ kalımı**
  2. **Tümörsüz yaşam**

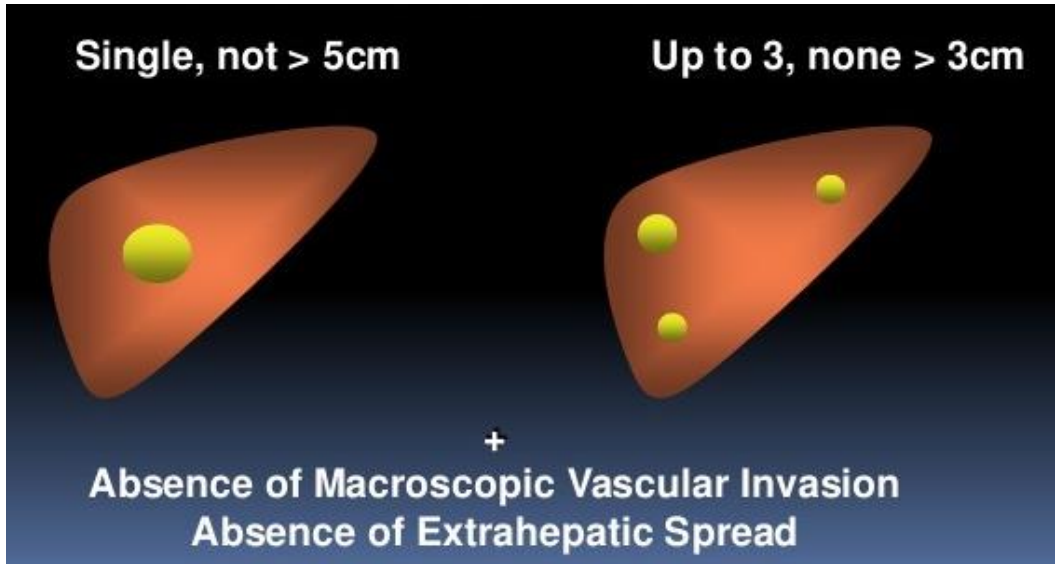
  5-yıllık hedef sağ kalım, minimum %50* – 61**

- **Başarının anahtarı "<u>Hasta Seçimi</u>"dir**

*Neuberger J, et al. Lancet 1999;354:1636–1639.
*Bruix J et al. Liver Transpl 2003; **9**: 700–702.
**Volk ML, et al. Am J Transplant. 2008 Apr;8(4):839-46.
**Mehta N, et al. Transplantation. 2020;104(6):1136-1142.

HCC için KN'de Hasta Seçimi – Milan K.

- **Milan kriterleri 1996*:**
  - **HCC için KN'de dönüm noktası**
  - **Hedeflenen yaşamlara ulaşıldı**
    - ***4-yıllık %85 sağkalım***
  - **Tüm dünyada ve Türkiye'de, HCC için kadavradan KN'de hasta seçim kriteri olarak kabul edildi**



*Mazzafero V, et al. N Engl J Med 1996;334(11):693-9.

HCC için KN'de Hasta Seçimi – Genişletilmiş K.

- **Genişletilmiş kriterler:**
  - **Milan kriterlerinin sonuçları mükemmel**
  - **Hedeflenen yaşamlara ulaşıldı**
  - **Ancak kriterler çok sıkı. Milan dışında kalan, ancak KN yapıldığında sağkalım sonuçları, Milan kriteri içindekilerle benzer olan hastaları, KN'den mahrum ediyor**
  - **Morfolojik parametrelere ek olarak, tümör davranışını tahmin edecek parametreler kullanılabilir**
  - **Milan kriterleri genişletilmeli**

HCC'de Karaciğer Nakli Sınırları Nedir, Nerede Durmalıyım?

Milanı Aşabiliriz!

1996 – Milan

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.)

THE value of orthotopic liver transplantation in the treatment of hepatocellular carcinoma has often been debated. Although liver replacement could be curative for patients with tumors confined to the liver, the long-term results of liver transplantation in patients with hepatocellular carcinoma have been disappointing, with an overall five-year survival rate ranging from 30 to 40 percent.[1-9]

In recent years, revisions of the tumor–node–metastasis (TNM) classification system[9] and other systems for determining the stage of hepatocellular carcinoma[10] have made possible a more detailed, retrospective analysis of treatment in these patients. In several studies, tumor stage before transplantation was directly related to the rate of recurrence of cancer after liver transplantation. Moreover, in patients with early-stage hepatocellular carcinoma, liver transplantation was more effective than resection of the liver.[11-13] To examine further the efficacy of transplantation, we undertook a prospective cohort study of patients with cirrhosis who had unresectable hepatocellular carcinomas and who received liver transplants; in this study we also assessed the influence of characteristics used to select patients for transplantation on the recurrence of cancer and on survival.

From the Liver Transplantation Unit, Department of Surgery (V.M., E.R., R.D., A.P., F.B., F.M., L.G.), and the Departments of Pathology (S.A.) and Anesthesia (M.A.), National Cancer Institute, and the Institute of Medical Statistics and Biometry, University of Milan (A.M.) — all in Milan, Italy. Address reprint requests to Dr. Gennari at the Liver Transplantation Unit, Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy.

Supported by the Italian Association for Cancer Research.

METHODS

Study Design

Between January 1991 and December 1994, 295 patients with hepatocellular carcinoma who were seen at the Division of Gastrointestinal Surgery of the National Cancer Institute in Milan, Italy, were judged to have cancer that was unresectable because of the location of the tumor in the liver, because the tumor was multifocal, or because the patient had advanced hepatic insufficiency related to cirrhosis. Among those 295 patients, 60 who had histologically proved cirrhosis (20 percent) were eligible for the present study because their tumors were at an early stage. The diagnosis of hepatocellular carcinoma was confirmed in all patients either by biopsy of the tumor or by a serum alpha-fetoprotein measurement above 300 ng per milliliter.

For patients with a single hepatocellular carcinoma to be eligible for the study, the tumor could not exceed 5 cm in diameter. In patients with multiple tumors, there could be no more than three tumors, none exceeding 3 cm in diameter. Patients in whom tumor invasion of blood vessels or lymph nodes was evident or suspected preoperatively were excluded.

Forty-eight patients received transplants during the study period, 1 patient died while awaiting transplantation, and 11 others were still awaiting transplantation on September 30, 1995. Once patients were accepted as candidates for transplantation, preoperative treatment of their tumor was scheduled, depending on their Child–Pugh class (indicating the adequacy of liver function) at that time (Table 1). Patients in Child–Pugh class A (12 patients) or class B (21 patients) received anticancer treatment before transplantation (hepatic-artery chemoembolization in 26 patients, percutaneous injection of alcohol in 1 patient, and hepatic resection three years before liver transplantation in the single patient with the fibrolamellar variant of hepatocellular carcinoma). The five remaining patients who were otherwise eligi-

2009 – Up To 7

Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis

*Vincenzo Mazzaferro, Josep M Llovet, Rosalba Miceli, Sherrie Bhoori, Marcello Schiavo, Luigi Mariani, Tiziana Camerini, Sasan Roayaie, Myron E Schwartz, Gian Luca Grazi, René Adam, Peter Neuhaus, Mauro Salizzoni, Jordi Bruix, Alejandro Forner, Luciano De Carlis, Umberto Cillo, Andrew K Burroughs, Roberto Troisi, Massimo Rossi, Giorgio E Gerunda, Jan Lerut, Jacques Belghiti, Ilka Boin, Jean Gugenheim, Fedja Rochling, Bart Van Hoek, Pietro Majno, on behalf of the Metroticket Investigator Study Group**

Summary

Background Patients undergoing liver transplantation for hepatocellular carcinoma within the Milan criteria (single tumour ≤5 cm in size or ≤3 tumours each ≤3 cm in size, and no macrovascular invasion) have an excellent outcome. However, survival for patients with cancers that exceed these criteria remains unpredictable and access to transplantation is a balance of maximising patients' chances of cure and organ availability. The aim of this study was to explore the survival of patients with tumours that exceed the Milan criteria, to assess whether the criteria could be less restrictive, enabling more patients to qualify as transplant candidates, and to derive a prognostic model based on objective tumour characteristics, to see whether the Milan criteria could be expanded.

Methods Data on patients who underwent transplantation for hepatocellular carcinoma despite exceeding Milan criteria at different centres were recorded via a web-based survey completed by specialists from each centre. The survival of these patients was correlated retrospectively with the size of the largest tumour nodule, number of nodules, and presence or absence of microvascular invasion detected at pathology. Contoured multivariable regression Cox models produced survival estimates by means of different combinations of the covariates. The primary aim of this study was to derive a prognostic model of overall survival based on tumour characteristics, according to the main parameters used in the Tumour Node Metastasis classification. The secondary aim was the identification of a subgroup of patients with hepatocellular carcinoma exceeding the Milan criteria, who achieved a 5-year overall survival of at least 70%—ie, similar to the outcome expected for patients who meet the Milan criteria.

Findings Over a 10-month period, between June 25, 2006, and April 3, 2007, data for 1556 patients who underwent transplantation for hepatocellular carcinoma were entered on the database by 36 centres. 1112 patients had hepatocellular carcinoma exceeding Milan criteria and 444 patients had hepatocellular carcinoma shown not to exceed Milan criteria at post-transplant pathology review. In the group of patients with hepatocellular carcinomas exceeding the criteria, the median size of the largest nodule was 40 mm (range 4–200) and the median number of nodules was four (1–20). 454 of 1112 patients (41%) had microvascular invasion and, for those transplanted outside the Milan criteria, 5-year overall survival was 53·6% (95% CI 50·1–57·0), compared with 73·3% (68·2–77·7) for those that met the criteria. Hazard ratios (HR) associated with increasing values of size and number were 1·34 (1·25–1·44) and 1·51 (1·21–1·88), respectively. The effect was linear for size, whereas for number of tumours, the effect tended to plateau above three tumours. The effect of tumour size and number on survival was mediated by recurrence (b=0·08, SE=0·12, p=0·476). The presence of microvascular invasion doubled HRs in all scenarios. The 283 patients without microvascular invasion, but who fell within the Up-to-seven criteria (hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours) achieved a 5-year overall survival of 71·2% (64·3–77·0).

Interpretation More patients with hepatocellular carcinoma could be candidates for transplantation if the current dual (yes/no) approach to candidacy, based on the strict Milan criteria, were replaced with a more precise estimation of survival contouring individual tumour characteristics and use of the up-to-seven criteria.

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See Reflection and Reaction page 5

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2018 – Metroticket 2.0

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CLINICAL—LIVER

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

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CLINICAL LIVER

BACKGROUND & AIMS: Outcomes of liver transplantation for hepatocellular carcinoma (HCC) are determined by cancer-related and non-related events. Treatments for hepatitis C virus infection have reduced non-cancer events among patients receiving liver transplants, so reducing HCC-related death might be an actionable end point. We performed a competing-risk analysis to evaluate factors associated with survival of patients with HCC and developed a prognostic model based on features of HCC patients before liver transplantation. **METHODS:** We performed multivariable competing-risk regression analysis to identify factors associated with HCC-specific death of patients who underwent liver transplantation. The training set comprised 1018 patients who underwent liver transplantation for HCC from January 2000 through December 2013 at 3 tertiary centers in Italy. The validation set comprised 341 consecutive patients who underwent liver transplantation for HCC during the same period at the Liver Cancer Institute in Shanghai, China. We collected pretransplantation data on etiology of liver disease, number and size of tumors, patient level of α-fetoprotein (AFP), model for end-stage liver disease score, tumor stage, numbers and types of treatment, response to treatments, tumor grade, microvascular invasion, dates, and causes of death. Death was defined as HCC-specific when related to HCC recurrence after transplantation, disseminated extra- and/or intrahepatic tumor relapse and worsened liver function in presence of tumor spread. The cumulative incidence of death was segregated for hepatitis C virus status. **RESULTS:** In the competing-risk regression, the sum of tumor number and size and of $\log_{10}$ level of AFP were significantly associated with HCC-specific death ($P < .001$), returning an average c-statistic of 0.780 (95% confidence interval, 0.763–0.798). Five-year cumulative incidence of non–HCC-related death was 8.6% in HCV-negative patients and 18.1% in HCV-positive patients. For patients with HCC to have a 70% chance of HCC-specific survival 5 years after transplantation, their level of AFP should be <200 ng/mL and the sum of number and size of tumors (in centimeters) should not exceed 7; if the level of AFP was 200–400 ng/mL, the sum of the number and size of tumors should be ≤5; if their level of AFP was 400–1000 ng/mL, the sum of the number and size of tumors should be ≤4. In the validation set, the model identified patients who survived 5 years after liver transplantation with 0.721 accuracy (95% confidence interval, 0.648%–0.793%). Our model, based on patients' level of AFP and HCC number and size, outperformed the Milan; University of California, San Francisco; Shanghai-Fudan; Up-to-7 criteria ($P < .001$); and AFP French model ($P = .044$) to predict which patients will survive for 5 years after liver transplantation. **CONCLUSIONS:** We developed a model based on level of AFP, tumor size, and tumor number, to determine risk of death from HCC-related factors after liver transplantation. This model might be used to select end points and refine selection criteria for liver transplantation for patients with HCC. To predict 5-year survival and risk of HCC-related death using an online calculator, please see www.hcc-olt-metroticket.org/. ClinicalTrials.gov ID NCT02898415.

Keywords: Liver Cancer; Prognosis; Mortality; Competing-Risk Analysis.

Hepatocellular carcinoma (HCC) has become a leading indication for liver transplantation (LT), even if LT for HCC remains an unfinished product searching for perfectibility.[1] The recent introduction of effective anti-hepatitis C virus (HCV) agents[2] together with the practice to down-stage tumors originally thought to be ineligible for transplantation[3] could increase the number of HCC within the transplant waiting lists[4–7] and lead to contrasts between cancer and non-cancer indications in the current scenario of persistent organ shortage.

Cancer vs non-cancer conditions are known to affect post-transplantation outcome of individual patients, as well as liver function at the time of surgery, etiology of liver disease, comorbidities, quality of the implanted graft, and perioperative management. All of these features weight differently in determining overall survival. In fact, in case of HCC-unadjusted survival, analysis may not fully discriminate among competing

Abbreviations used in this paper: AFP, α-fetoprotein; CI, confidence interval; CID, cumulative incidence of death; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease.

Most current article

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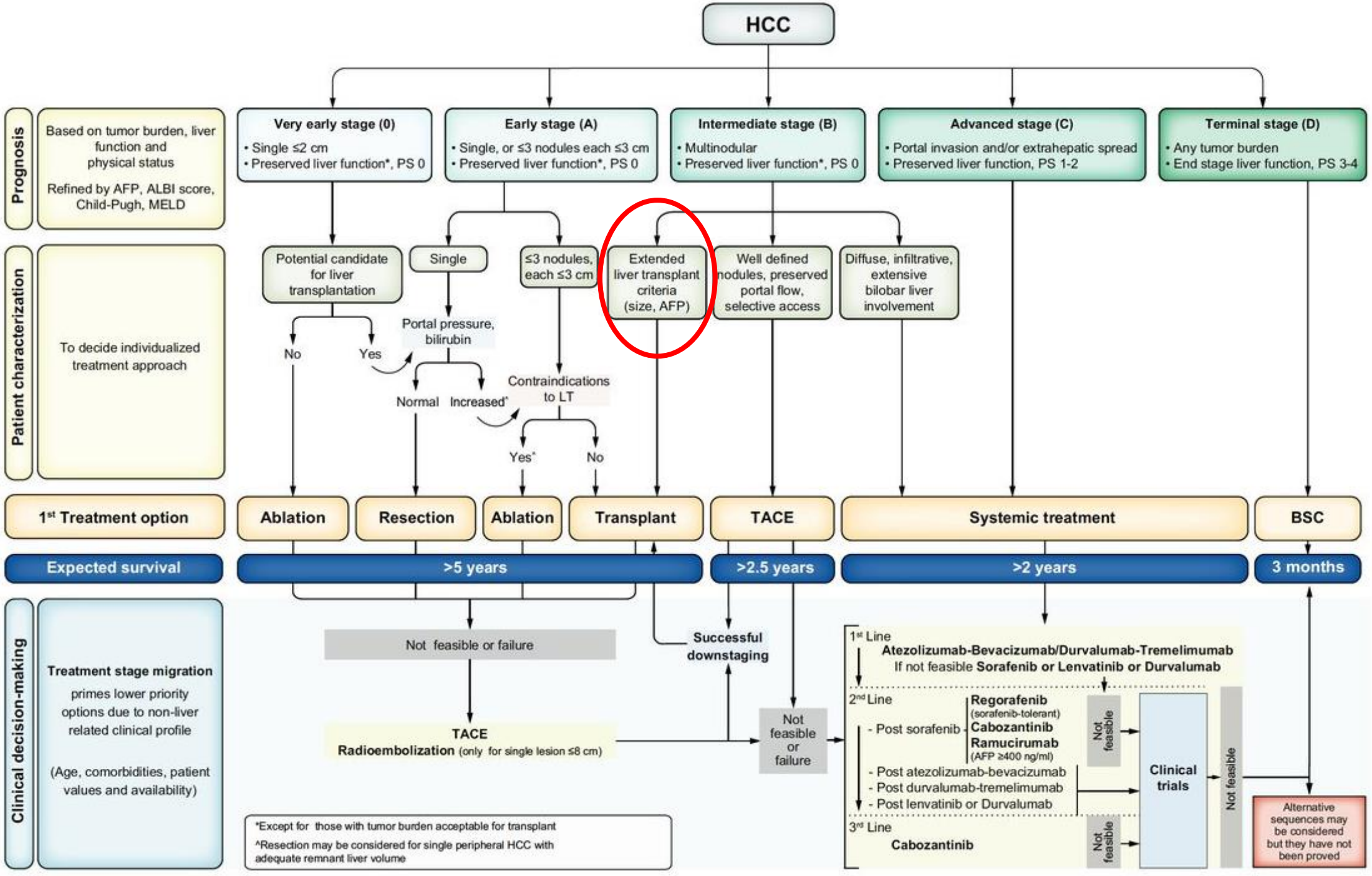

HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased^
Contraindications to LT
Yes^
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib
(sorafenib-tolerant)
Cabozantinib
Ramucirumab
(AFP ≥400 ng/ml)
Not feasible
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
Clinical trials
Not feasible
3rd Line
Cabozantinib
Not feasible
Alternative sequences may be considered but they have not been proved
*Except for those with tumor burden acceptable for transplant
^Resection may be considered for single peripheral HCC with adequate remnant liver volume

HCC için Karaciğer Nakli Kriterleri

HCC için Karaciğer Nakli Kriterleri

No	Ülke	Kriter Sayısı	Kriter ismi
1	İtalya	4	**Milan,** UpTo7, AFP-TTD, **Metroticket 2.0**
2	Japonya	4	Kyoto, Tokyo, Kyushi, **5-5-500**
3	USA	4	**UCSF,** Onaca, **MoRAL, NYCA**
4	Kanada	3	Extended Criteria, AFP-TTV, **Extended Toronto**
5	İspanya	3	**BCLC**, CUN (Navarra), Valencia
6	G.Kore	3	**Asan**, Samsung, SNAPP
7	Çin	2	**Hangzhou**, Shangai
8	Fransa	2	Paul-Brousse, AFP-Model
9	Almanya	1	Berlin
10	**Türkiye**	**2**	**Malatya kriterleri, Extended Malatya**

10 ülkeden yayınlanmış >25 transplant kriteri var

Kriterler Hangi Parametrelerden Oluşuyor?

HCC rekürrensini tahmin eden parametreler

- **Morfolojik parametreler**
  - Tümör çapı
  - Tümör sayısı
  - Toplam tümör çapı
  - Toplam tümör volümü
  - MTD+Tümör sayısı

- **Inflamatuvar parametreler**
  - Nötrofil/Lenfosit oranı

- **Biyolojik markerlar**
  - AFP
  - PIVKA-II (DCP)
  - GGT
  - LRT'ye yanıt
  - PET/CT tutulumu

- **Histopatolojik parametreler**
  - Diferansiasyon
  - Mikrovasküler invazyon

*

Criteria	Single tumor LTD, cm	Multiple Tumor (NN)	Multiple Tumor LTD, cm	TTD, cm	LTD+ NN	TTV, cm^3	AFP, ng/mL	PIVKA-II	GGT, IU/L	Differantiation	MiVi	OS / DFS %
Milan	≤ 5	2-3	≤ 3	-	-	-	-	-	-	-	-	85
UCSF	≤ 6.5	2-3	≤ 4.5	≤ 8	-	-	-	-	-	-	-	75.2
BCLC	≤ 7	2-3 4-5	≤ 5 ≤ 7	-	-	-	-	-	-	-	-	80.2
Extended C	≤ 7.5	2-3	≤ 5	-	-	-	-	-		(>5 cm with poor diff also excluded)	-	82.9
Berlin	≤ 6	No limit	≤ 6	≤ 15	-	-	-	-	-	-	-	68
Kyoto	≤ 5	2-10	≤ 5	-	-	-	-	≤ 400	-	-	-	86.7
Tokyo	≤ 5	2-5	≤ 5	-	-	-	-	-	-	-	-	75
Onaca	≤ 6	2-4	≤ 5	-	-	-	-	-	-	-	-	64.6
Hangzhou	≤ 8 >8	- -	- -	≤ 8 >8	-	-	- ≤ 400	- -	- -	- Well/moderate	-	62.4
Asan	≤ 5	2-6	≤ 5	-	-	-	-	-	-	-	-	76.3
CUN	≤ 6	2-3	≤ 5	-	-	-	-	-	-	-	-	73
Valencia	≤ 5	2-3	≤ 5	≤ 10	-	-	-	-	-	-	-	67
Shangai	≤ 9	2-3	≤ 5	≤ 9	-	-	-	-	-	-	-	78.1
UpToSeven	≤ 6	-	-	-	≤ 7	-	-	-	-	-	negative	71.2
TTV/AFP	-	-	-	-	-	≤ 115	≤ 400	-	-	-	-	60
Kyushu	≤ 5	No limit	≤ 5	-	-	-	-	≤ 300	-	-	-	82.7
Ext Toronto	No limit	No limit	No limit	-	-	-	-	-	-	Well/moderate	-	68
AFP-TTD	≤ 8	-	-	≤ 8	-	-	≤ 400	-	-	-	-	74.4
Samsung	≤ 6	2-7	≤ 6	-	-	-	≤ 1000	-	-	-	-	89.6
5-5-500	≤ 5	2-5	≤ 5	-	-	-	≤ 500	-	-	-	-	75.8
Malatya	≤ 6	No limit	≤ 6	-	-	-	≤ 200	-	≤ 104	Well/moderate	-	79.7
Ext Malatya	≤ 10	No limit	≤ 10	-	-	-	≤ 200	-	≤ 104	-	-	77.6

AFP: alpha fetoprotein; GGT: Gamma glutamyl transferase; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NN: Number of nodules; TTD: Total tumor diameter; TTV: Total tumor volume; PIVKA II: Protein induced by vitamin K absence or antagonist II.

Criteria	Single tumor LTD, cm	Multiple Tumor (NN)	Multiple Tumor LTD, cm	TTD, cm	LTD+ NN	TTV, cm^3	AFP, ng/mL	PIVKA-II	GGT, IU/L	Differantiation	MiVi	OS / DFS %
Milan	≤ 5	2-3	≤ 3	-	-	-	-	-	-	-	-	85
UCSF	≤ 6.5	2-3	≤ 4.5	≤ 8	-	-	-	-	-	-	-	75.2
BCLC	≤ 7	2-3 4-5	≤ 5 ≤ 7	-	-	-	-	-	-	-	-	80.2
Extended C	≤ 7.5	2-3	≤ 5	-	-	-	-	-		(>5 cm with poor diff also excluded)	-	82.9
Berlin	≤ 6	No limit	≤ 6	≤ 15	-	-	-	-	-	-	-	68
Kyoto	≤ 5	2-10	≤ 5	-	-	-	-	≤ 400	-	-	-	86.7
Tokyo	≤ 5	2-5	≤ 5	-	-	-	-	-	-	-	-	75
Onaca	≤ 6	2-4	≤ 5	-	-	-	-	-	-	-	-	64.6
Hangzhou	≤ 8 >8	- -	- -	≤ 8 >8	-	-	- ≤ 400	- -	- -	- Well/moderate	-	62.4
Asan	≤ 5	2-6	≤ 5	-	-	-	-	-	-	-	-	76.3
CUN	≤ 6	2-3	≤ 5	-	-	-	-	-	-	-	-	73
Valencia	≤ 5	2-3	≤ 5	≤ 10	-	-	-	-	-	-	-	67
Shangai	≤ 9	2-3	≤ 5	≤ 9	-	-	-	-	-	-	-	78.1
UpToSeven	≤ 6	-	-	-	≤ 7	-	-	-	-	-	negative	71.2
TTV/AFP	-	-	-	-	-	≤ 115	≤ 400	-	-	-	-	60
Kyushu	≤ 5	No limit	≤ 5	-	-	-	-	≤ 300	-	-	-	82.7
Ext Toronto	No limit	No limit	No limit	-	-	-	-	-	-	Well/moderate	-	68
AFP-TTD	≤ 8	-	-	≤ 8	-	-	≤ 400	-	-	-	-	74.4
Samsung	≤ 6	2-7	≤ 6	-	-	-	≤ 1000	-	-	-	-	89.6
5-5-500	≤ 5	2-5	≤ 5	-	-	-	≤ 500	-	-	-	-	75.8
Malatya	≤ 6	No limit	≤ 6	-	-	-	≤ 200	-	≤ 104	Well/moderate	-	79.7
Ext Malatya	≤ 10	No limit	≤ 10	-	-	-	≤ 200	-	≤ 104	-	-	77.6

AFP: alpha fetoprotein; GGT: Gamma glutamyl transferase; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NN: Number of nodules; TTD: Total tumor diameter; TTV: Total tumor volume; PIVKA II: Protein induced by vitamin K absence or antagonist II.

Criteria	Single tumor LTD, cm	Multiple Tumor (NN)	Multiple Tumor LTD, cm	TTD, cm	LTD+ NN	TTV, cm^3	AFP, ng/mL	PIVKA-II	GGT, IU/L	Differantiation	MiVi	OS / DFS %
Milan	≤ 5	2-3	≤ 3	-	-	-	-	-	-	-	-	85
UCSF	≤ 6.5	2-3	≤ 4.5	≤ 8	-	-	-	-	-	-	-	75.2
BCLC	≤ 7	2-3 4-5	≤ 5 ≤ 7	-	-	-	-	-	-	-	-	80.2
Extended C	≤ 7.5	2-3	≤ 5	-	-	-	-	-		(>5 cm with poor diff also excluded)	-	82.9
Berlin	≤ 6	No limit	≤ 6	≤ 15	-	-	-	-	-	-	-	68
Kyoto	≤ 5	2-10	≤ 5	-	-	-	-	≤ 400	-	-	-	86.7
Tokyo	≤ 5	2-5	≤ 5	-	-	-	-	-	-	-	-	75
Onaca	≤ 6	2-4	≤ 5	-	-	-	-	-	-	-	-	64.6
Hangzhou	≤ 8 >8	- -	- -	≤ 8 >8	-	-	- ≤ 400	- -	- -	- Well/moderate	-	62.4
Asan	≤ 5	2-6	≤ 5	-	-	-	-	-	-	-	-	76.3
CUN	≤ 6	2-3	≤ 5	-	-	-	-	-	-	-	-	73
Valencia	≤ 5	2-3	≤ 5	≤ 10	-	-	-	-	-	-	-	67
Shangai	≤ 9	2-3	≤ 5	≤ 9	-	-	-	-	-	-	-	78.1
UpToSeven	≤ 6	-	-	-	≤ 7	-	-	-	-	-	negative	71.2
TTV/AFP	-	-	-	-	-	≤ 115	≤ 400	-	-	-	-	60
Kyushu	≤ 5	No limit	≤ 5	-	-	-	-	≤ 300	-	-	-	82.7
Ext Toronto	No limit	No limit	No limit	-	-	-	-	-	-	Well/moderate	-	68
AFP-TTD	≤ 8	-	-	≤ 8	-	-	≤ 400	-	-	-	-	74.4
Samsung	≤ 6	2-7	≤ 6	-	-	-	≤ 1000	-	-	-	-	89.6
5-5-500	≤ 5	2-5	≤ 5	-	-	-	≤ 500	-	-	-	-	75.8
Malatya	≤ 6	No limit	≤ 6	-	-	-	≤ 200	-	≤ 104	Well/moderate	-	79.7
Ext Malatya	≤ 10	No limit	≤ 10	-	-	-	≤ 200	-	≤ 104	-	-	77.6

AFP: alpha fetoprotein; GGT: Gamma glutamyl transferase; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NN: Number of nodules; TTD: Total tumor diameter; TTV: Total tumor volume; PIVKA II: Protein induced by vitamin K absence or antagonist II.

Summary of the features of the transplant criteria and scoring systems which are defined in the literature, in a chronological raw

Scoring System	Features of the scoring system and points	Posttransplant Recurrence Risk	OS, %
AFP Model, 2012	**LTD point** • ≤ 3cm = 0 • 3-6cm = 1 • >6cm = 4 **Num.Nod.(NN) point** • 1-3 nodule = 0 • >4 nodule = 2 **AFP point** • ≤ 100 = 0 • 100-1000 = 2 • >1000 = 3	**Total point = score (0-9)** Score ≤ 2, low risk Score > 2, high risk	 67.8 47.5
RETREAT, 2017	**LTD+NVT point** • 0 = 0 • 1.1-4.9 = 1 • 5.0-9.9 = 2 • ≥10 = 3 **MiVi point** • Positive = 2 **AFP at Tx point** • 0-20 = 0 • 21-99 = 1 • 100-999 = 2 • ≥1000 = 3	**Total point = score (0-8)** Score = 0, Rec.Rate <3% Score < 5, low risk Score ≥ 5, high risk (RR>75%)	 Rec 2.9% Rec 75%
MoRAL, 2017	**Pre-Tx-MoRAL point** • LTD > 3cm = 3 • NLR > 5 = 6 • AFP > 200 = 4 **Post-Tx-MoRAL point** • LTD>3cm = 3 • NN>3 nodules = 2 • Grade 4 tumor = 6 • MiVi positive = 2	**Total point = score (0-13)** Score ≤ 6, low + medium risk Score > 6, high + very high risk	 70 42
NYCA, 2018	**LTD at diagnosis Point** • 0-3cm = 0 • >3-6cm = 2 • >6cm = 4 **NN at diagnosis Point** • 1 nodule = 0 • 2-3 nodule = 2 • ≥4 nodule = 4 **AFP response Point** • AFP always < 200 = 0 Responders • Max > 200-1000 to final < 200 = 2 • Max >1000 to final <1000 (must be 50% drop) = 2 Nonresponders • Max > 200-400 to final >200 = 3 • Max > 400-1000 to final >200 = 4 • Max > 1000 to final >1000 = 6	**Total point = score (0-14)** Score 0-2, low risk Score 3-6, acceptable risk Score ≥7, high risk	 90 70 42
Metroticket 2.0, 2018	LTD + NN ≤ 7 and AFP ≤ 200 or LTD + NN ≤ 5 and AFP 200-400 or LTD + NN ≤ 4 and AFP 400-1000	Low risk	78
SNAPP, 2020	**LTD point** • ≤ 3cm = 0 • 3-6cm = 1 • >6cm = 2 **NN point** • 1 nodule = 0 • 2-3 nodule = 1 • ≥4 nodule = 2 **AFP and PIVKA point** • AFP≤150 + PIVKA≤100 = 0 • AFP≤150 + PIVKA>100 = 1 • AFP>150 + PIVKA≤100 = 2 • AFP>150 + PIVKA>100 = 3 **PET-CT point** • Isometabolic = 0 • Hypermetabolic = 1	**Total point = score (0-8)** Score ≤ 2, low risk Score 3-4, medium risk Score > 5, high risk	 97 71 31

AFP: alpha fetoprotein; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; NVT: Number of Viable Tumor, PIVKA II: Protein induced by vitamin K absence or antagonist II.

Summary of the features of the transplant criteria and scoring systems which are defined in the literature, in a chronological raw

Scoring System	Features of the scoring system and points	Posttransplant Recurrence Risk	OS, %
AFP Model, 2012	**LTD point** • ≤ 3cm = 0 • 3-6cm = 1 • >6cm = 4 **Num.Nod.(NN) point** • 1-3 nodule = 0 • >4 nodule = 2 **AFP point** • ≤ 100 = 0 • 100-1000 = 2 • >1000 = 3	**Total point = score (0-9)** Score ≤ 2, low risk Score > 2, high risk	 67.8 47.5
RETREAT, 2017	**LTD+NVT point** • 0 = 0 • 1.1-4.9 = 1 • 5.0-9.9 = 2 • ≥10 = 3 **MiVi point** • Positive = 2 **AFP at Tx point** • 0-20 = 0 • 21-99 = 1 • 100-999 = 2 • ≥1000 = 3	**Total point = score (0-8)** Score = 0, Rec.Rate <3% Score < 5, low risk Score ≥ 5, high risk (RR>75%)	 Rec 2.9% Rec 75%
MoRAL, 2017	**Pre-Tx-MoRAL point** • LTD > 3cm = 3 • NLR > 5 = 6 • AFP > 200 = 4 **Post-Tx-MoRAL point** • LTD>3cm = 3 • NN>3 nodules = 2 • Grade 4 tumor = 6 • MiVi positive = 2	**Total point = score (0-13)** Score ≤ 6, low + medium risk Score > 6, high + very high risk	 70 42
NYCA, 2018	**LTD at diagnosis Point** • 0-3cm = 0 • >3-6cm = 2 • >6cm = 4 **NN at diagnosis Point** • 1 nodule = 0 • 2-3 nodule = 2 • ≥4 nodule = 4 **AFP response Point** • AFP always < 200 = 0 Responders • Max > 200-1000 to final < 200 = 2 • Max >1000 to final <1000 (must be 50% drop) = 2 Nonresponders • Max > 200-400 to final >200 = 3 • Max > 400-1000 to final >200 = 4 • Max > 1000 to final >1000 = 6	**Total point = score (0-14)** Score 0-2, low risk Score 3-6, acceptable risk Score ≥7, high risk	 90 70 42
Metroticket 2.0, 2018	LTD + NN ≤ 7 and AFP ≤ 200 or LTD + NN ≤ 5 and AFP 200-400 or LTD + NN ≤ 4 and AFP 400-1000	Low risk	78
SNAPP, 2020	**LTD point** • ≤ 3cm = 0 • 3-6cm = 1 • >6cm = 2 **NN point** • 1 nodule = 0 • 2-3 nodule = 1 • ≥4 nodule = 2 **AFP and PIVKA point** • AFP≤150 + PIVKA≤100 = 0 • AFP≤150 + PIVKA>100 = 1 • AFP>150 + PIVKA≤100 = 2 • AFP>150 + PIVKA>100 = 3 **PET-CT point** • Isometabolic = 0 • Hypermetabolic = 1	**Total point = score (0-8)** Score ≤ 2, low risk Score 3-4, medium risk Score > 5, high risk	 97 71 31

AFP: alpha fetoprotein; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules; NVT: Number of Viable Tumor, PIVKA II: Protein induced by vitamin K absence or antagonist II.

Recurrence Risk Reassessment (R3) – AFP score

Scoring System	Features of the scoring system and points					Posttransplant Recurrence Risk	OS, %
R3-AFP Score, 2022	**LTD** **point** • ≤ 3cm = 0 • 3-6cm = 1 • >6cm = 5	**Num.Nod.(NN)** **point** • 1-3 nodule = 0 • >4 nodule = 1	**MiVi** **point** • Negative = 0 • Positive = 2	**Nuclear Grade** **point** • Well / Moderate = 0 • Poor = 1	**AFP** **point** • ≤ 100 = 0 • 100-1000 = 1 • >1000 = 2	**Total point = score (0-11)** Score 0, very low risk (5.5%) Score 1 - 2, low risk (15.1%) Score 3 - 6, high risk (39.1) Score >6 , very high risk (73.6)	 77.2 67.8 57.2 19.8

AFP: alpha fetoprotein; LTD: Largest tumor diameter; MiVi: Microvascular invasion; NLR: Neutrophile to lymphocyte ratio; NN: Number of nodules.

Kriterlerin Ortak Özellikleri

- **Makrovasküler invazyon olmayacak**
- **Karaciğer dışı tümör yayılımı olmayacak**
- **5 yıllık OS > %60**

*

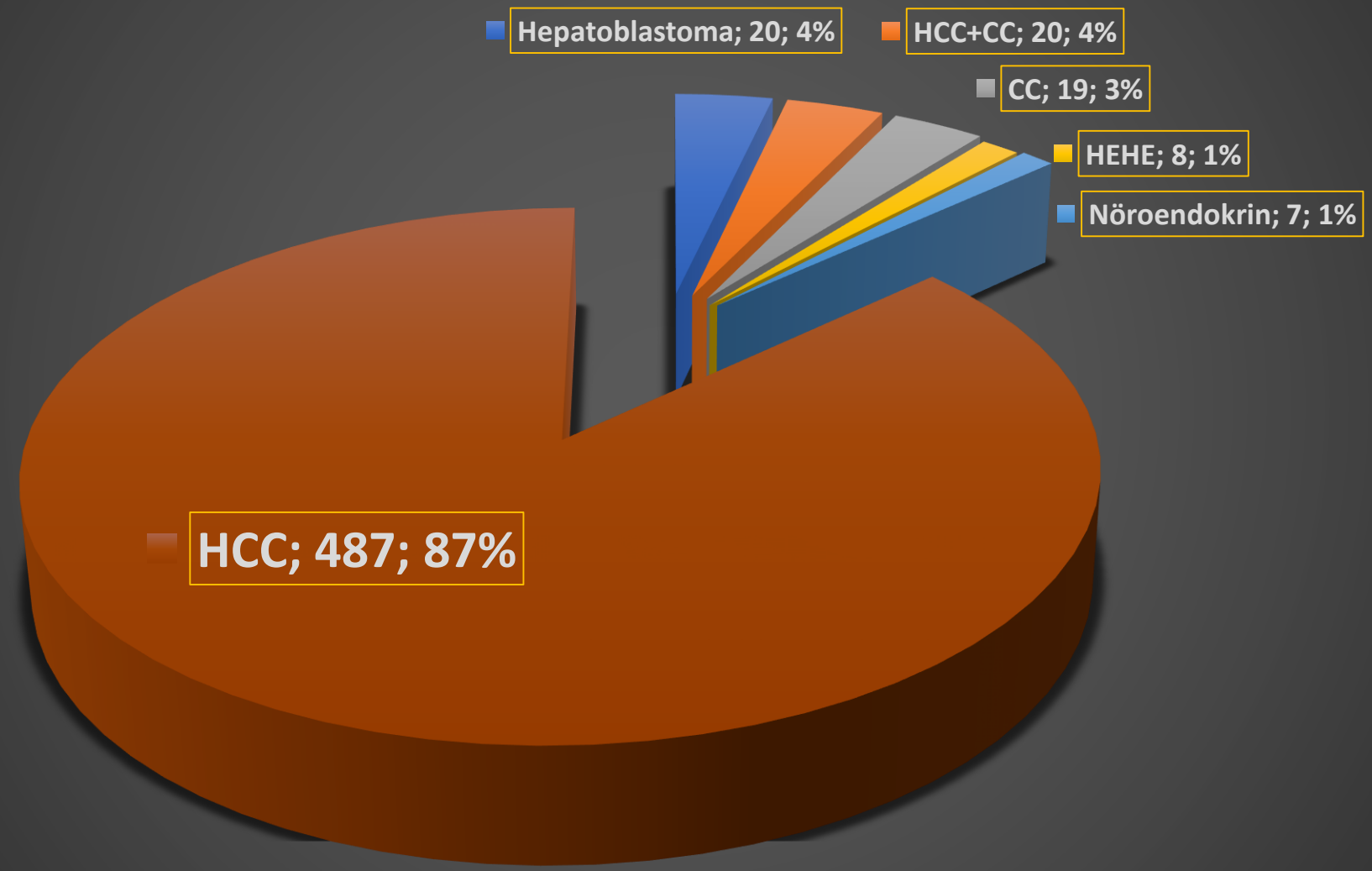
Hepatosellüler Kanserde Karaciğer Nakli : Malatya Deneyimi

İnönü Üniversitesi - Karaciğer Nakli Enstitüsü

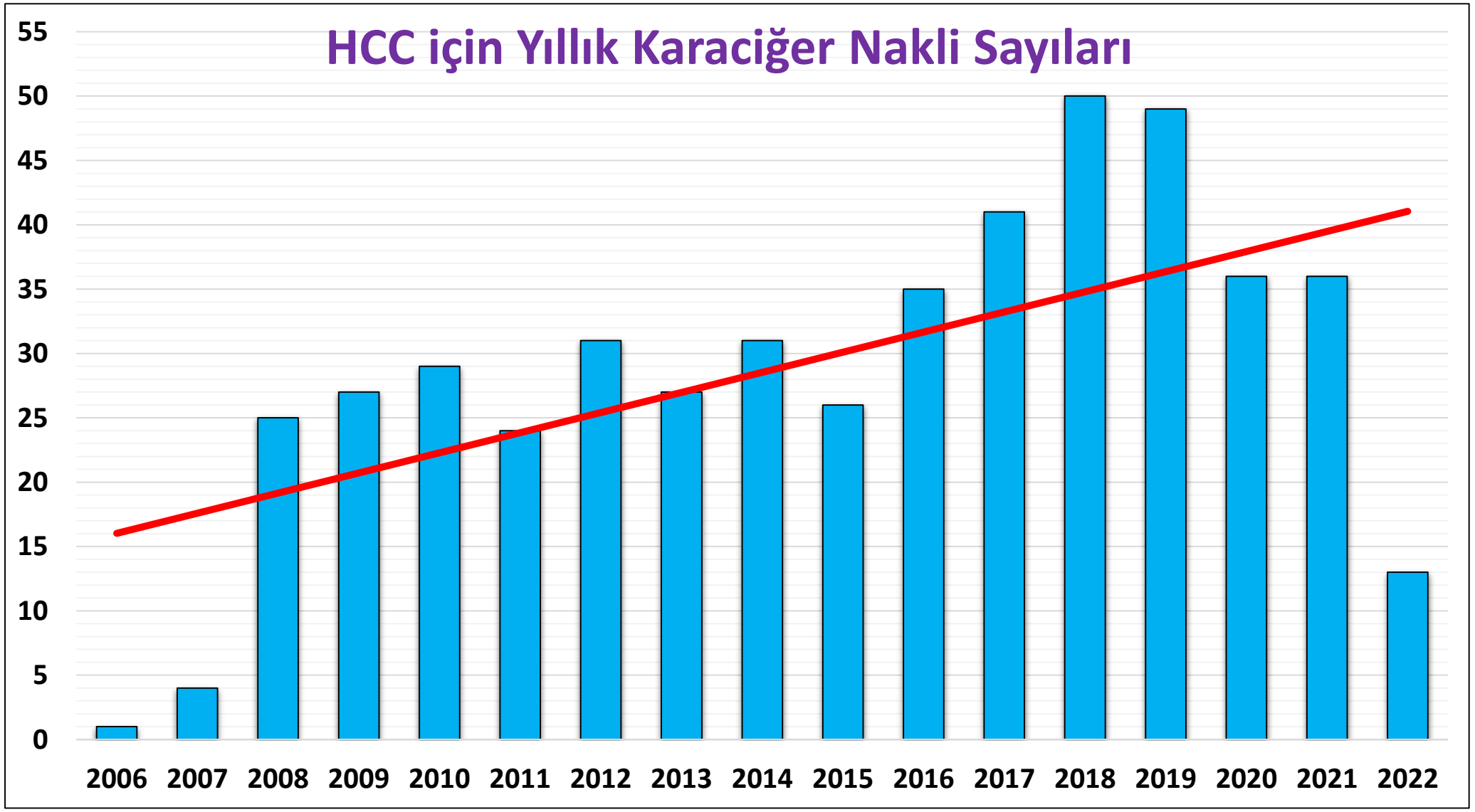
İnönü Üniversitesi - Karaciğer Nakli Enstitüsü

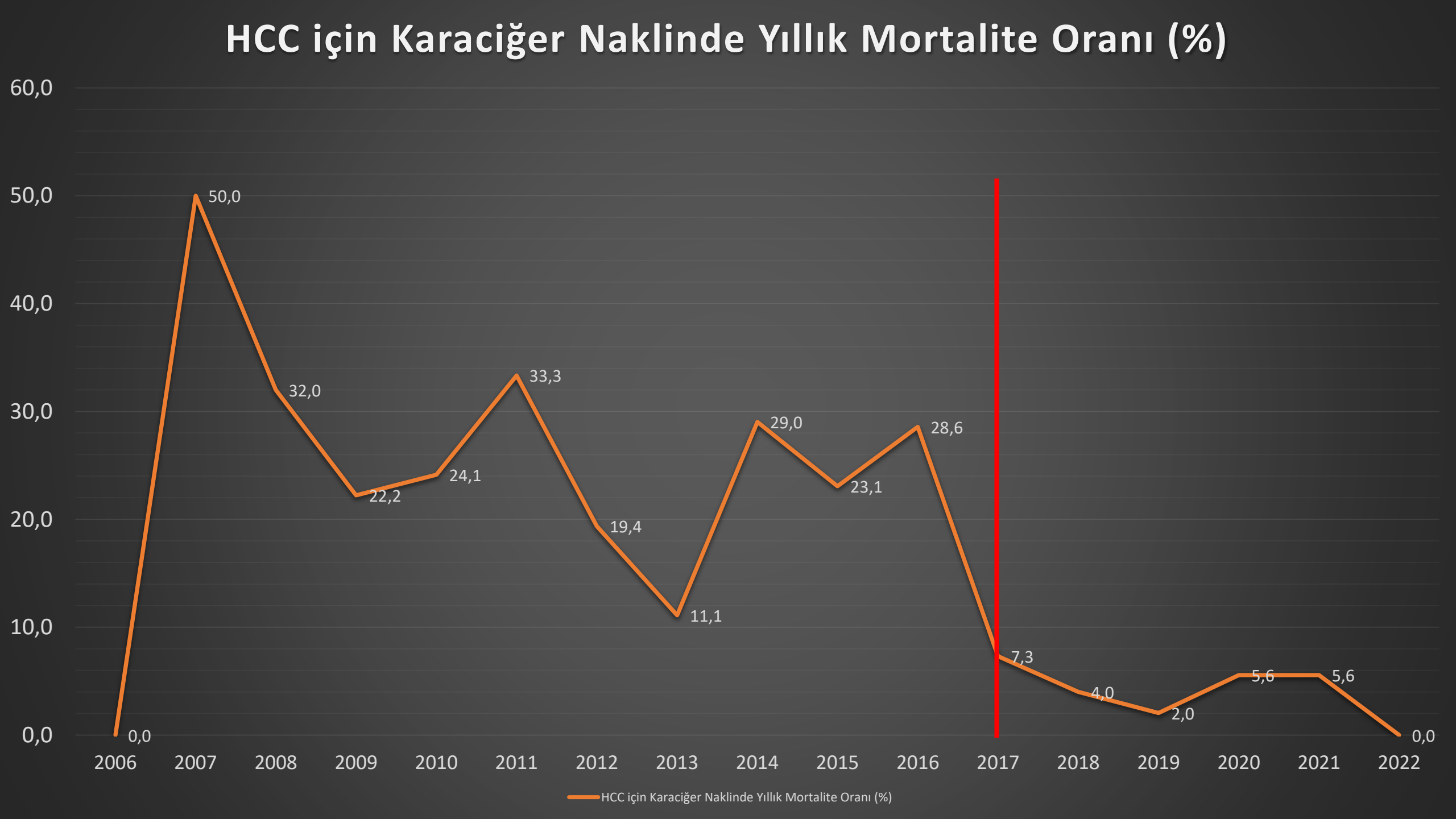
- **2002 Mart – 2022 Haziran**
- **Toplam karaciğer nakli: 3300**
- **HCC: 487 (%15)**

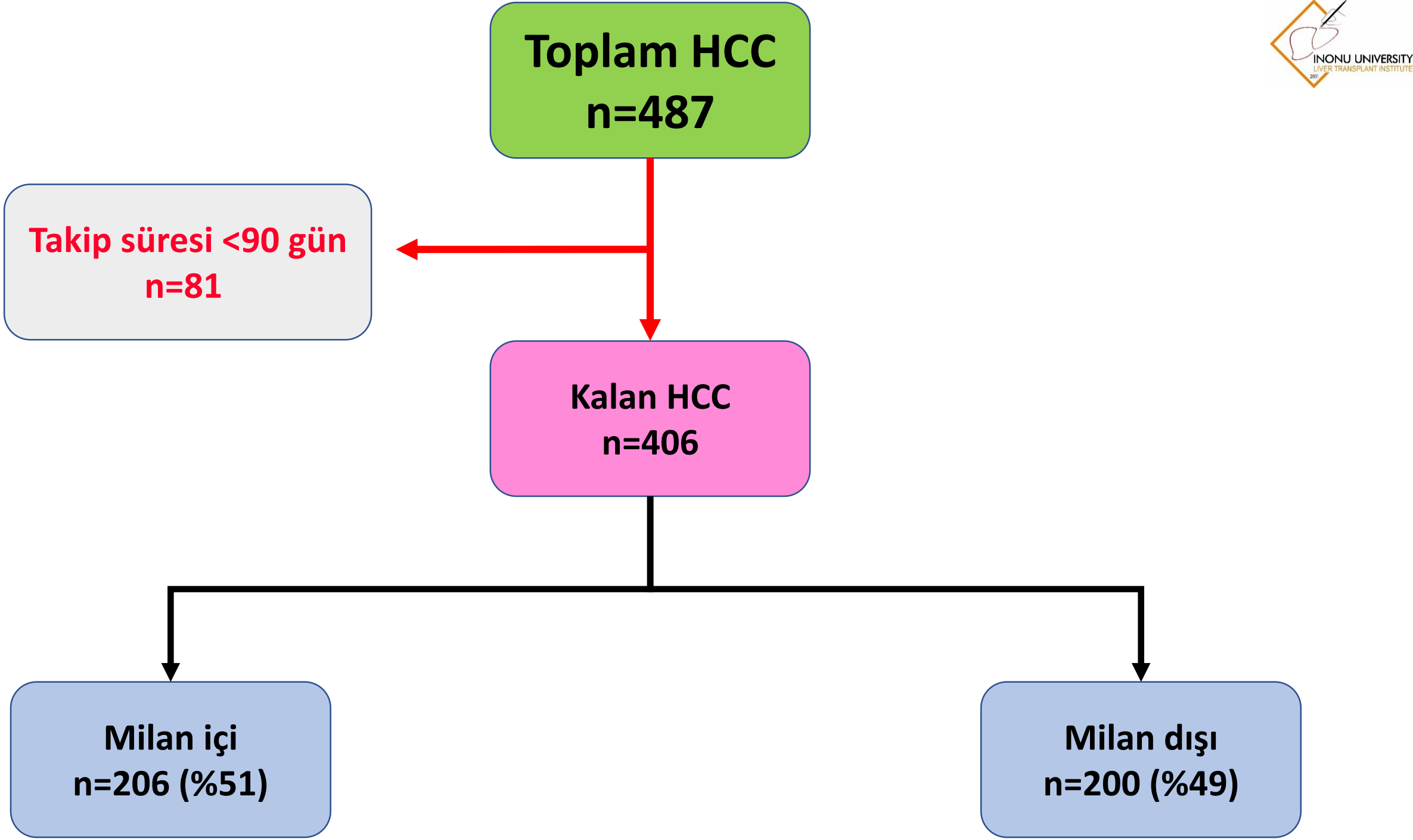
Karaciğer Tümörleri için Karaciğer Nakli Sayıları (n=561)



İnönü Üniversitesi Karaciğer Nakli Enstitüsü




HCC için Karaciğer Naklinde Yıllık Mortalite Oranı (%)
60,0
50,0
40,0
30,0
20,0
10,0
0,0
50,0
32,0
22,2
24,1
33,3
19,4
11,1
29,0
23,1
28,6
7,3
4,0
2,0
5,6
5,6
0,0
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
HCC için Karaciğer Naklinde Yıllık Mortalite Oranı (%)


Toplam HCC
n=487
Takip süresi <90 gün
n=81
Kalan HCC
n=406
Milan içi
n=206 (%51)
Milan dışı
n=200 (%49)

Demografik veriler ve Tümör Morfolojisi

Parametre	Median	Minimum	Maximum
Yaş	56	2	72
MELD	13	6	41
BSA	1,9	0,38	2,54
BMI	26	16,3	46,9
Platelet	94	16	528
Albumin	2,9	1,2	5,2
T. Bilirubin	1,9	0,23	44,7
GGT	70,5	11	1396
AST	59	9	7789
ALT	43	10	3535
Tümör Morfolojisi			
En Büyük Tümör Çapı (cm)	3	0,1	24
Tümör Sayısı	2	1	36

Parametre	n	%
Cinsiyet, E	349	86
CHILD		
A	136	33,5
B	176	43,3
C	94	23,2
MELD ≤ 14	249	61,3
Etiyoloji		
Viral hepatit	324	79,8
Kriptojenik	52	12,8
Budd-chiari	9	2,2
Etanol	6	1,5
Metabolik Hastalık	6	1,5
Diğer	9	2,2
GRWR < 0,8	44	11,1

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MELD	13	6	41
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Metabolik Hastalık	6	1,5
Diğer	9	2,2
GRWR < 0,8	44	11,1

Tümör Biyolojisi

Parametre	Median	Minimum	Maximum
AFP	12,8	0,2	20179
İnflamatuvar belirteçler			
Platelet	94	16	528
NLR	2,6	0,1	35,3
PLR	81,3	2,6	683
Albumin	2,9	1,2	5,2
T. Bilirubin	1,89	0,23	44,7
GGT	70	11	1396
CRP (n=260)	1,02	0,16	305

NLR: nötrofil lenfosit ratio; PLR: platelet lenfosit ratio

Parametre	n	%
AFP < 200	330	81,3
Diferansiyasyon		
İyi	170	41,9
Orta	171	42,1
Kötü	65	16
Mikrovasküler inv (-)	219	53,9
Mikrovasküler inv (+)	139	34,2
Makrovasküler inv (+)	48	11,8
PET / CT tutulum (+)	55	13,9
TAKE / TARE (+)	72	17,7

Tümör Biyolojisi

Parametre	Median	Minimum	Maximum
AFP	12,8	0,2	20179
İnflamatuvar belirteçler			
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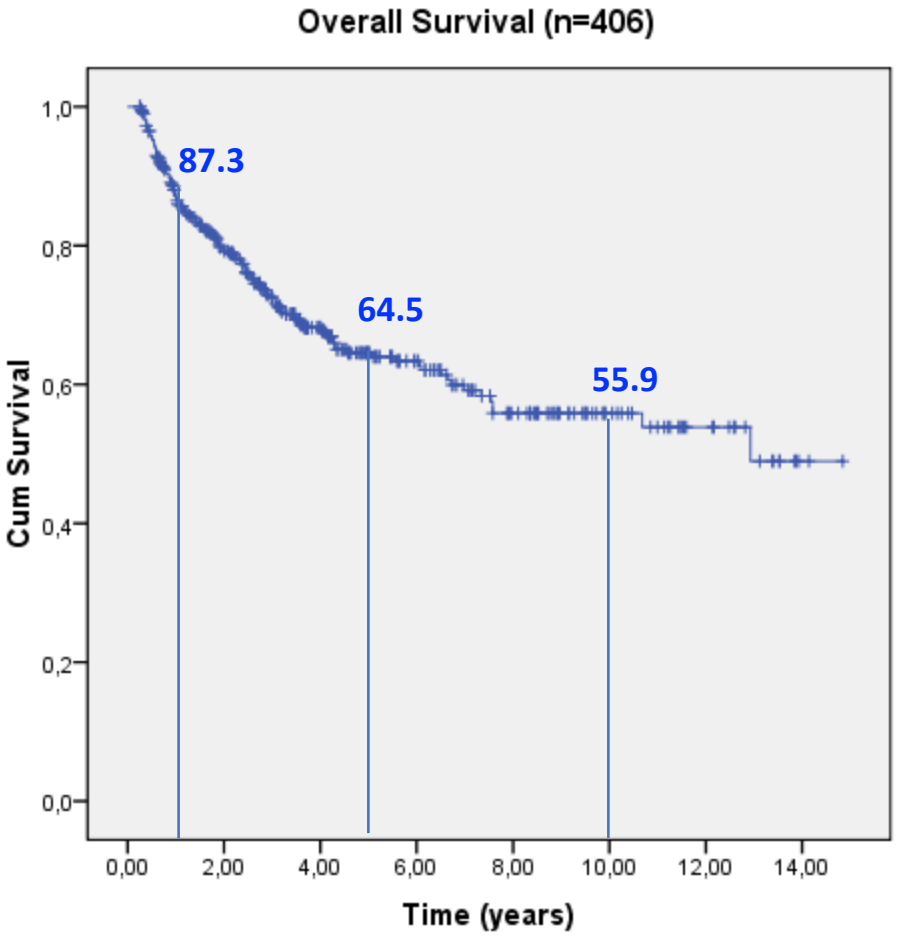
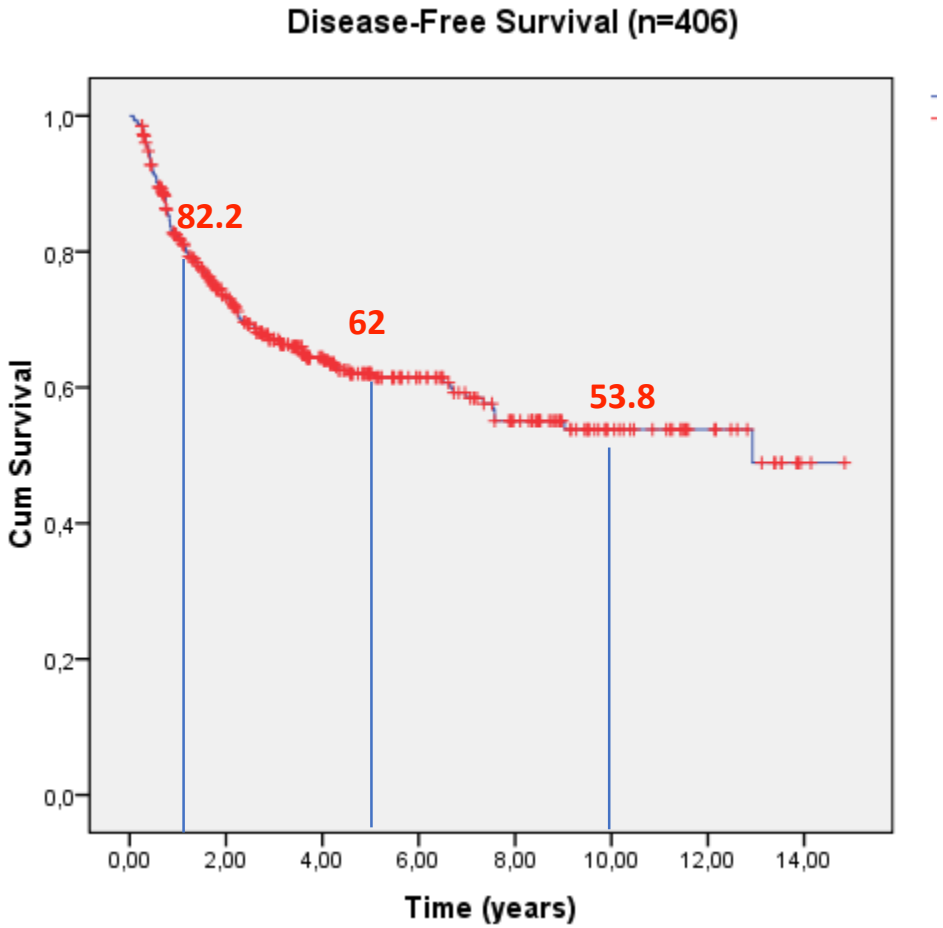
PET / CT tutulum (+)	55	13,5
TAKE / TARE (+)	72	17,7

Hepatoselluler Kanserde Karaciğer Nakli (Genel Sonuçlar)

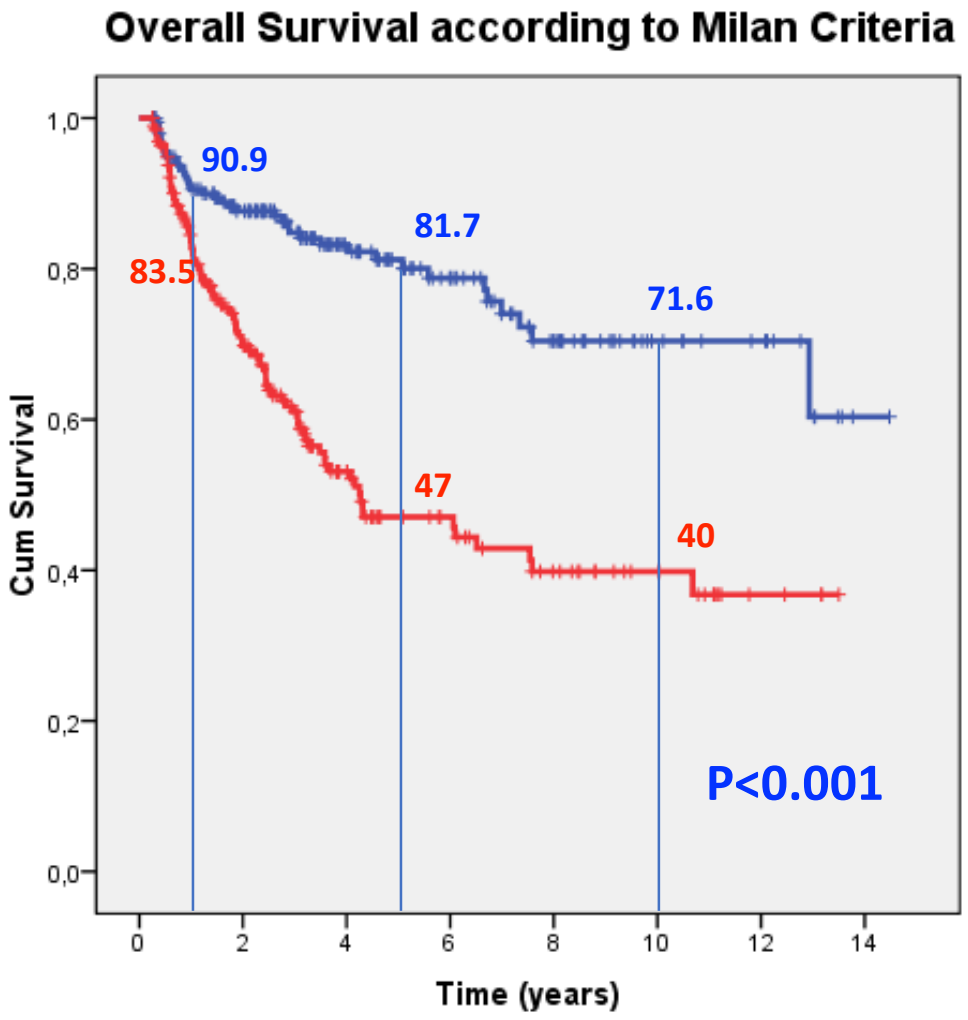
Ortalama İzlem: 9.37 ± 0.38 (8.6 – 10.1 yıl, 95% CI)

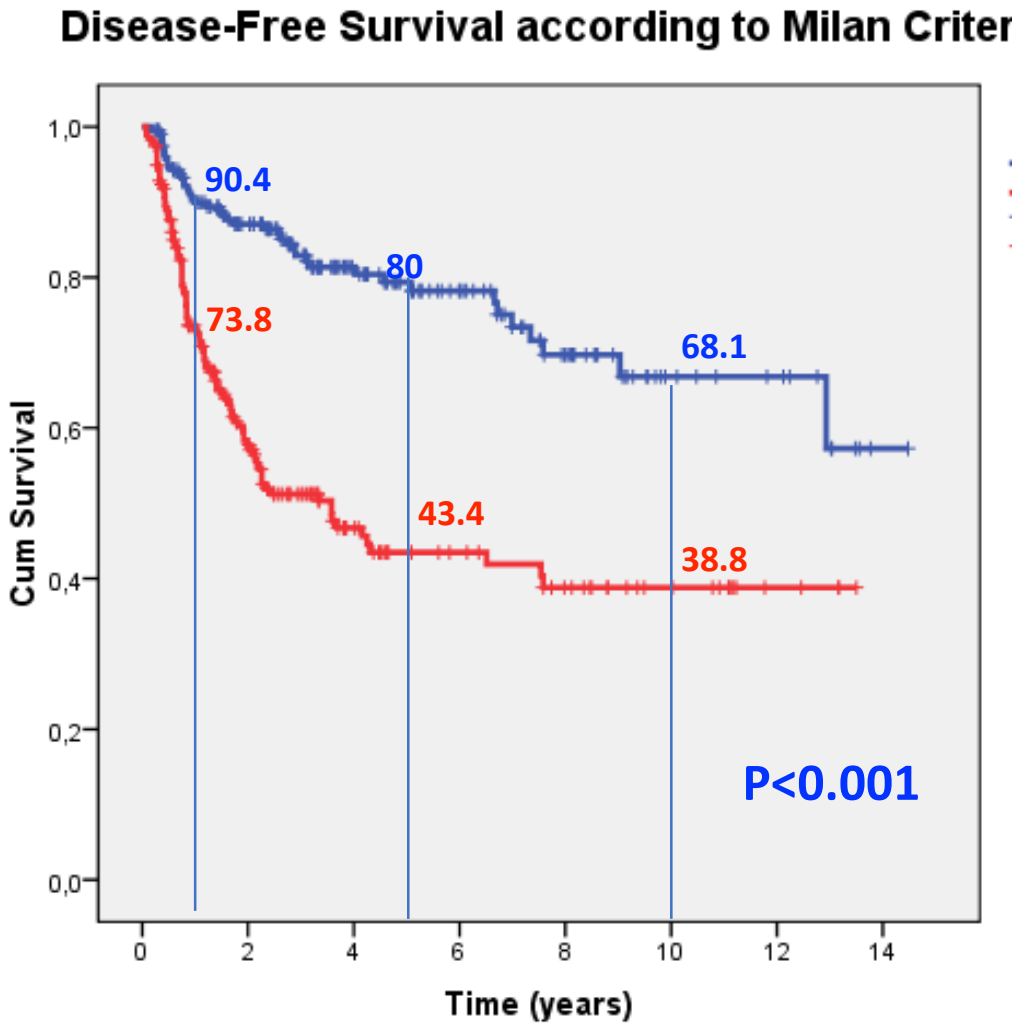
Post-Tx Recurrence Rate 19% (n=77)





Milan Kriterlerine Göre Sağkalım





Malatya Kriterleri

Malatya Kriterleri

ILTS 25th Annual International Congress — May 15 – 18, 2019 in Toronto, Canada

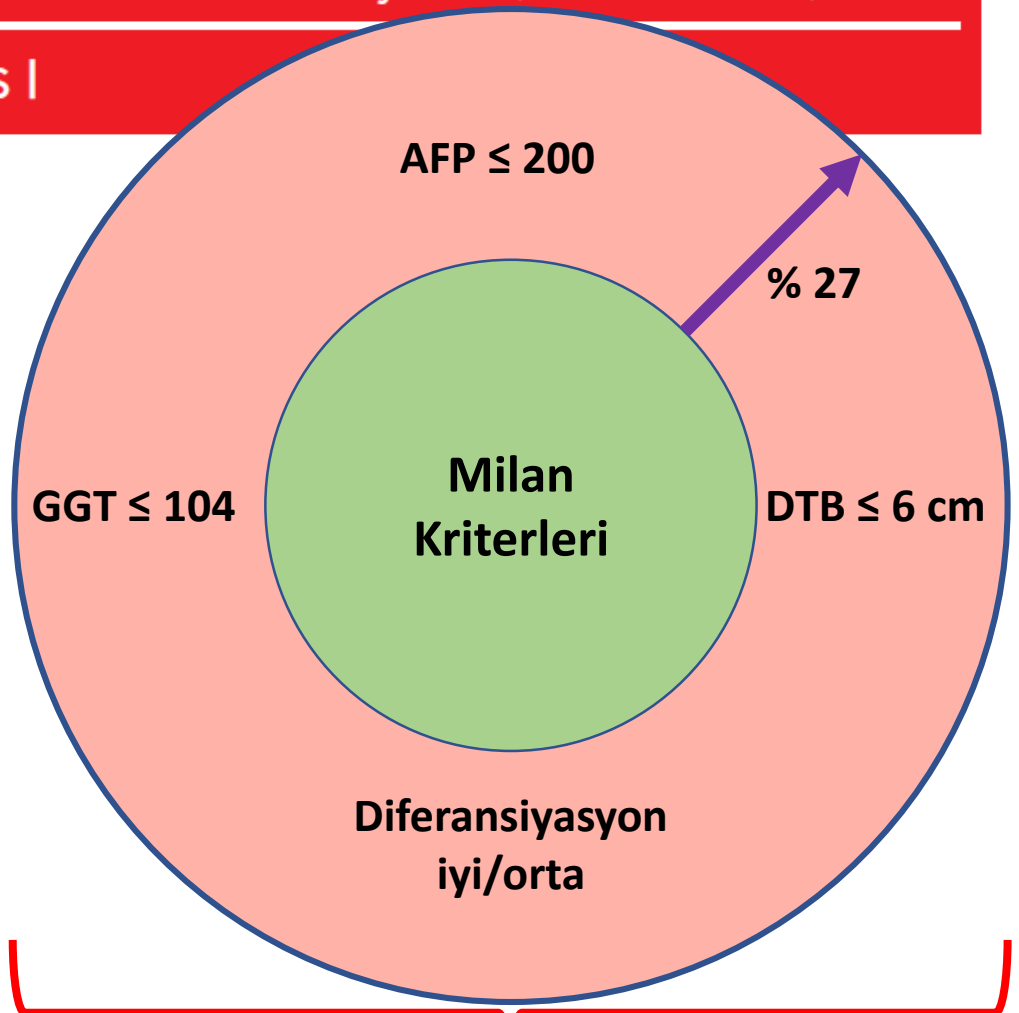
Concurrent Oral Abstract Session Latebreaking Abstracts I

LB 0-006

New and different expanded criteria for liver transplantation in hepatocellular carcinoma: Malatya criteria

Ince V.[1], Akbulut S.[1], Otan E.[1], Ersan V.[1], Karakas S.[1], Sahin T.T.[1], Baskiran A.[1], Samdanci E.[2], Bag H.G.[3], Isik B.[1], Kayaalp C.[1], Emre S.[1], Yilmaz S.[1]

[1]Inonu University, Liver Transplantation Institute, General Surgery, Malatya, Turkey, [2]Inonu University, School of Medicine, Pathology, Malatya, Turkey, [3]Inonu University, School of Medicine, Biostatistics, Malatya, Turkey



Malatya Kriterleri

Malatya Kriterleri

Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-020-00424-w

ORIGINAL RESEARCH

Liver Transplantation for Hepatocellular Carcinoma: Malatya Experience and Proposals for Expanded Criteria

Volkan Ince[1] · A. Sami Akbulut[1] · Emrah Otan[1] · Veysel Ersan[1] · Serdar Karakas[1] · Tolga Tevfik Sahin[1] · Brian I Carr[1] · Adil Baskiran[1] · Emine Samdanci[2] · Harika Gozukara Bag[3] · Cemalettin Koc[1] · Sertac Usta[1] · Fatih Ozdemir[1] · Bora Barut[1] · Fatih Gonultas[1] · Baris Sarici[1] · Koray Kutluturk[1] · Murat Sait Dogan[1] · Dincer Ozgor[1] · Mustafa Dikilitas[4] · Murat Harputluoglu[5] · Murat Aladag[5] · Ramazan Kutlu[6] · Ilknur Varol[7] · Abuzer Dirican[1] · Cemalettin Aydin[1] · Burak Isik[1] · Cengiz Ara[1] · Cuneyt Kayaalp[1] · Sukru Emre[1] · Sezai Yilmaz[1]

Updates in Surgery (2021) 73:1599–1614
https://doi.org/10.1007/s13304-021-01078-4

REVIEW ARTICLE

Hepatocellular cancer selection systems and liver transplantation: from the tower of babel to an ideal comprehensive score

Jan Lerut[1] · Maxime Foguenne[2] · Quirino Lai[3]

Received: 14 February 2021 / Accepted: 3 May 2021 / Published online: 18 May 2021

Abstract

The Milan criteria (MC) remain the cornerstone for the selection of patients with hepatocellular cancer (HCC) to be listed for liver transplantation (LT). Recently, several expanded criteria have been proposed to increase the transplantability of HCC patients without compromising their (oncologic) outcome. This paper aims to systematically review the different reported HCC-LT selection systems looking thereby at their ability to increase the number of transplantable patients and the overall survival and oncological outcome. A systematic review of the literature covering the period 1993 (date of the first reported HCC-LT selection system)–2021 identified 59 different inclusion criteria of HCC for LT. Among the 59 studies reporting HCC-LT selection systems, 15 (28.3%) were exclusively based on morphological aspects of the tumor; 29 (54.7%) included biologic, seven (13.2%) radiological, and two (3.8%) only included pathological tumor features. Overall, 31% more patients could be transplanted when adhering to the new HCC-LT selection systems. Despite the increased number of LT, 5-year patient and disease-free survival rates were similar between MC-IN and MC-OUT/new HCC-LT-IN criteria. A careful extension of the inclusion criteria should allow many more patients to access a potentially curative LT without compromising their outcome. The development of a widely accepted "comprehensive" HCC-LT Score able to offer a fair chance of justified transplantation to more patients should become a priority within the liver transplant community. Further studies are needed to develop internationally accepted, expanded selection criteria for liver transplantation of HCC patients.

Keywords Liver transplantation · Hepatocellular cancer · Score · Selection criteria · Recurrent tumor

Abbreviations

AFP	Alpha-fetoprotein
CI	Confidence intervals
DFS	Disease-free survival
HCC	Hepatocellular cancer
I2	Higgins statistic squared
LDLT	Living donor liver transplantation
LT	Liver transplantation
MC	Milan criteria
mRECIST	Modified-response evaluation criteria in solid tumors
NLR	Neutrophil-to-lymphocyte ratio
OR	Odds ratio
PIVKA-II	Protein induced by vitamin K absence-II
PLR	Platelet-to-lymphocyte ratio
PS	Patient survival
UCSF	University of California, San Francisco

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[2] University Hospitals Saint-Luc Université Catholique de Louvain (UCL), Brussels, Belgium

[3] General Surgery and Organ Transplantation Unit, Sapienza University of Rome, Rome, Italy

Introduction

Thomas Starzl designed liver transplantation (LT) to treat unresectable primary and secondary hepatobiliary tumors [1, 2]. The first 'successful' LT was performed on July 23, 1967, in a child presenting with a large hepatocellular cancer (HCC) in the context of biliary atresia. The child died after 400 days, during which time she underwent many reinterventions to treat both thoracic and abdominal tumor recurrences. Due to the lack of selection criteria, the concept of LT as the primary treatment of hepatobiliary malignancies

Table 1 (continued)

Ref	Author	Center	Year	Morphology	Biology	Radiology	Pathology
[46]	Grat	Warsawa	2017	Up to 7/UCSF	AFP ≤ 100 ng/mL	–	–
[47]	Halazun	MoRAL New York	2017	Pre-MoRAL: NLR > 5 = 6 points; Largest T diam > 3 cm = 3 points Post-MoRAL: Grade 4 = 6 points; Vascular invasion = 2 points; Largest T diam > 3 cm = 3 points; T > 3 = 2 points	AFP > 200 ng/mL = 4 points	–	–
[48]	Halazun	NYCA New York-UCLA	2018	Largest T diam < 3 cm = 0 points; 3–6 cm = 2 points, > 6 cm = 4 points / 1 T = 0 points; 2–3 T = 2 points; ≥ 4 T = 4 points	AFP < 200 (always) = 0 points; AFP-responder = 2 points; AFP non-responder = 3 to 6 points	–	–
[49]	Mazzaferro	Metroticket 2.0 Italy (Training)/Fudan Shanghai (Validation)	2018	Up to 7; Up to 5; Up to 4	AFP < 200; 200–400; 400–1000	– –	– –
[50]	Shimamura	5–5-500	2018	≤ 5 T with each T ≤ 5 cm	AFP ≤ 500 ng/mL	–	–
[51]	Fiel	HALT Cleveland	2019	(2.31*ln(AFP)) + (1.33*(CTPS)) + (0.25*MELDNa) – (5.57*Ascia)			
[52]	Ince	Malatya	2020	MC-in within the criteria. If MC-out: Largest T diam ≤ 6 cm	MC-in within the criteria. If MC-out: AFP ≤ 200 ng/mL + GGT ≤ 104 IU/L + grade I/II	–	–
[53]	Daoud	UNOS data	2021	Milan criteria and AFP ≤ 2500 ng/mL UCSF criteria ≤ 150 ng/mL		–	–
[54]	Mazzotta	AFP-Model modified	2021	High-risk for number of nodules: > 5 instead of > 3		–	–
[55]	Goldberg	LiTES-HCC	2021	Age, bilirubin, chronic kidney disease, INR, diabetes, etiology of liver disease, difference TTD at LT vs. waiting list, difference AFP at LT vs. waiting list, pre-LT location, pre-LT ventilation		–	–
[56]	Hwang	ADV < 5log	2021	Log10(AFP* DCP*total volume)		–	–
Combined morphologic, biological, and radiological HCC characteristics							
[57]	Roayaie	Mount Sinai New York	2002	1 T > 5 cm	–	TACE	–
[58]	Kornberg	Munich	2012	–	–	PET-CT negative	–
[59]	Lai	EurHeCaLT	2013	Milan criteria	AFP slope ≥ 15 ng/mL/month	mRECIST progression	–
[60]	Kornberg	Munich	2014	–	–	Bridging response necrosis > 50%	–
[61]	Lee	NCCK	2016	TTD ≤ 10 cm	–	PET-CT SUV < 3.08	–
[62]	Hsu	Koahsiung Chang Gung—Taiwan	2016	UCSF criteria	–	PET-CT negative (TNR < 2)	–
[63]	Lai	TRAIN Brussels (Training)/Ancona (Validation)	2016	0.988 if mRECIST-PD + 0.838 if AFP slope > 15 ng/mL/month + 0.452 if NLR > 5.0 + 0.03*WT (in months) Low TRAIN < 1.0			–
[64]	Bhangui	Medanta	2021	UCSF criteria/Milan criteria	AFP ≥ 100 ng/mL	PET-CT [18F]FDG avidity	–
Only pathological HCC characteristics							
[65]	Cillo	Padua	2004	No tumor size/tumor number restriction	–	–	Moderately or well differentiated tumor
[66]	DuBay	Toronto	2011	No tumor size/tumor number restriction	–	–	No systemic symptoms. Not poorly differentiated if MC-OUT

Ref reference, *HCC* hepatocellular cancer, *T* tumor, *TTD* total tumor diameter, *DCP* des-gamma-carboxy prothrombin, *AFP* alpha-fetoprotein, *B* biology-related parameters, *TTD* total tumor diameter, *TTV* total tumor volume, *TBS* tumor burden score, *TACE* trans-arterial chemo-embolization, *PET* positron emission tomography, *CT* computed tomography, *AFP* alpha-fetoprotein, *mRECIST* modified response evaluation criteria in solid tumors, *RF* risk factors, *TTD* total tumor diameter, *SUV* standardized uptake value

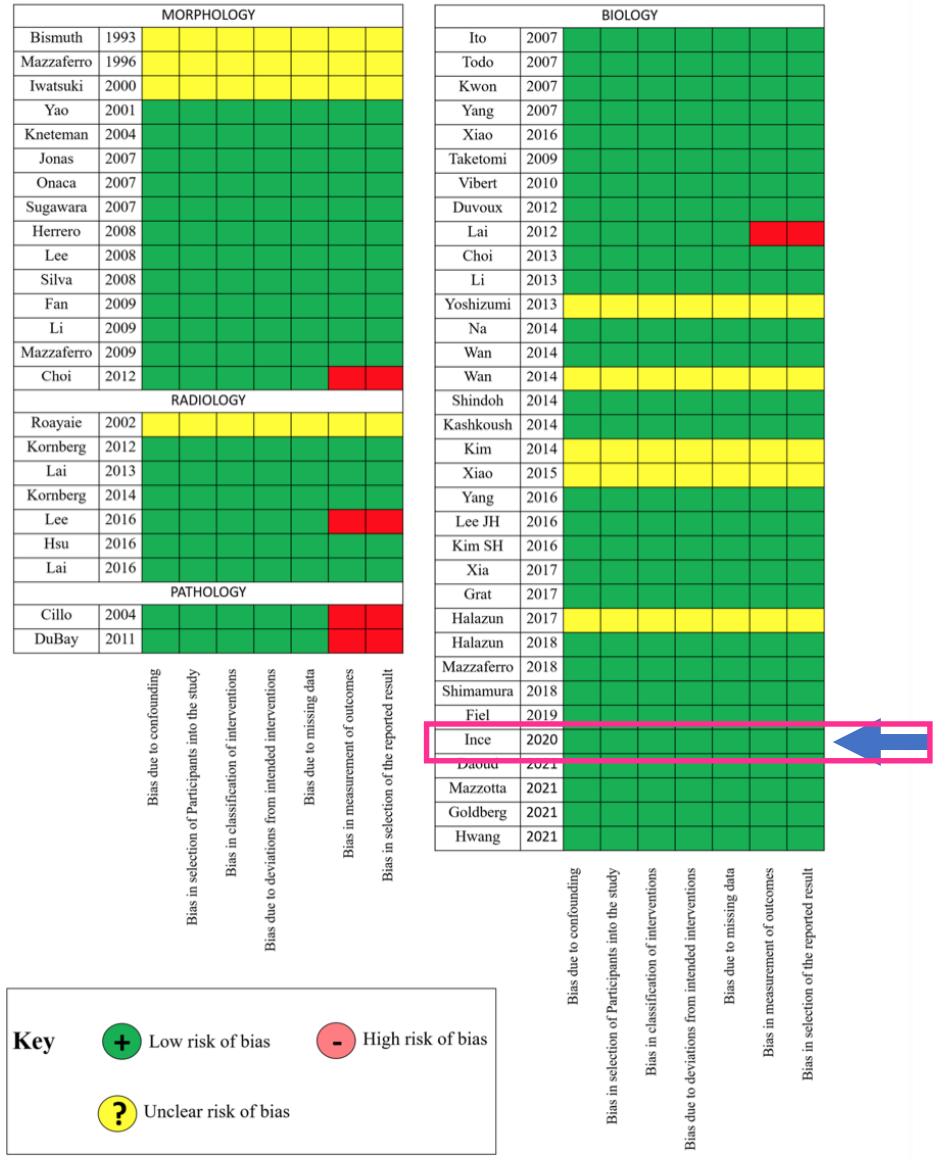
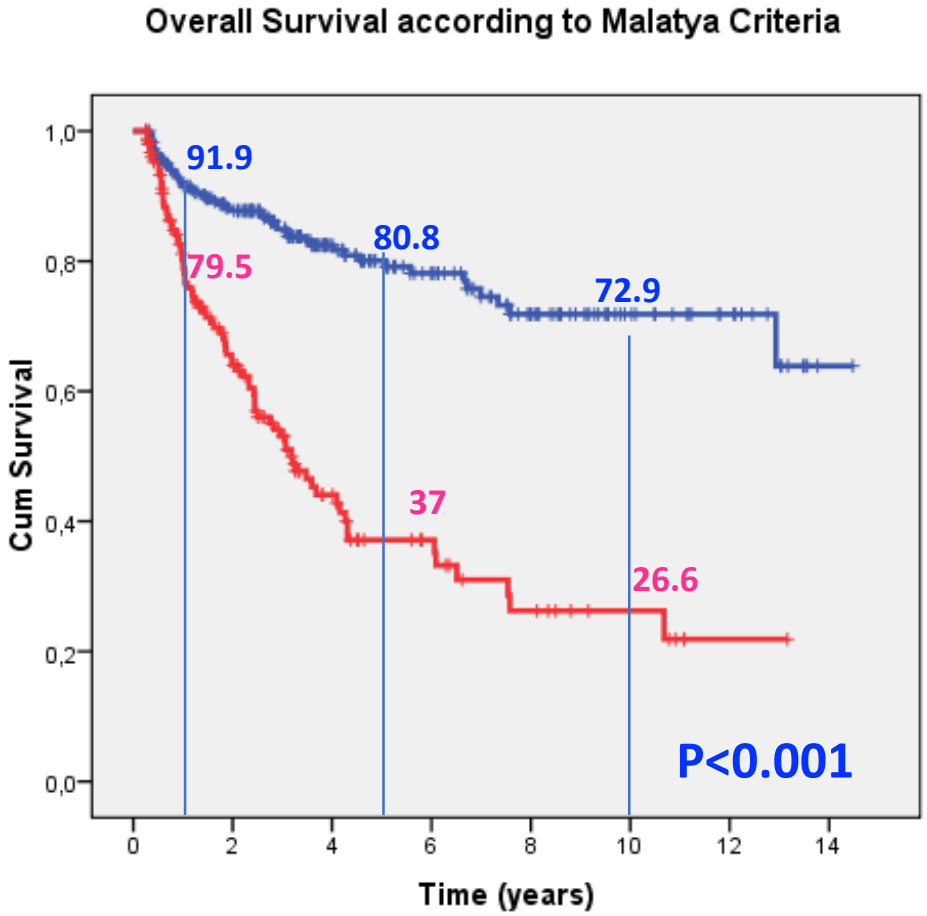


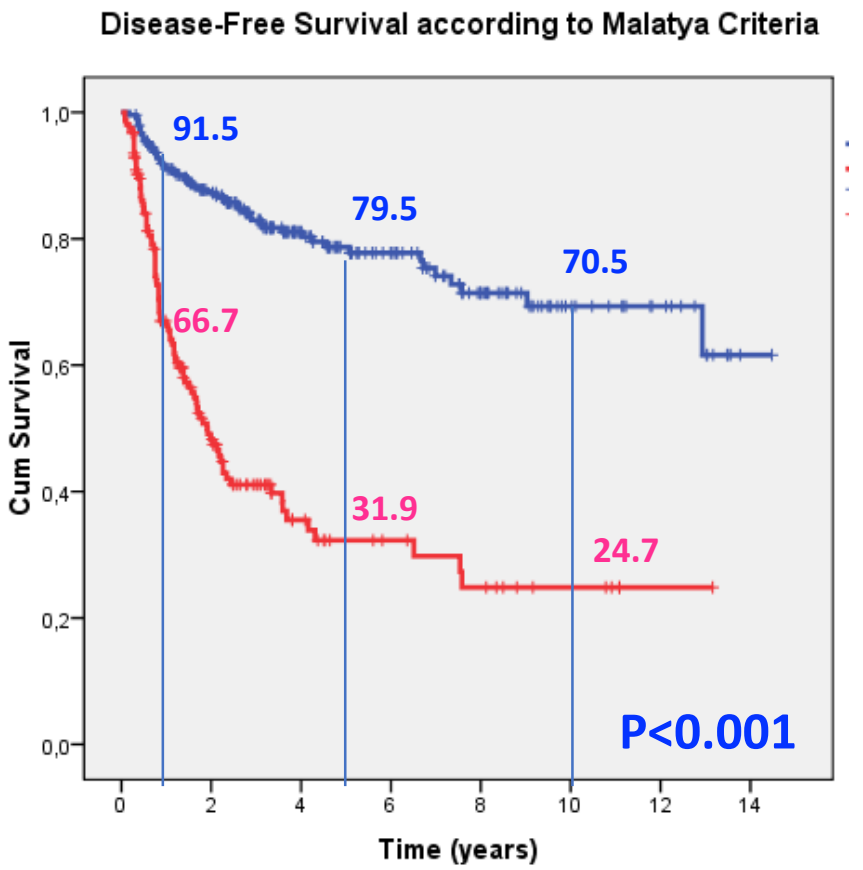
Fig. 2 ROBINS-I qualitative assessment of the included studies

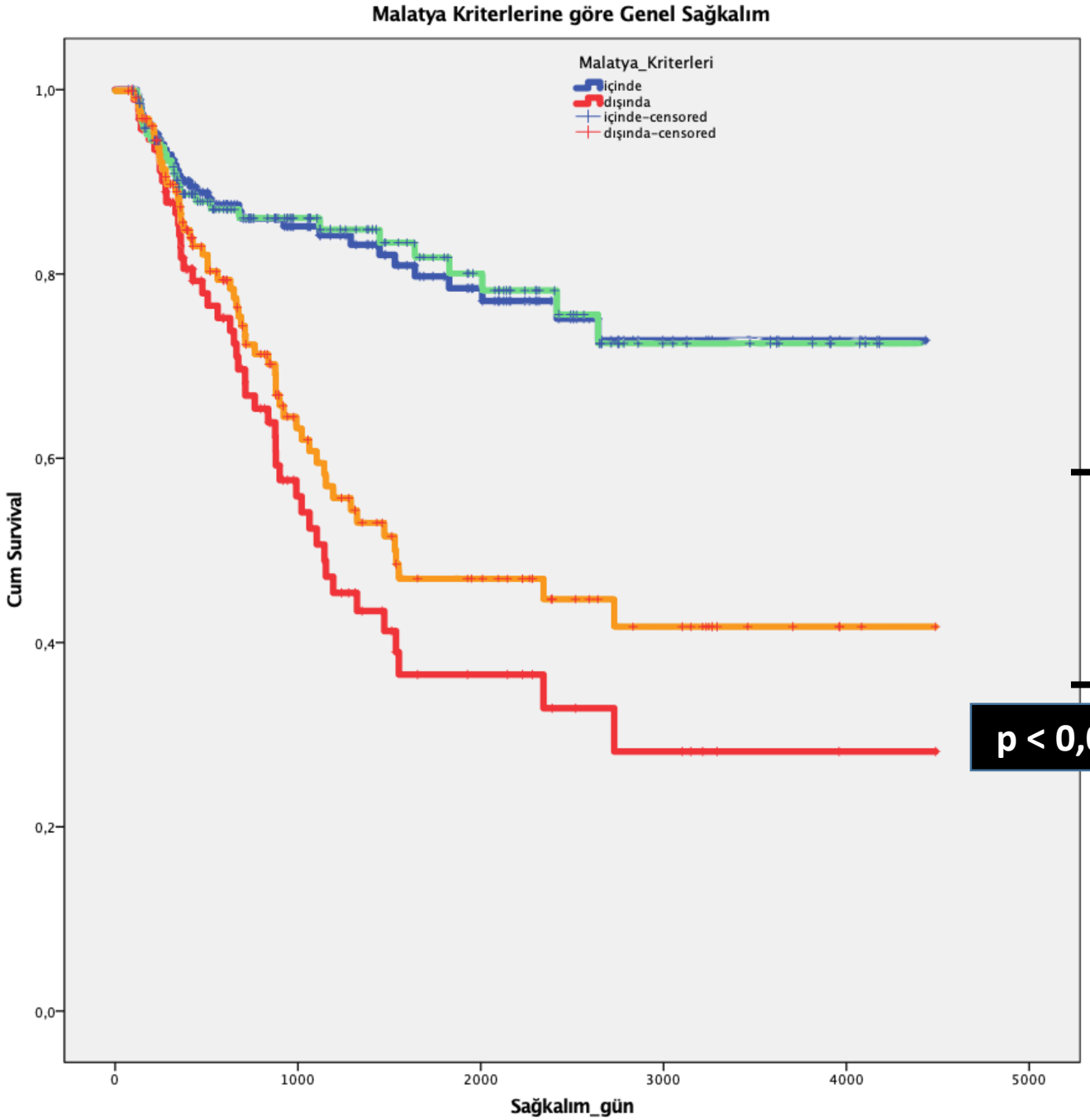
Table 2 (continued)

Ref	Center	Nr	New IN	MC-IN	MC-OUT	Additive LT cases			5-yr OS %			5-yr DFS %			LDLT (%)
						Nr	%		New IN	MC-OUT New IN	New OUT	New IN	MC-OUT/ new IN	New OUT	
[37]	Shanghai	130	35	0	130	35	–	74		–	–	74	–	–	–
[38]	Tokyo bis	124	110	80	44	30	27	88		–	20	98	–	20	124 (100)
[39]	Alberta	115	88	61	54	27	31	82		82	–	88	–	55	–
[40]	SMC criteria	180	146	NA	NA	NA	NA	–		–	–	90	–	57	157 (87)
[41]	Chengdu	305	27	NA	NA	NA	NA	62		–	12	75	–	10	–
[42]	Pusan University	88	65	59	23	6	9	89 (3 yr)		–	80 (3 yr)	90 (3 yr)	88 (3 yr)	43 (3 yr)	72 (82)
[43]	MoRAL South Korea	566	NA	361	205	NA	NA	83		83	–	68	66	–	
[44]	ASAN Seoul AMC group	461	397	305	156	92	23	83		–	63	92	–	55	461 (100)
[45]	Zheijiang	348	184	144	204	40	22	–		–	–	73	73	15	41 (12)
[46]	Warsawa	240	172	143	97	29	17	75		82	55	92	100	45	–
[47]	MoRAL New York	339	NA	226	113	NA	NA	–		–	–	Pre: gr 1 = 99; gr 2 = 70 Post: gr 1 = 97; gr 2 = 75	78	–	–
[48]	NYCA New York-UCLA	1450	1416	1215	235	201	14	75 low risk		–	40	90 low risk 72 high risk	–	72	–
[49]	Metroticket 2.0 Italy (Training)	1018	NA	NA	NA	NA	NA	80		–	50	90	–	45	–
	Fudan Shanghai (Validation)	341	NA	NA	NA	NA	NA	81		–	60	86	93	60	–
[50]	5–5-500	965	735	664	301	71	10	76		–	52	73	–	43	965 (100)
[51]	HALT Cleveland	4089	NA	3059	1030	NA	NA	82 HALT < 5 32 HALT > 35		–	–	91 HALT < 5 30 HALT > 35	–	–	–
[52]	Malatya	215	104	152	63	41	19	80		72	37	–	–	–	NA

Malatya Kriterlerine Göre Sağkalım







Malatya Kriterleri

Genel Sağkalım %

	Milan +	Milan -	Malatya +	Malatya -
1 yıl	90.9	83.5	91.9	79.5
5 yıl	81.7	47	80.8	37
10 yıl	71.6	40	72.9	26.7

p < 0,001

Malatya Kriterleri

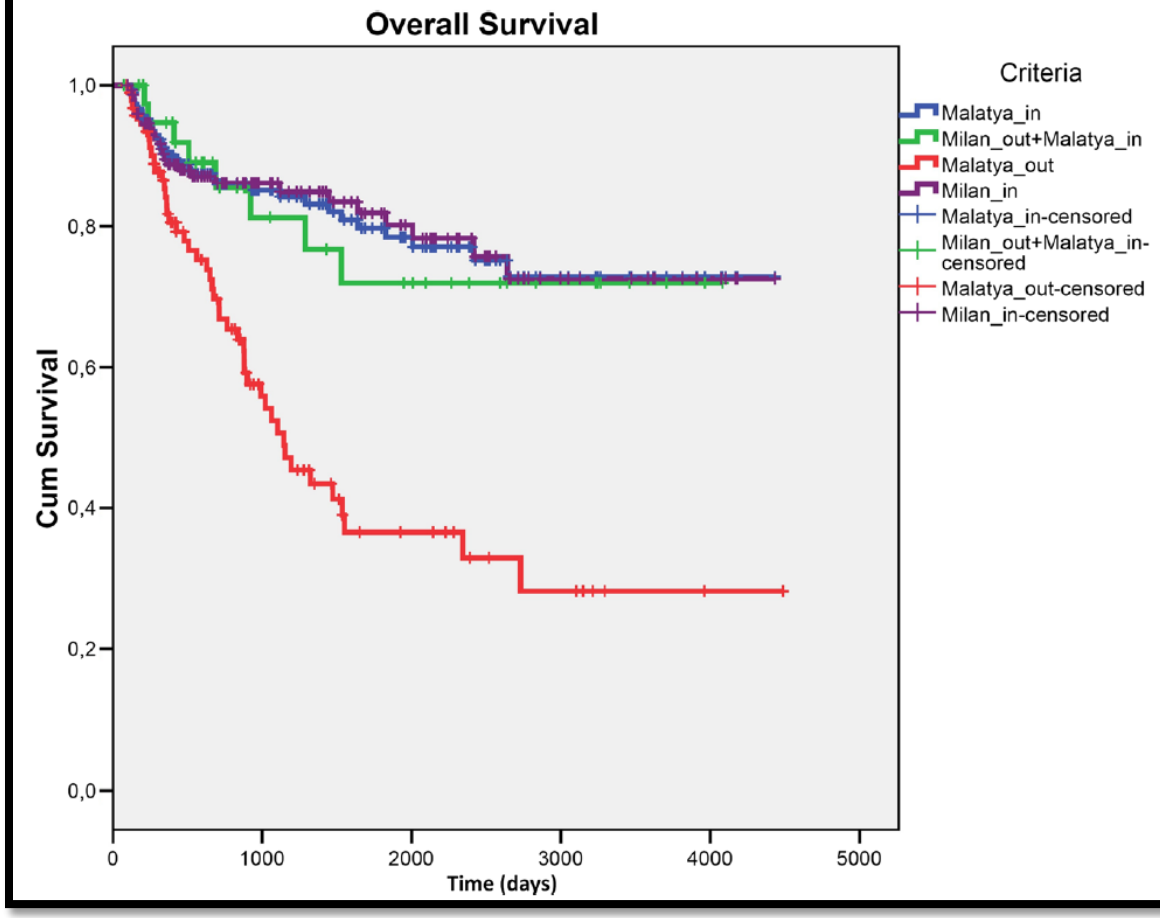
Journal of Gastrointestinal Cancer
https://doi.org/10.1007/s12029-020-00424-w

ORIGINAL RESEARCH

Liver Transplantation for Hepatocellular Carcinoma: Malatya Experience and Proposals for Expanded Criteria

Volkan Ince[1] · A. Sami Akbulut[1] · Emrah Otan[1] · Veysel Ersan[1] · Serdar Karakas[1] · Tolga Tevfik Sahin[1] · Brian I Carr[1] · Adil Baskiran[1] · Emine Samdanci[2] · Harika Gozukara Bag[3] · Cemalettin Koc[1] · Sertac Usta[1] · Fatih Ozdemir[1] · Bora Barut[1] · Fatih Gonultas[1] · Baris Sarici[1] · Koray Kutluturk[1] · Murat Sait Dogan[1] · Dincer Ozgor[1] · Mustafa Dikilitas[4] · Murat Harputluoglu[5] · Murat Aladag[5] · Ramazan Kutlu[6] · Ilknur Varol[7] · Abuzer Dirican[1] · Cemalettin Aydin[1] · Burak Isik[1] · Cengiz Ara[1] · Cuneyt Kayaalp[1] · Sukru Emre[1] · Sezai Yilmaz[1]

J Gastrointest Canc (2020) 51:998–1005



Malatya Kriterleri

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ORIGINAL RESEARCH

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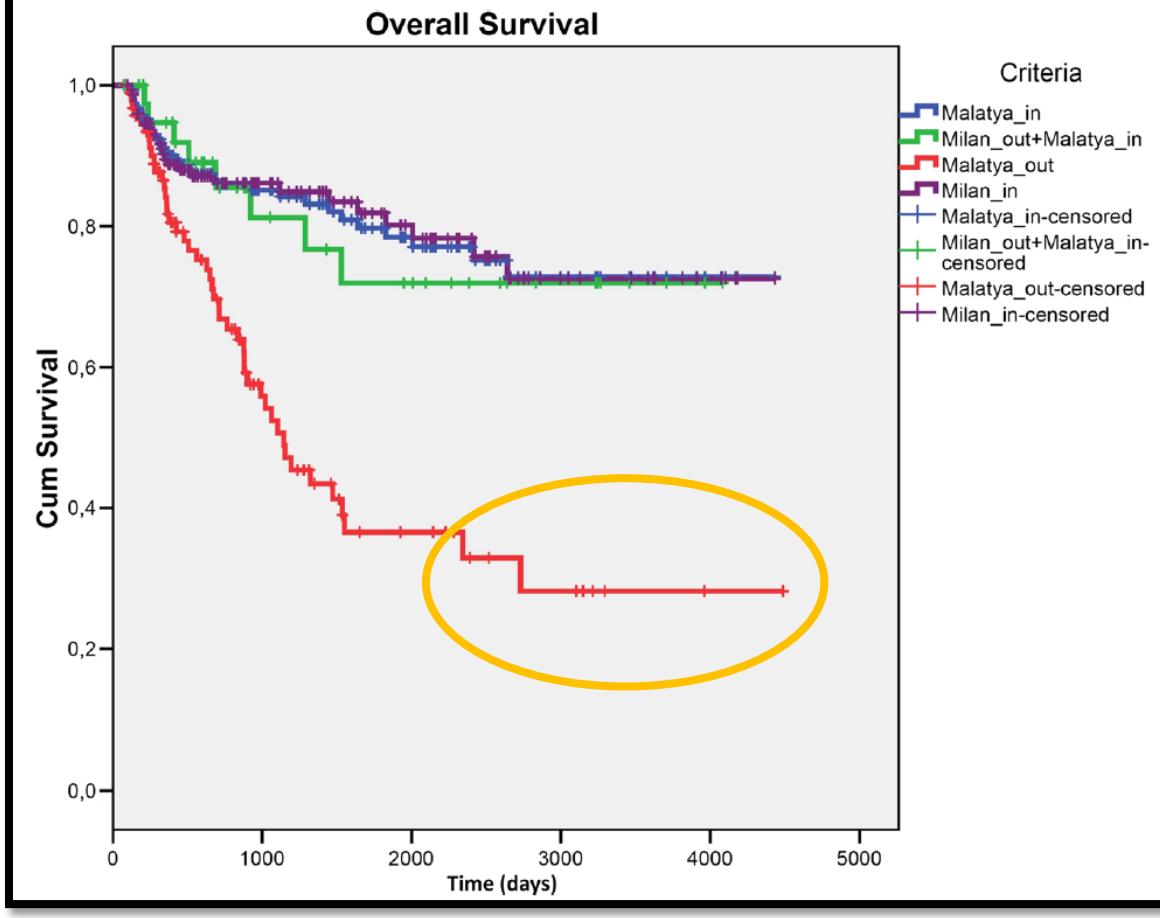


Extended Malatya Kriterleri

Liver Transplant for Large HCC in Malatya

World Journal of Gastrointestinal Surgery

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Surg 2020 December 27; 12(12): 520-533

DOI: 10.4240/wjgs.v12.i12.520

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Liver transplant for large hepatocellular carcinoma in Malatya: The role of gamma glutamyl transferase and alpha-fetoprotein, a retrospective cohort study

Volkan Ince, Brian I Carr, Harika Gozukara Bag, Veysel Ersan, Sertac Usta, Cemalettin Koc, Fatih Gonultas, Baris Kemal Sarici, Serdar Karakas, Koray Kutluturk, Adil Baskiran, Sezai Yilmaz

	Overall survival, years, (%)			
6<MTD≤10	1	3	5	p
AFP≤200+GGT≤104 (n=14)	85,7	76,2	76,2	0,002
All other AFP+GGT combinations (n=25)	65,3	31,4	-	

	Overall survival, years, (%)			
MTD>10cm	1	3	5	p
AFP≤200+GGT≤104 (n=0)	-	-	-	-
All other AFP+GGT combinations (n=11)	55,6	22,2	-	

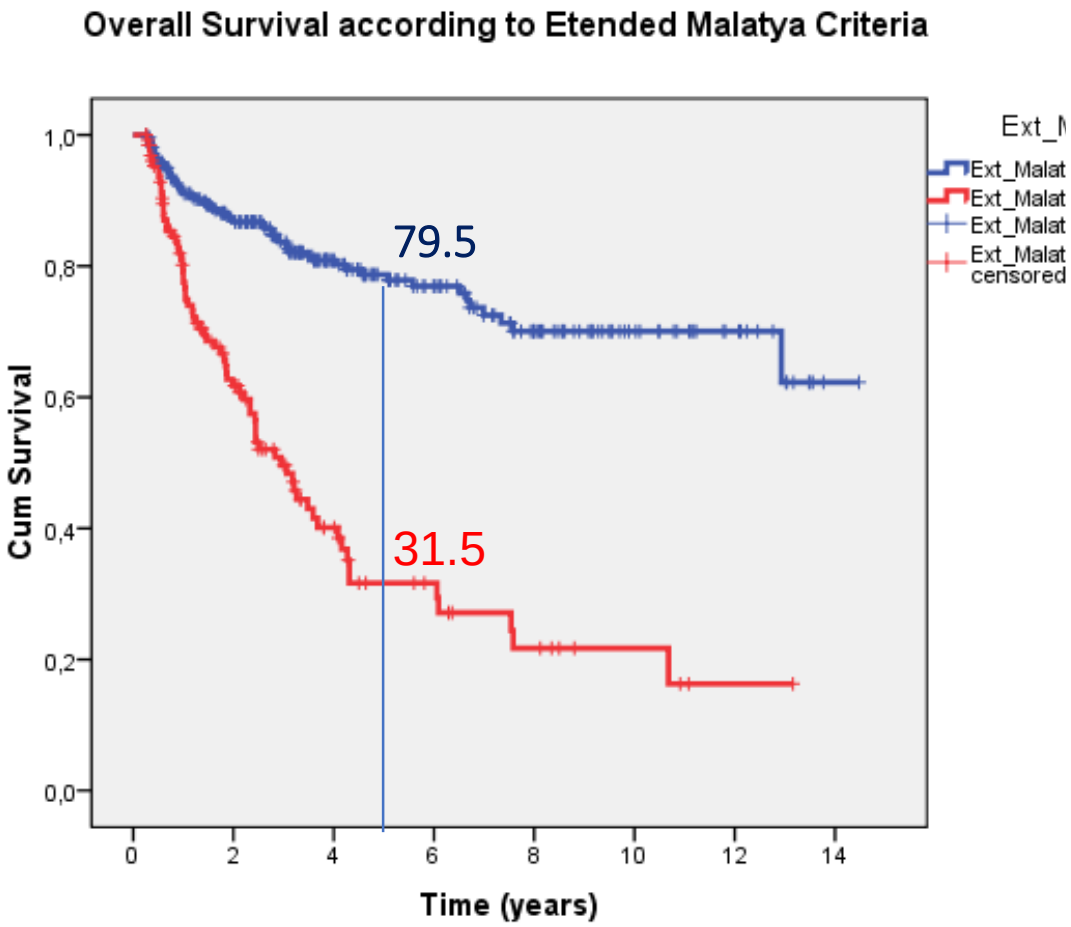
Genişletilmiş Malatya kriterleri:

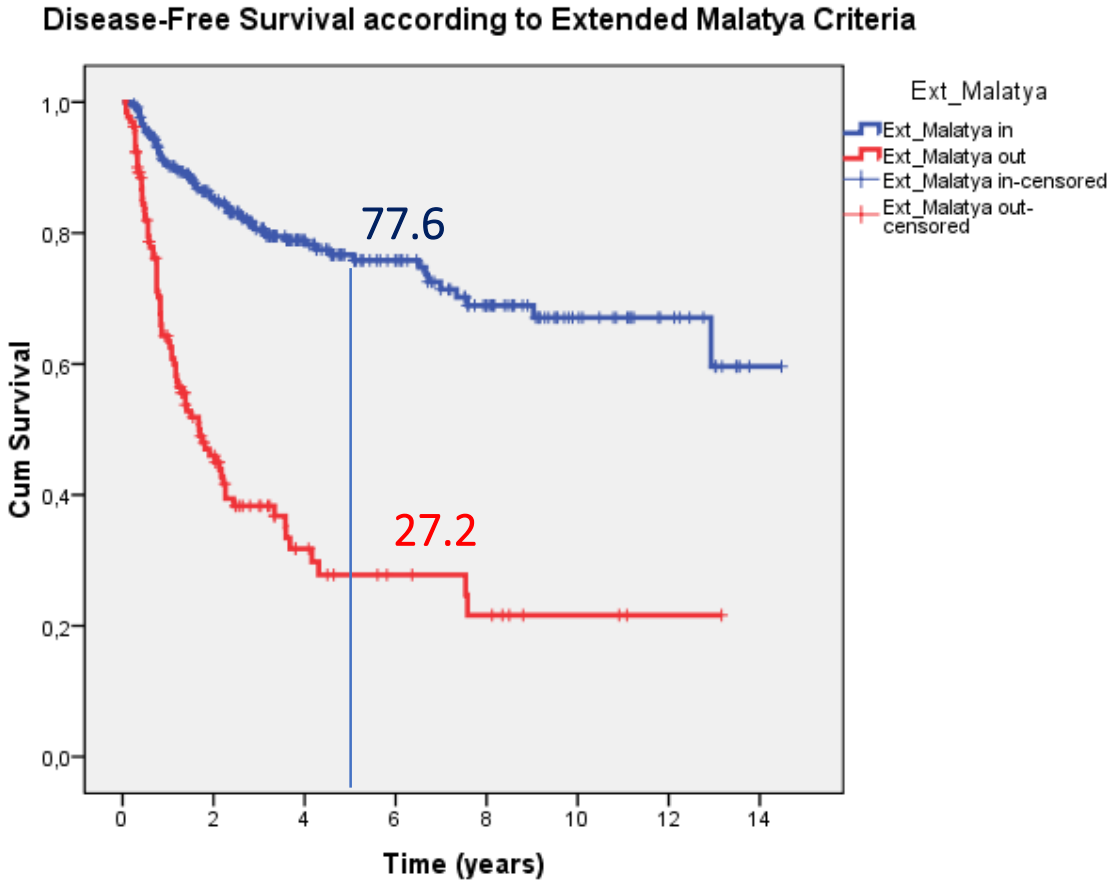
1-Milan içi olması

2-Milan dışında ise

a. MTD ≤ 10 cm
b. AFP ≤ 200
c. GGT ≤ 104 olması

Extended Malatya Kriterlerine Göre Sağkalım





Transplant Kriterlerinin Malatya Kohortuna Uygulanması

Retrospektif Klinik Çalışma

2022

23 genişletici kriterin Malatya kohortuna uygulanması

Within Criteria	n	Expansion rate of Milan	5 year DFS	Recurrence Rate %	Milan in, Criteria out Patient number	Milan in, Criteria out Patient 5-year OS	Milan out, Criteria in Patient 5-year DFS
All Cohort	406		62	19			
Milan	206	Reference Criteria	80	3.4			
UCSF	242	17,5	74,9	5,8			47,4
BCLC	263	27,7	75,3	5,7			56
Extended	295	43,2	74	7,5			60,2
Berlin	290	40,8	76,8	5,9			67,3
Tokyo	257	24,8	77,9	4,7			68
Onaca	254	23,3	77,7	5,1			67,5
Hangzhou	328	59,2	70,9	9,8			57,5
Asan	263	27,7	77,7	4,6			68,1
CUN-Navarra	242	17,5	77,2	5,0			63,8
Valencia	234	13,6	78,3	4,3			70,4
Shangai	254	23,3	74,1	6,7			55,9
UpToSeven	185	-10,2	77,1	3,2	45	88	73,2
ETC	319	54,9	71,9	9,7			59,3
AFP Model	252	22,3	78,2	3,6	11	71.6	68,3
AFP-TTD	244	18,4	77,9	4,0	20	70	66,9
Samsung	260	26,2	78,2	4,8	12	75	70,6
PostMoRAL	292	41,7	74,4	6,5	7	100	66,8
PreMoRAL	302	46,6	72,2	8,6	9	75	57,6
Metrotic2.0	228	10,7	78,6	3,1	15	80	65,6
5-5-500	235	14,1	80,1	2,1	18	72.2	72,9
Malatya	254	23,3	79,5	3,5			76,3
Extended Malatya	278	35,0	77,6	4,7			72,5

- **1. Hepatocellular karsinomada kullanılan expanded kriterlerden hangisi % 75'in üzerinde 5 yıllık DFS'a sahiptir ?**

5 yıllık sağ kalım > % 75 (n=15)

Criteria with >75% 5-yDFS	5-year DFS	Recurrence	Expansion rate of Milan
BCLC	75,3	5,7	27,7
Berlin	76,8	5,9	40,8
Tokyo	77,9	4,7	24,8
Onaca	77,7	5,1	23,3
Asan	77,7	4,6	27,7
CUN-Navarra	77,2	5,0	17,5
Valencia	78,3	4,3	13,6
UpToSeven	77,1	4,8	18,4
AFP Model	78,2	3,6	22,3
AFP-TTD	77,9	4,0	18,4
Samsung	78,2	4,8	26,2
Metrotic2.0	78,6	3,1	10,7
5-5-500	80,1	2,1	14,1
Malatya	79,5	3,5	23,3
Extended Malatya	77,6	4,7	35,0

- **2. Hepatocellular karsinomada kullanılan expanded kriterlerden hangisi % 75'in üzerinde 5 yıllık DFS'a ve % 5'in altında recurrence oranlarına sahiptir ?**

5 yıllık sağ kalım > % 75
Recurrence oranı < % 5 (n=12)

Criteria with >75% 5-yDFS and <5% Recurrence	5-year DFS	Recurrence	Expansion rate of Milan
Tokyo	77,9	4,7	24,8
Asan	77,7	4,6	27,7
CUN-Navarra	77,2	5,0	17,5
Valencia	78,3	4,3	13,6
UpToSeven	77,1	4,8	18,4
AFP Model	78,2	3,6	22,3
AFP-TTD	77,9	4,0	18,4
Samsung	78,2	4,8	26,2
Metrotic2.0	78,6	3,1	10,7
5-5-500	80,1	2,1	14,1
Malatya	79,5	3,5	23,3
Extended Malatya	77,6	4,7	35,0

- **3. Hepatocellular karsinomada kullanılan expanded kriterlerden hangisi**
  - ✓ **% 75'in üzerinde 5 yıllık DFS'a,**
  - ✓ **% 5'in altında rekürrens oranlarına ve**
  - ✓ **% 35'in üzerinde daha fazla hastaya transplant şansını aynı anda sunabilir ?**

INONU UNIVERSITY
LIVER TRANSPLANT INSTITUTE

>75% 5-year DFS and

<5% Recurrence rate and

>35% Expansion rate of Milan

Criteria with >75% 5-yDFS and <5% Recurrence and >35% Expantion rate	5-year DFS	Recurrence	Expansion rate of Milan
Extended Malatya	77,6	4,7	35

Genişletilmiş Kriterlerin Malatya Kohortuna Uygulanması

- Sonuç olarak,
  - Kriterler genişletildikçe,
    - Genel sağkalımda azalma
    - Hastalıksız sağkalımda azalma
    - Nüks oranında artma ile sonuçlanıyor

- Tüm bu kriterler arasında, sadece Genişletilmiş Malatya Kriterleri aşağıdaki üç koşulu birden sunuyor
  - >%75, 5-yıllık DFS
  - <%5, post-Tx tümör nüksü
  - >%35, Milanı genişletme oranı (Milan dışındaki, 72 yeni hasta KN şansı buldu)

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Volkan Ince

Co-Author(s): Sertac Usta, Brian I. Carr , Veysel Ersan , Cemalettin Koc , Fatih Ozdemir , Hariha G. Bag , Sezai Yilmaz

Liver Transplant Institute, Inonu University, Turkey

Sung-Gyu Lee, M.D., Ph.D.
President
Organizing Committee of ISLS 2021 Symposium

Ki-Hun Kim, M.D., Ph.D.
Secretary General
Organizing Committee of ISLS 2021 Symposium

İleri Evre HCC için Karaciğer Nakli

Kriterlerin Ortak Özellikleri

- **Makrovasküler invazyon olmayacak**
- **Karaciğer dışı tümör yayılımı olmayacak**
- **5 yıllık OS > %60**

*

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

Hilar LAP şüphesi

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

Hilar LAP şüphesi

Macrovascular Invasion Is Not an Absolute Contraindication for Living Donor Liver Transplantation

Kwang-Woong Lee,[1] Suk-Won Suh,[1] YoungRok Choi,[1] Jaehong Jeong,[1] Nam-Joon Yi,[1] Hyeyoung Kim,[1] Kyung Chul Yoon,[1] Suk Kyun Hong,[1] Hyo-Sin Kim,[1] Kyung-Bun Lee,[2] and Kyung-Suk Suh[1]

Departments of [1]Surgery and [2]Pathology, Seoul National University College of Medicine, Seoul, South Korea

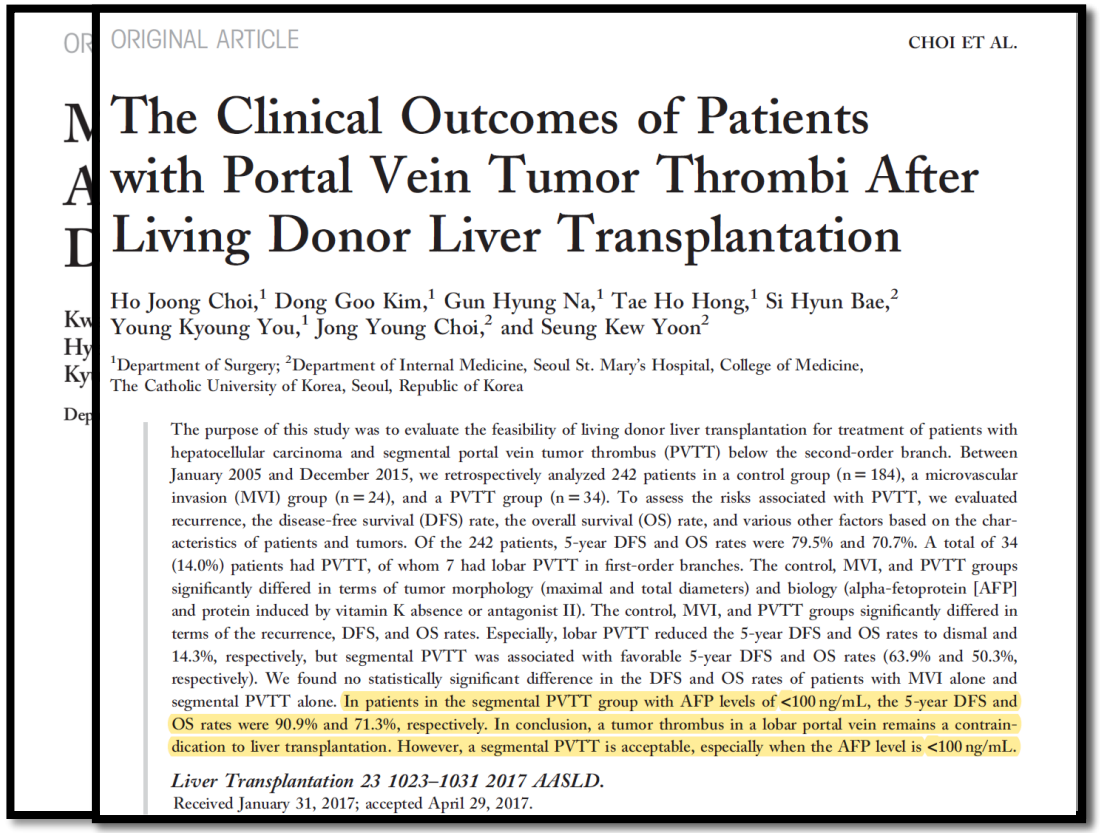
The indication of liver transplantation (LT) for the treatment of advanced hepatocellular carcinoma (HCC) is expanding. However, portal vein tumor thrombus (PVTT) has been still accepted as an absolute contraindication. We experienced an unexpectedly good prognosis in selected patients. Therefore, we tried to identify the prognostic factors after LT for HCC with major PVTT. Among 282 patients who underwent living donor liver transplantation (LDLT) for HCC from January 2009 to December 2013, 11 (3.9%) patients with major PVTT that was preoperatively diagnosed were investigated. The 1-, 3-, and 5-year recurrence-free survival rates were 63.6%, 45.5%, and 45.5%, respectively, and all recurrent cases showed intrahepatic and extrahepatic recurrence. The 1-, 3-, and 5-year overall survival rates were 72.7%, 63.6%, and 63.6%, respectively, and 2 patients with delayed recurrence survived approximately 5 years after LT. Main portal vein (PV) invasion ($P<0.01$), high alpha-fetoprotein × protein induced by vitamin K absence/antagonist-II (AP) score ($\geq$20,000; $P<0.01$), high standardized uptake value (SUV) ratio (tumor/background liver) in positron emission tomography ($\geq$2.1; $P<0.01$), and a large original tumor ($\geq$7 cm; $P=0.03$) were significant risk factors for recurrence. In conclusion, if the PVTT has not expanded to the main PV and the AP score is not high, we can consider LDLT as a curative treatment option.

Liver Transplantation 23:19–27 2017 AASLD.
Received April 3, 2016; accepted August 6, 2016.

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

Hilar LAP şüphesi



ORIGINAL ARTICLE CHOI ET AL.

The Clinical Outcomes of Patients with Portal Vein Tumor Thrombi After Living Donor Liver Transplantation

Ho Joong Choi,[1] Dong Goo Kim,[1] Gun Hyung Na,[1] Tae Ho Hong,[1] Si Hyun Bae,[2] Young Kyoung You,[1] Jong Young Choi,[2] and Seung Kew Yoon[2]

[1]Department of Surgery; [2]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

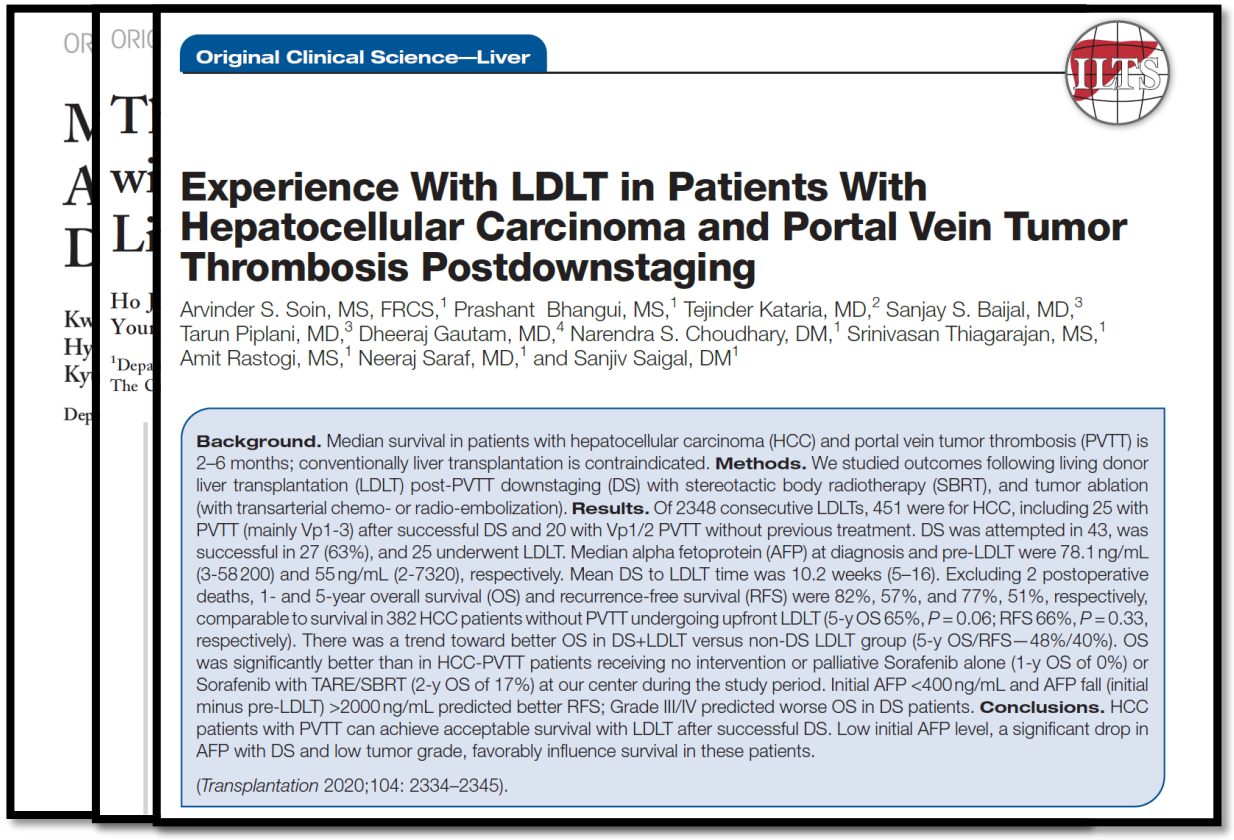
The purpose of this study was to evaluate the feasibility of living donor liver transplantation for treatment of patients with hepatocellular carcinoma and segmental portal vein tumor thrombus (PVTT) below the second-order branch. Between January 2005 and December 2015, we retrospectively analyzed 242 patients in a control group (n = 184), a microvascular invasion (MVI) group (n = 24), and a PVTT group (n = 34). To assess the risks associated with PVTT, we evaluated recurrence, the disease-free survival (DFS) rate, the overall survival (OS) rate, and various other factors based on the characteristics of patients and tumors. Of the 242 patients, 5-year DFS and OS rates were 79.5% and 70.7%. A total of 34 (14.0%) patients had PVTT, of whom 7 had lobar PVTT in first-order branches. The control, MVI, and PVTT groups significantly differed in terms of tumor morphology (maximal and total diameters) and biology (alpha-fetoprotein [AFP] and protein induced by vitamin K absence or antagonist II). The control, MVI, and PVTT groups significantly differed in terms of the recurrence, DFS, and OS rates. Especially, lobar PVTT reduced the 5-year DFS and OS rates to dismal and 14.3%, respectively, but segmental PVTT was associated with favorable 5-year DFS and OS rates (63.9% and 50.3%, respectively). We found no statistically significant difference in the DFS and OS rates of patients with MVI alone and segmental PVTT alone. In patients in the segmental PVTT group with AFP levels of <100 ng/mL, the 5-year DFS and OS rates were 90.9% and 71.3%, respectively. In conclusion, a tumor thrombus in a lobar portal vein remains a contraindication to liver transplantation. However, a segmental PVTT is acceptable, especially when the AFP level is <100 ng/mL.

Liver Transplantation 23 1023–1031 2017 AASLD.
Received January 31, 2017; accepted April 29, 2017.

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

Hilar LAP şüphesi



Original Clinical Science—Liver

Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

Arvinder S. Soin, MS, FRCS,[1] Prashant Bhangui, MS,[1] Tejinder Kataria, MD,[2] Sanjay S. Baijal, MD,[3] Tarun Piplani, MD,[3] Dheeraj Gautam, MD,[4] Narendra S. Choudhary, DM,[1] Srinivasan Thiagarajan, MS,[1] Amit Rastogi, MS,[1] Neeraj Saraf, MD,[1] and Sanjiv Saigal, DM[1]

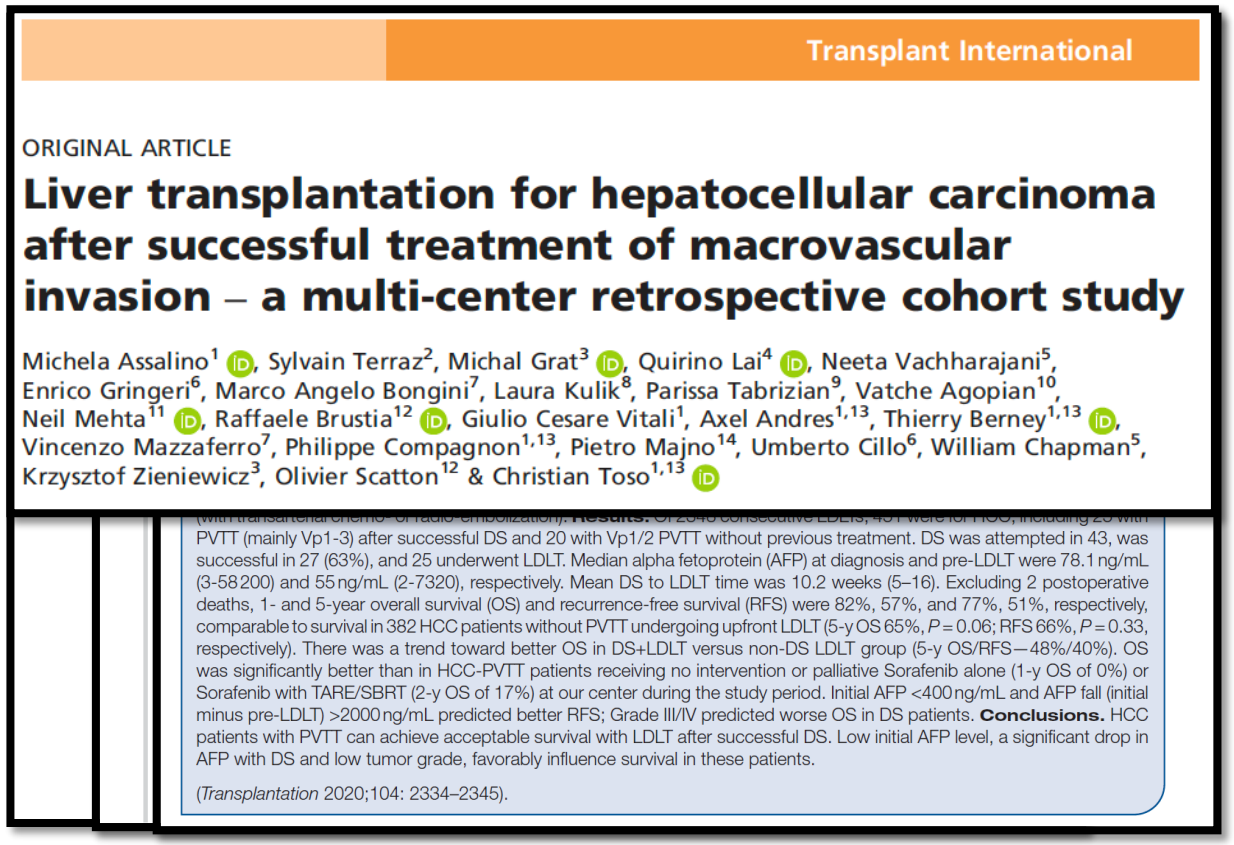
Background. Median survival in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) is 2–6 months; conventionally liver transplantation is contraindicated. **Methods.** We studied outcomes following living donor liver transplantation (LDLT) post-PVTT downstaging (DS) with stereotactic body radiotherapy (SBRT), and tumor ablation (with transarterial chemo- or radio-embolization). **Results.** Of 2348 consecutive LDLTs, 451 were for HCC, including 25 with PVTT (mainly Vp1-3) after successful DS and 20 with Vp1/2 PVTT without previous treatment. DS was attempted in 43, was successful in 27 (63%), and 25 underwent LDLT. Median alpha fetoprotein (AFP) at diagnosis and pre-LDLT were 78.1 ng/mL (3-58 200) and 55 ng/mL (2-7320), respectively. Mean DS to LDLT time was 10.2 weeks (5–16). Excluding 2 postoperative deaths, 1- and 5-year overall survival (OS) and recurrence-free survival (RFS) were 82%, 57%, and 77%, 51%, respectively, comparable to survival in 382 HCC patients without PVTT undergoing upfront LDLT (5-y OS 65%, $P = 0.06$; RFS 66%, $P = 0.33$, respectively). There was a trend toward better OS in DS+LDLT versus non-DS LDLT group (5-y OS/RFS—48%/40%). OS was significantly better than in HCC-PVTT patients receiving no intervention or palliative Sorafenib alone (1-y OS of 0%) or Sorafenib with TARE/SBRT (2-y OS of 17%) at our center during the study period. Initial AFP <400 ng/mL and AFP fall (initial minus pre-LDLT) >2000 ng/mL predicted better RFS; Grade III/IV predicted worse OS in DS patients. **Conclusions.** HCC patients with PVTT can achieve acceptable survival with LDLT after successful DS. Low initial AFP level, a significant drop in AFP with DS and low tumor grade, favorably influence survival in these patients.

(*Transplantation* 2020;104: 2334–2345).

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

Hilar LAP şüphesi



Transplant International

ORIGINAL ARTICLE

Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion – a multi-center retrospective cohort study

Michela Assalino[1], Sylvain Terraz[2], Michal Grat[3], Quirino Lai[4], Neeta Vachharajani[5], Enrico Gringeri[6], Marco Angelo Bongini[7], Laura Kulik[8], Parissa Tabrizian[9], Vatche Agopian[10], Neil Mehta[11], Raffaele Brustia[12], Giulio Cesare Vitali[1], Axel Andres[1,13], Thierry Berney[1,13], Vincenzo Mazzaferro[7], Philippe Compagnon[1,13], Pietro Majno[14], Umberto Cillo[6], William Chapman[5], Krzysztof Zieniewicz[3], Olivier Scatton[12] & Christian Toso[1,13]

PVTT (mainly Vp1-3) after successful DS and 20 with Vp1/2 PVTT without previous treatment. DS was attempted in 43, was successful in 27 (63%), and 25 underwent LDLT. Median alpha fetoprotein (AFP) at diagnosis and pre-LDLT were 78.1 ng/mL (3-58 200) and 55 ng/mL (2-7320), respectively. Mean DS to LDLT time was 10.2 weeks (5–16). Excluding 2 postoperative deaths, 1- and 5-year overall survival (OS) and recurrence-free survival (RFS) were 82%, 57%, and 77%, 51%, respectively, comparable to survival in 382 HCC patients without PVTT undergoing upfront LDLT (5-y OS 65%, $P = 0.06$; RFS 66%, $P = 0.33$, respectively). There was a trend toward better OS in DS+LDLT versus non-DS LDLT group (5-y OS/RFS—48%/40%). OS was significantly better than in HCC-PVTT patients receiving no intervention or palliative Sorafenib alone (1-y OS of 0%) or Sorafenib with TARE/SBRT (2-y OS of 17%) at our center during the study period. Initial AFP <400 ng/mL and AFP fall (initial minus pre-LDLT) >2000 ng/mL predicted better RFS; Grade III/IV predicted worse OS in DS patients. **Conclusions.** HCC patients with PVTT can achieve acceptable survival with LDLT after successful DS. Low initial AFP level, a significant drop in AFP with DS and low tumor grade, favorably influence survival in these patients.

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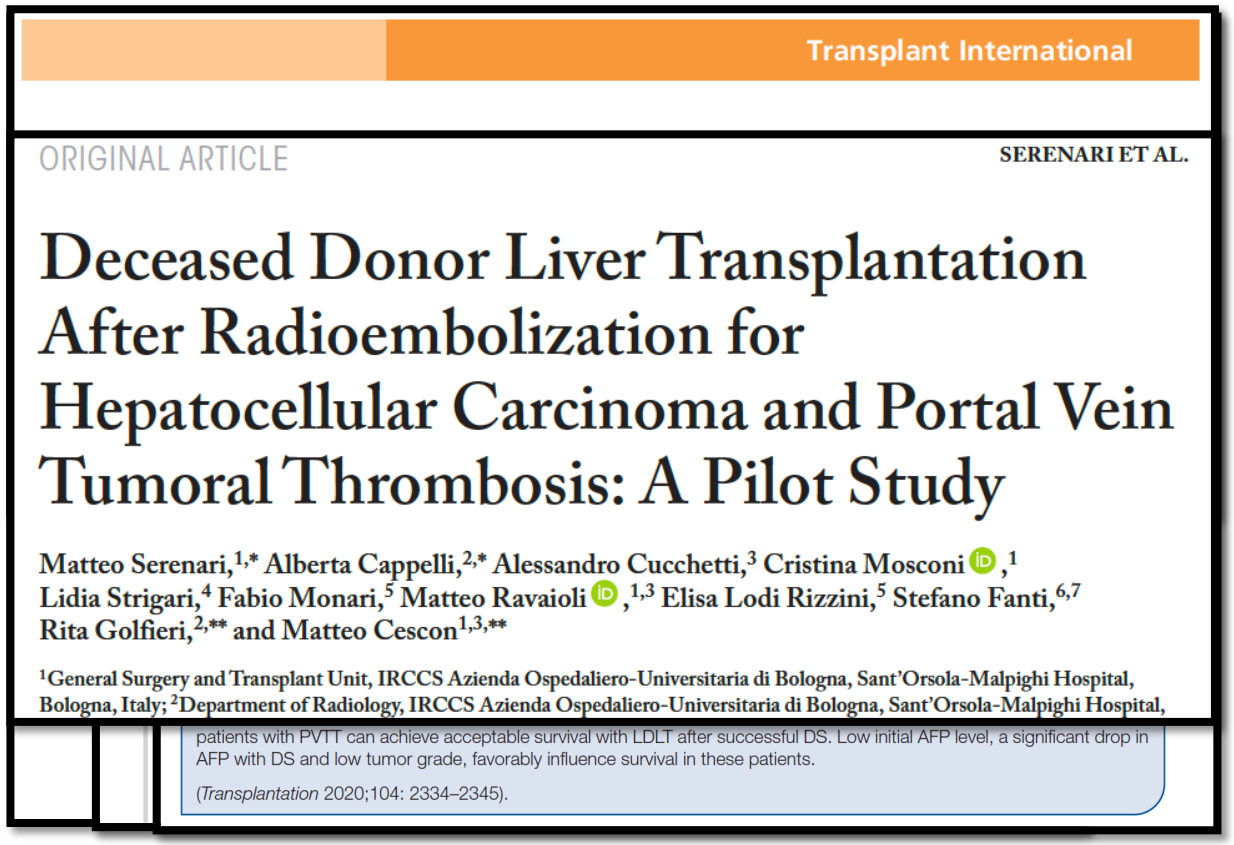

Transplant International

Deceased Donor Liver Transplantation After Radioembolization for Hepatocellular Carcinoma and Portal Vein Tumoral Thrombosis: A Pilot Study

Matteo Serenari,[1,*] Alberta Cappelli,[2,*] Alessandro Cucchetti,[3] Cristina Mosconi,[1] Lidia Strigari,[4] Fabio Monari,[5] Matteo Ravaioli,[1,3] Elisa Lodi Rizzini,[5] Stefano Fanti,[6,7] Rita Golfieri,[2,**] and Matteo Cescon[1,3,**]

[1]General Surgery and Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Sant'Orsola-Malpighi Hospital, Bologna, Italy; [2]Department of Radiology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Sant'Orsola-Malpighi Hospital,

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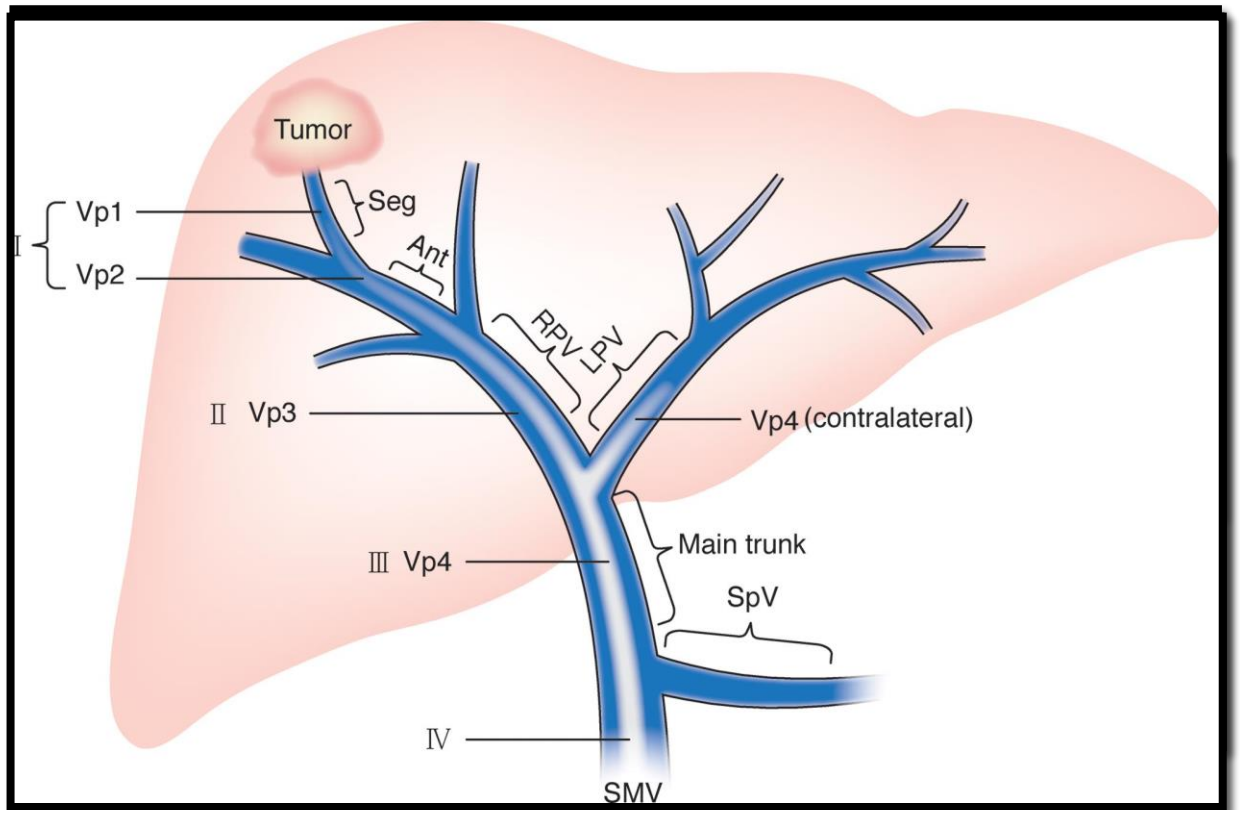
İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT

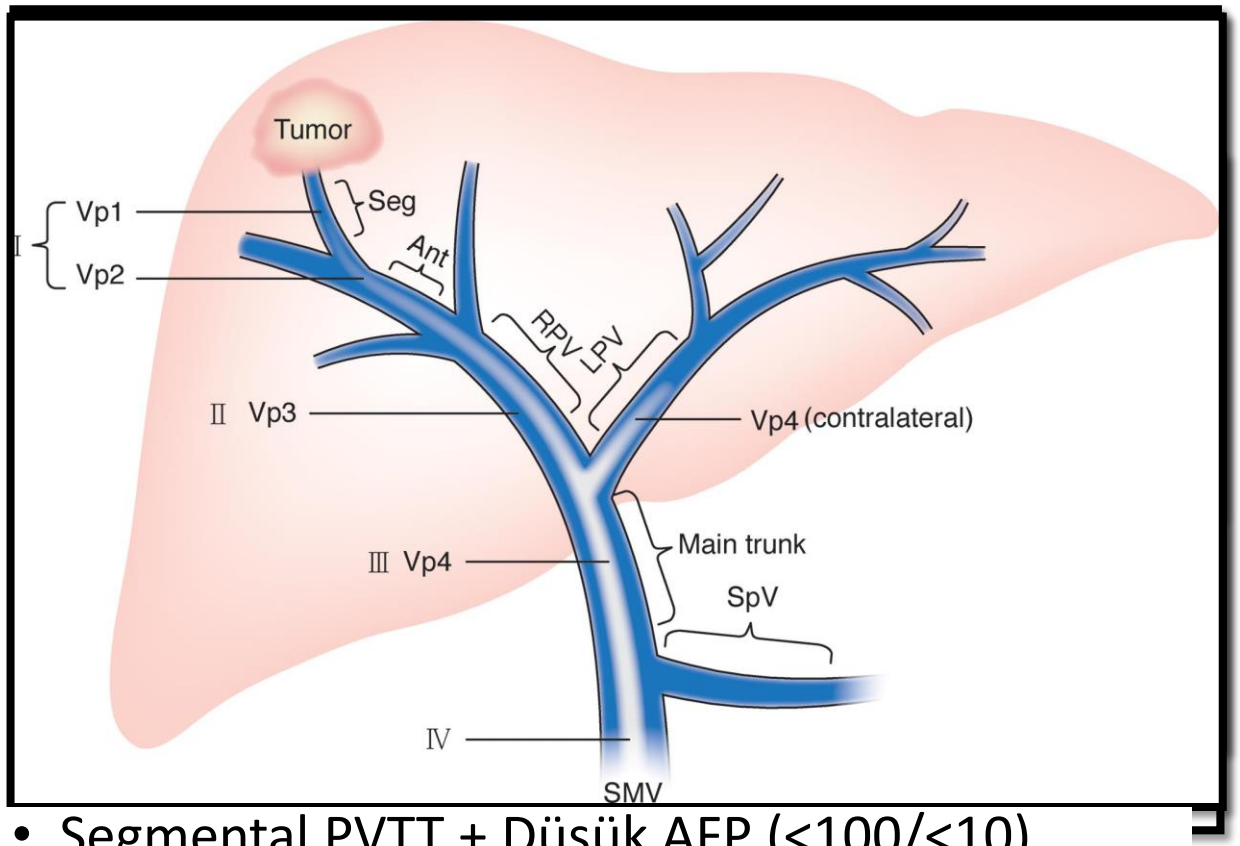


- Segmental PVTT + Düşük AFP (<100/<10)
- LRT yanıt sonrası 6 ay izlem => **5 yıl OS > %60**

Hilar LAP şüphesi

İleri Evre HCC için Karaciğer Nakli

Makroskopik PVTT



- Segmental PVTT + Düşük AFP (<100/<10)
- LRT yanıt sonrası 6 ay izlem => **5 yıl OS > %60**

Hilar LAP şüphesi

- **Pre-Tx PET CT çekilen 77 hastanın raporları geriye dönük olarak incelendiğinde, 5 hastada hilar LAP şüpheli tutulum saptandı. Bu hastaların, eksplant patolojilerinde, sadece 2 hastada lenf nodu metastazı saptandı.**
- **Hilar lenf nodu metastazı sonuçları çok kötü, Medyan yaşam 1.8yıl**
- **Bu hastalarda lenf nodu örneklemesi (frozen) düşünülebilir**

Çıkarımlar

- Tüm kriterler hedef sağkalımı yakalıyor
- Genişletilmiş kriterler arasında Expanded Malatya Kriterleri'nin avantajları
  - >%75 5-yıllık DFS
  - <%5 post-Tx rekürrens
  - >%35 Milanı genişletme oranı
- Multidisipliner konseyin önemi (Bireyselleştirilmiş yaklaşım)
- LRT ve Kombine tedavileri olabildiğince uyguluyoruz (Evre düşürme)
  - Yanıt sonrası 6 ay izlem (min 3 ay)
- Makrovasküler invazyon – seçilmiş hastalarda umut verici
- Hilar LAP varlığında, metastaz şüphesi, endoskopik/perkütan/cerrahi biyopsi ile kesinleştirilmeli

Multidisipliner konsey


AMELİYATHANE

İNÖNÜ ÜNİVERSİTESİ KARACİĞER NAKLİ ENSTİTÜSÜ

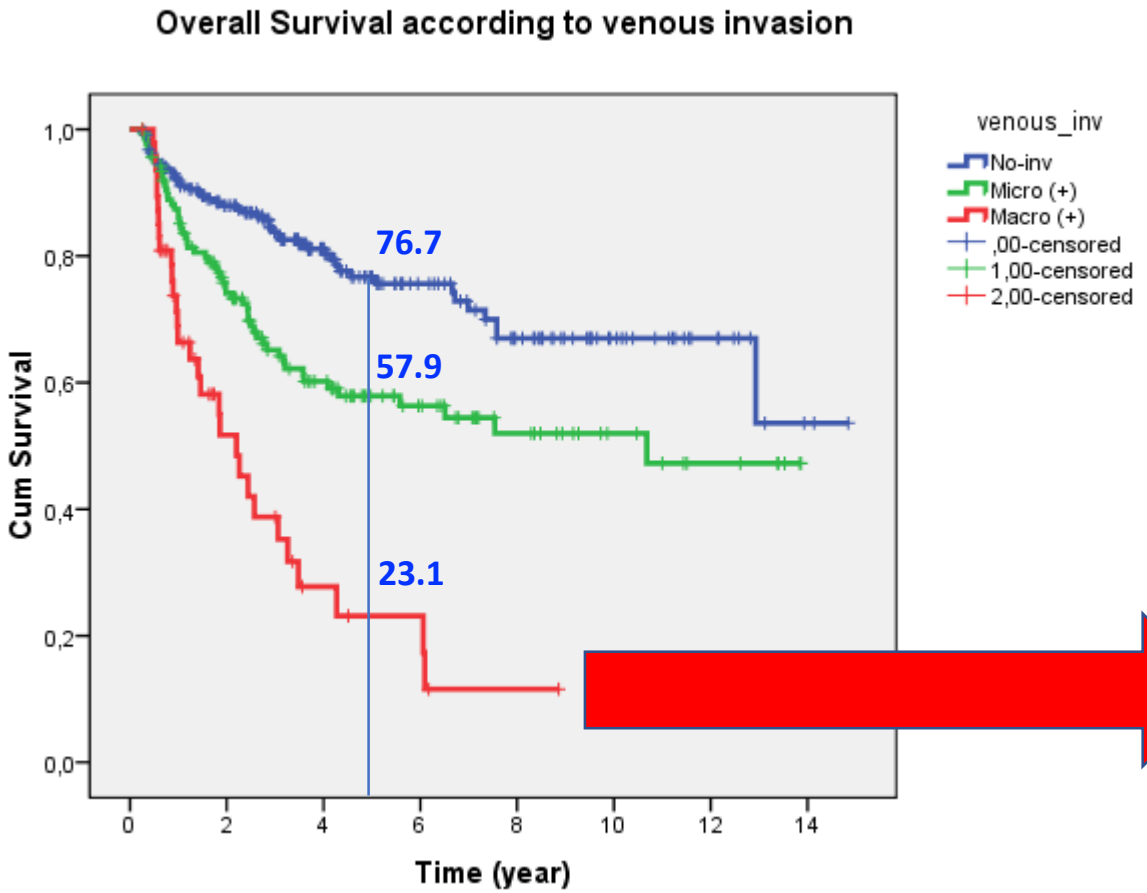
Soru

- Aşağıdaki Tx kriterlerinden hangisi veya hangileri uygulandığında 5 yıllık sağkalım hedefi %60'ın üzerindedir?

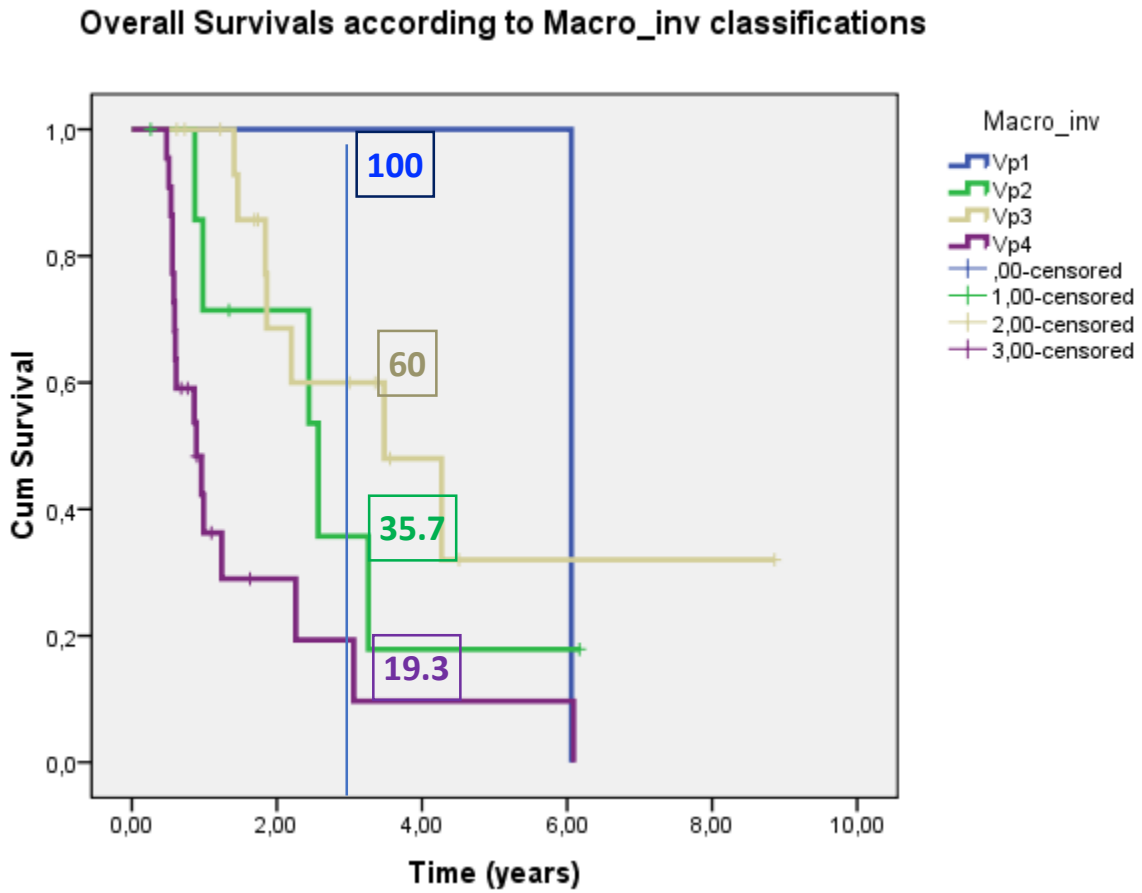
A. Milan
B. UCSF
C. Extended Malatya
D. AFP Model
E. Hepsi

Vasküler İnvazyon ve Karaciğer Nakli - Malatya

Venöz invazyon durumuna göre – OS



Macro_inv Sınıflamasına göre – OS



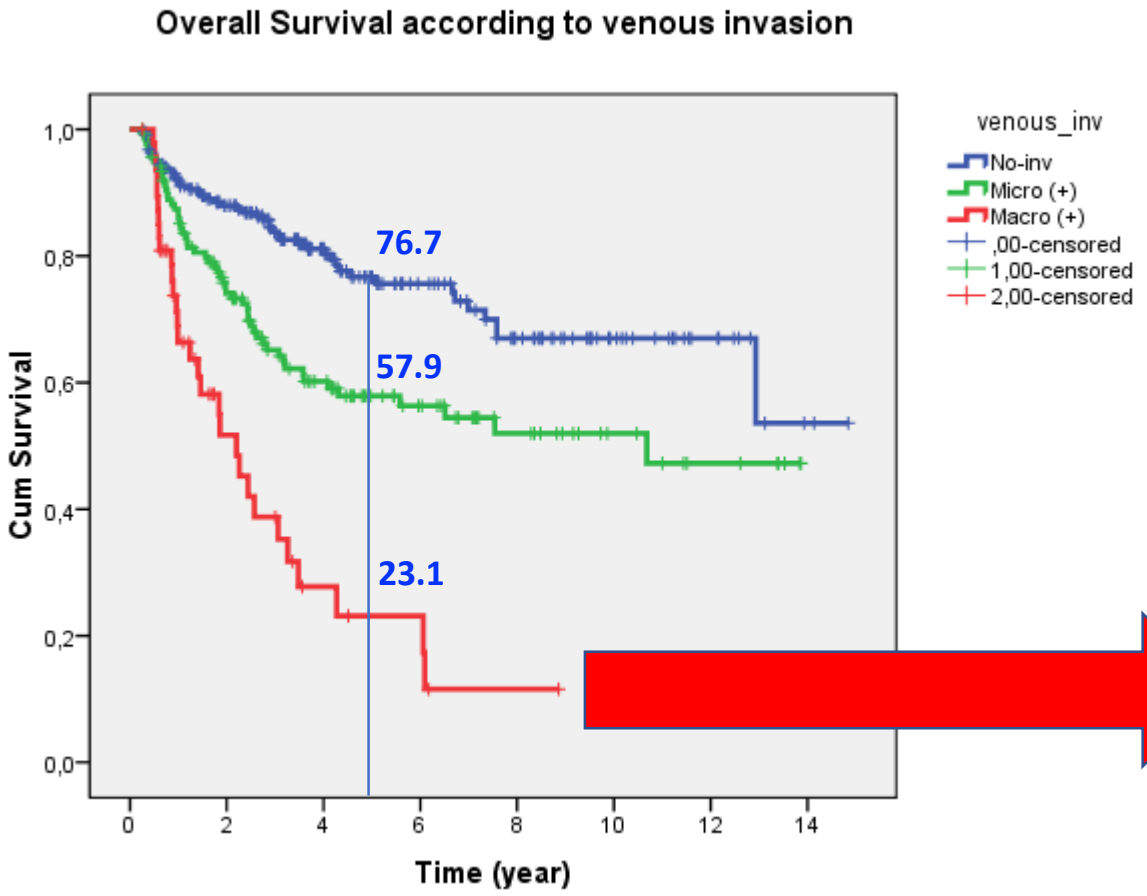
Vasküler İnvazyon Derecesi ve Karaciğer Nakli

Malatya Deneyimi

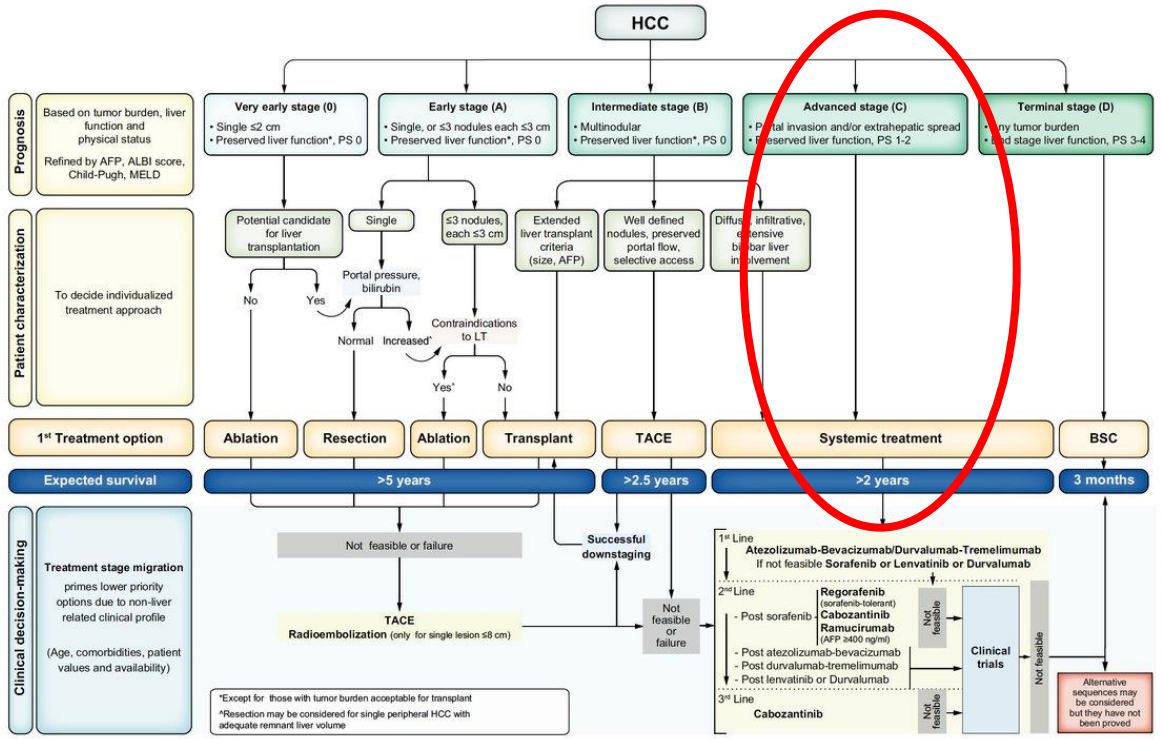
Yayınlanmamış Veri

Vasküler İnvazyon ve Karaciğer Nakli - Malatya

Venöz invazyon durumuna göre – OS

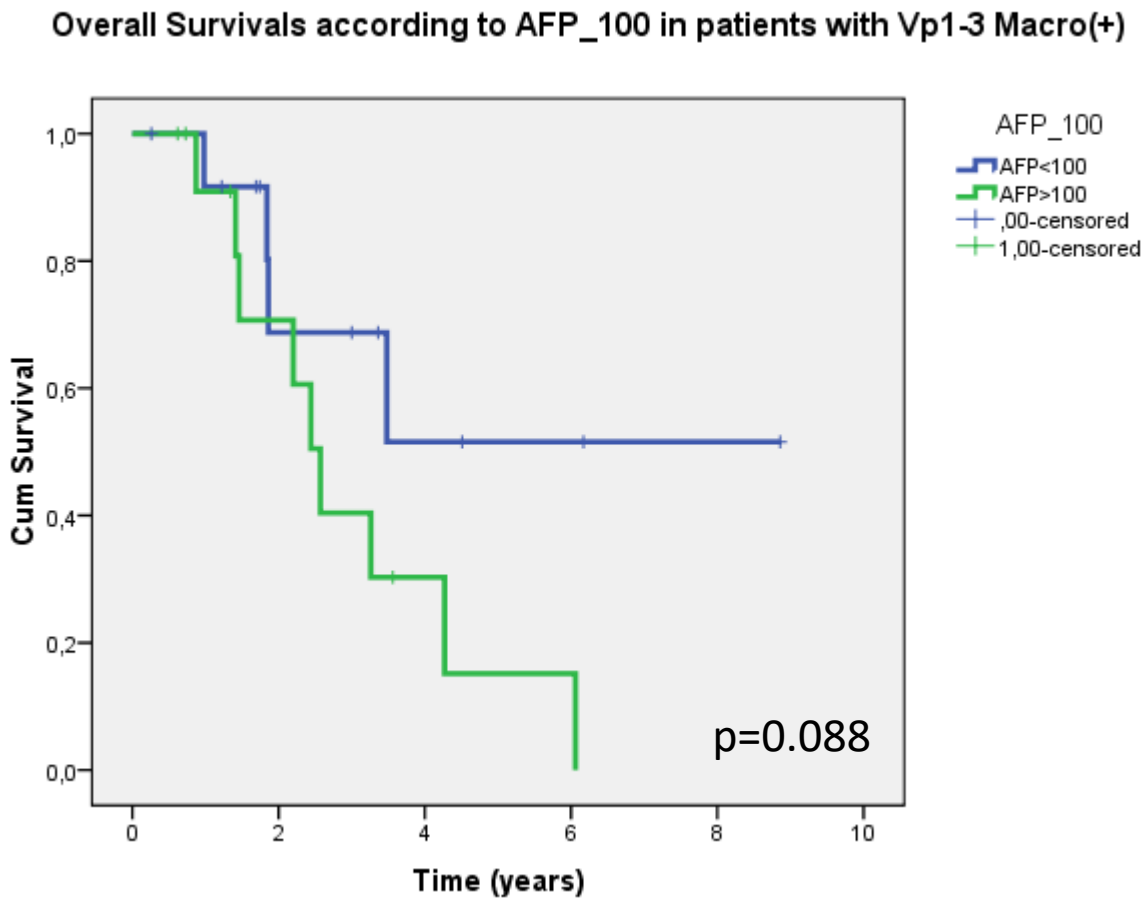


Macro_inv Sınıflamasına göre – OS



Vasküler İnvazyon ve Karaciğer Nakli - Malatya

- Vp1-3 Macro PVTT olanların AFP_100'e göre OS sonuçları



Vasküler İnvazyon ve Karaciğer Nakli - Malatya

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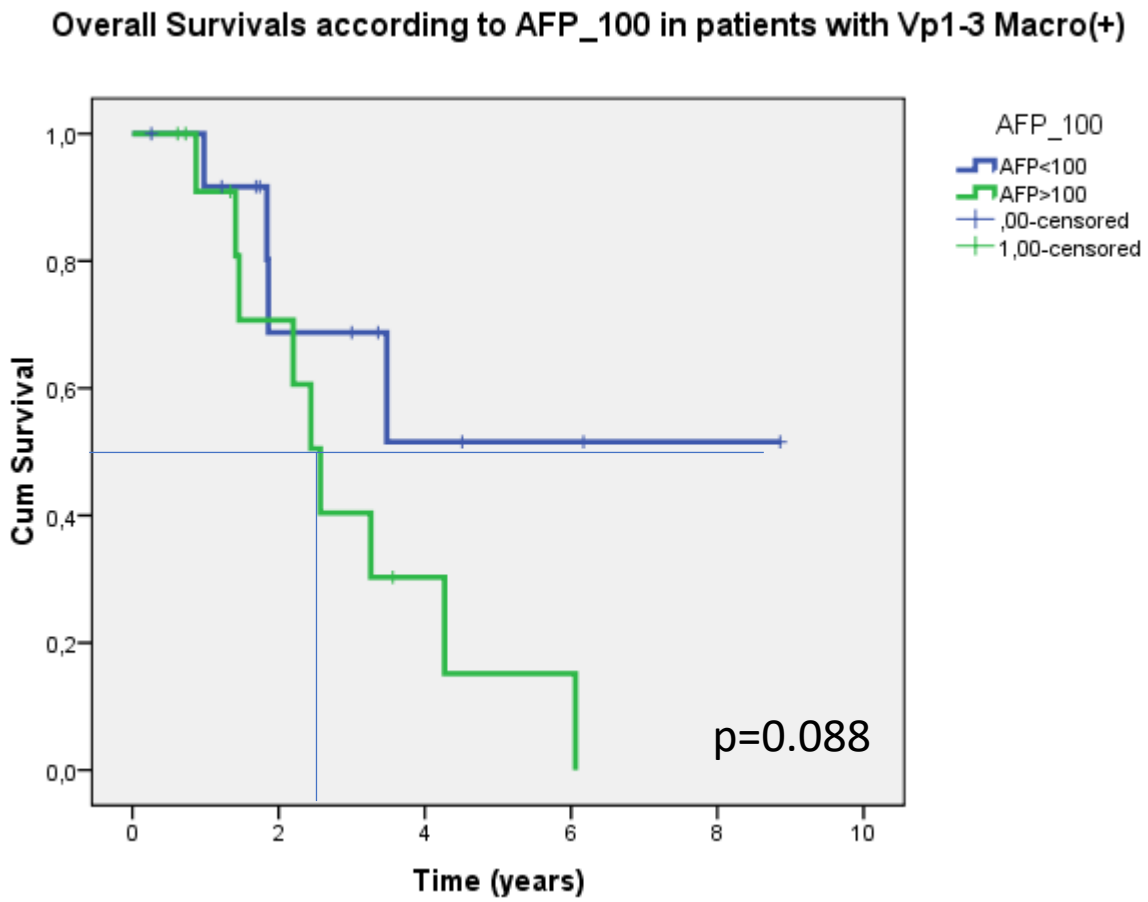


İleri Evre HCC için Karaciğer Nakli

Portal Hilusda Lenf Nodu Tutulumu (+)

PET CT ve Hilar LAP (+)

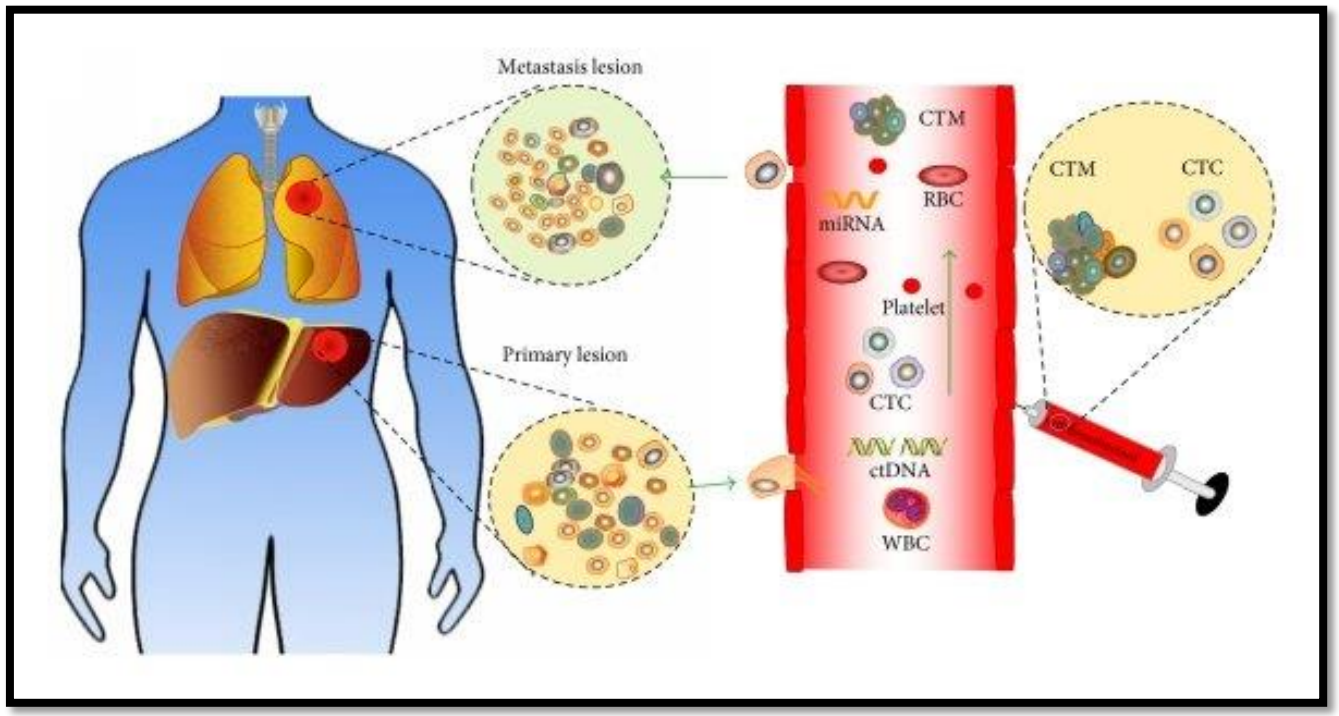
- **Pre-Tx PET CT çekilen 77 hastanın raporları geriye dönük olarak incelendiğinde, 5 hastada hilar LAP şüpheli tutulum saptandı. Bu hastaların, eksplant patolojilerinde, sadece 2 hastada lenf nodu metastazı saptandı.**

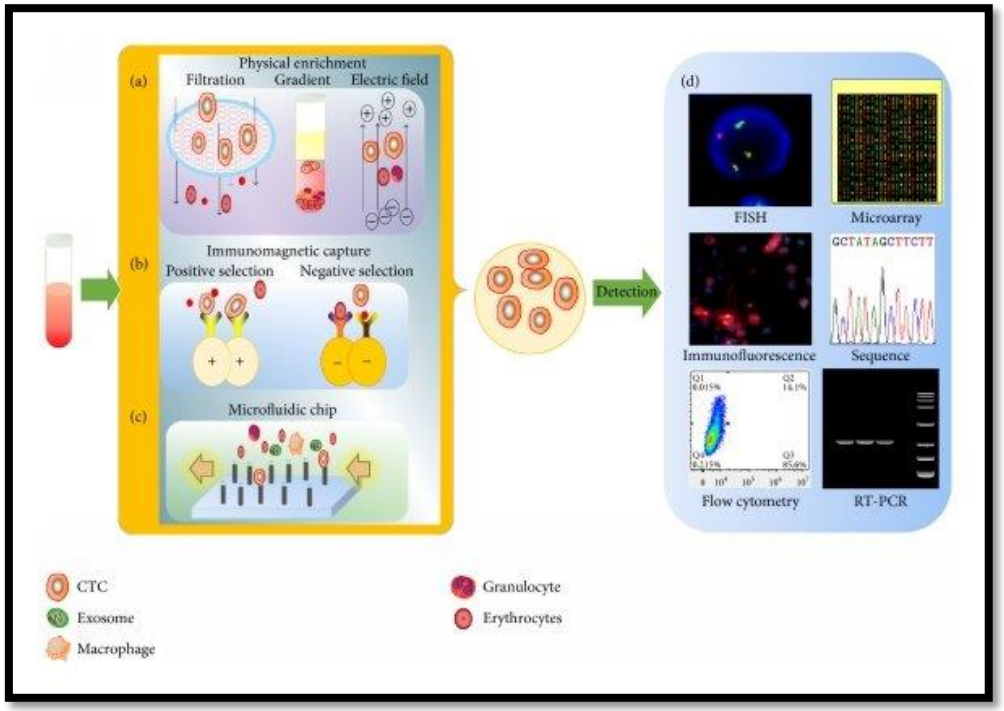
- **Hilar lenf nodu metastazı sonuçları çok kötü, Medyan yaşam 1.8yıl**

- **Bu hastalarda lenf nodu örneklemesi (frozen) düşünülebilir**

Radiomics , Genomics ve Liquid biyopsi

Liquid biyopsi





Radiomics

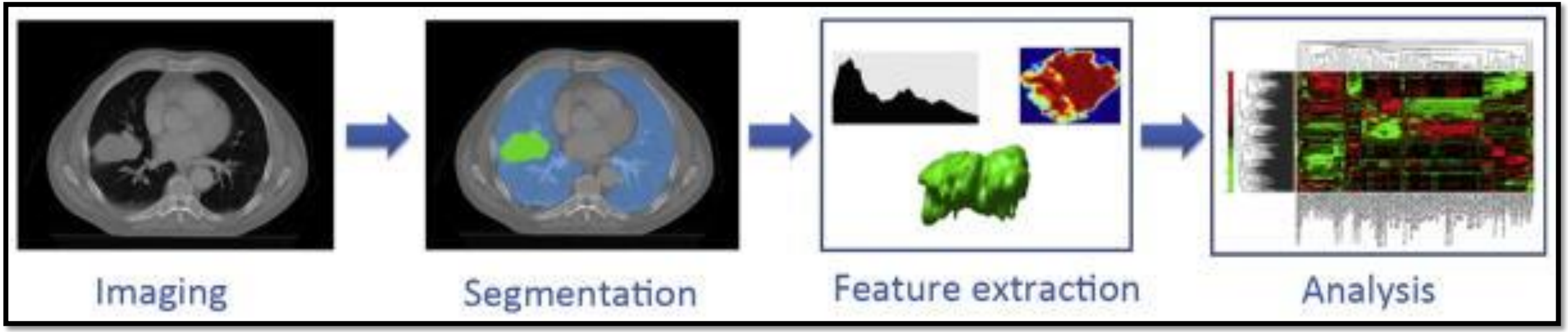
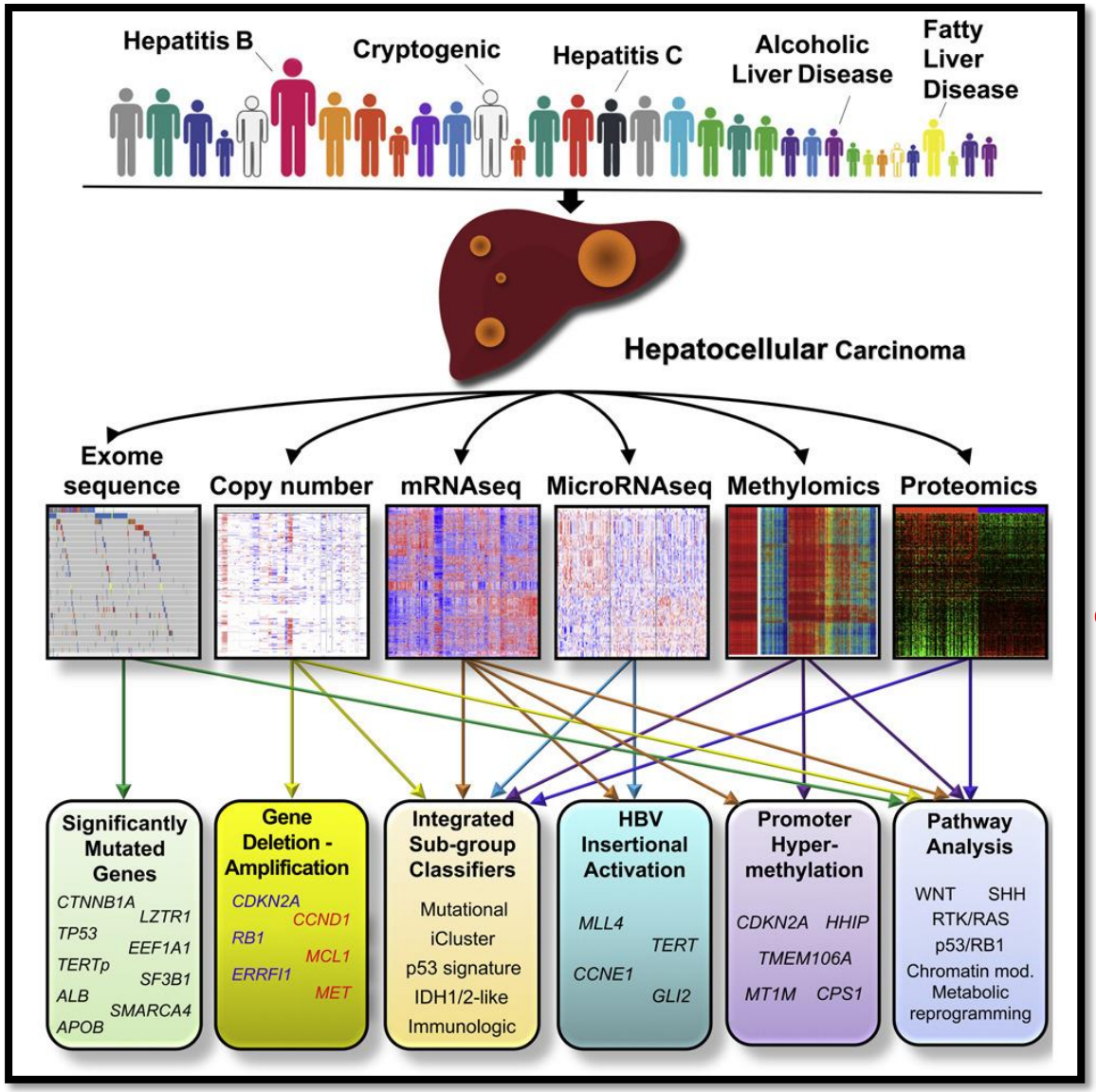
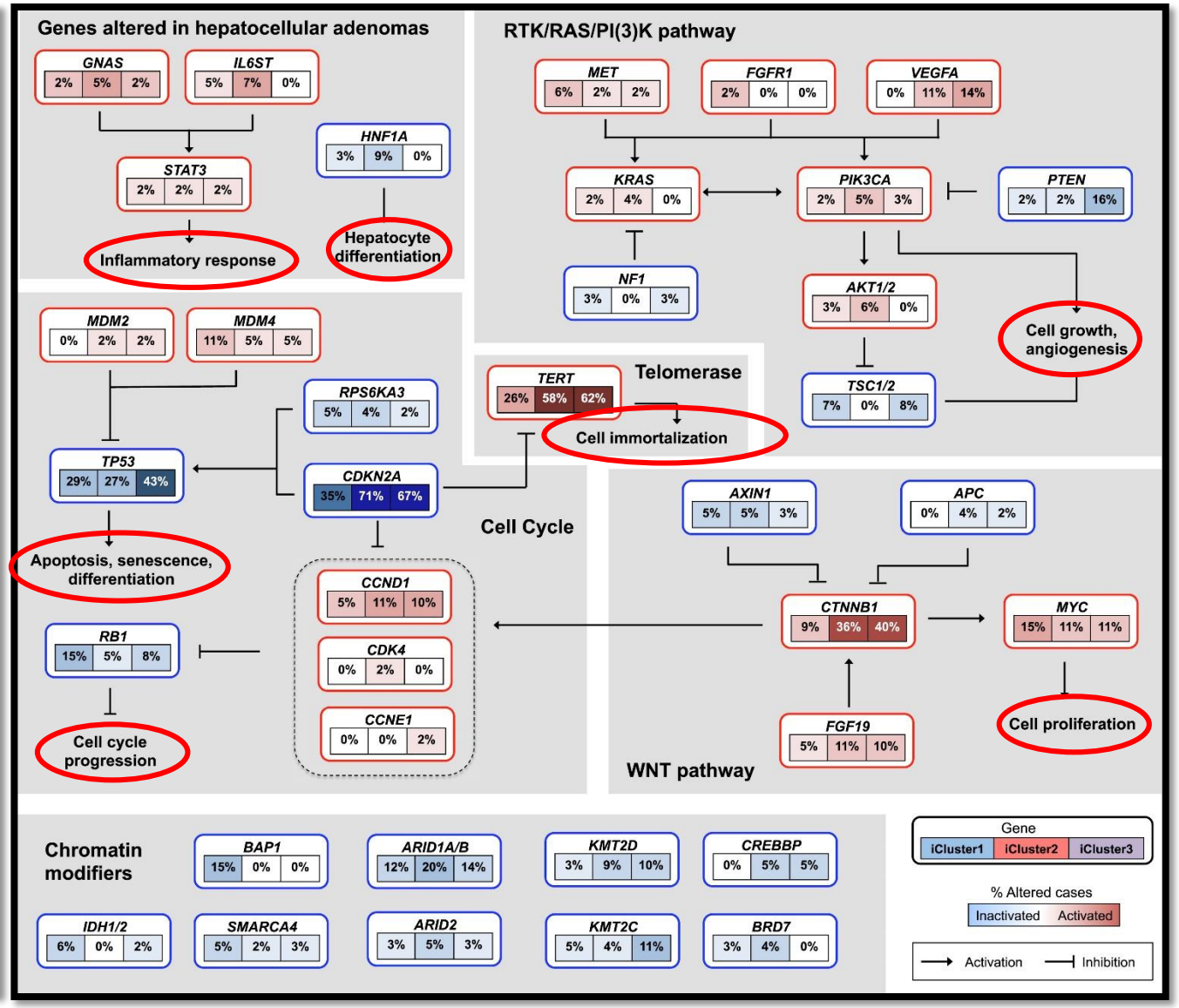


Fig. 4 The Radiomics workflow.
On the medical images, segmentation is performed to define the tumour region. From this region the features are extracted, e.g. features based on tumour intensity, texture and shape. Finally, these features are used for analysis, e.g. the features are assessed for their prognostic power, or linked with stage, or gene expression.

Genomics


Hepatitis B
Cryptogenic
Hepatitis C
Alcoholic Liver Disease
Fatty Liver Disease
Hepatocellular Carcinoma
Exome sequence
Copy number
mRNAseq
MicroRNAseq
Methylomics
Proteomics
Significantly Mutated Genes
CTNNB1A
LZTR1
TP53
EEF1A1
TERTp
SF3B1
ALB
SMARCA4
APOB
Gene Deletion - Amplification
CDKN2A
CCND1
RB1
MCL1
ERRFI1
MET
Integrated Sub-group Classifiers
Mutational
iCluster
p53 signature
IDH1/2-like
Immunologic
HBV Insertional Activation
MLL4
TERT
CCNE1
GLI2
Promoter Hyper-methylation
CDKN2A
HHIP
TMEM106A
MT1M
CPS1
Pathway Analysis
WNT
SHH
RTK/RAS
p53/RB1
Chromatin mod.
Metabolic reprogramming


Genes altered in hepatocellular adenomas
GNAS 2% 5% 2%
IL6ST 5% 7% 0%
STAT3 2% 2% 2%
HNF1A 3% 9% 0%
Inflammatory response
Hepatocyte differentiation
RTK/RAS/PI(3)K pathway
MET 6% 2% 2%
FGFR1 2% 0% 0%
VEGFA 0% 11% 14%
KRAS 2% 4% 0%
PIK3CA 2% 5% 3%
PTEN 2% 2% 16%
NF1 3% 0% 3%
AKT1/2 3% 6% 0%
TSC1/2 7% 0% 8%
Cell growth, angiogenesis
TERT 26% 58% 62%
Telomerase
Cell immortalization
MDM2 0% 2% 2%
MDM4 11% 5% 5%
RPS6KA3 5% 4% 2%
TP53 29% 27% 43%
CDKN2A 35% 71% 67%
Cell Cycle
Apoptosis, senescence, differentiation
CCND1 5% 11% 10%
CDK4 0% 2% 0%
CCNE1 0% 0% 2%
RB1 15% 5% 8%
Cell cycle progression
AXIN1 5% 5% 3%
APC 0% 4% 2%
CTNNB1 9% 36% 40%
MYC 15% 11% 11%
FGF19 5% 11% 10%
Cell proliferation
WNT pathway
Chromatin modifiers
BAP1 15% 0% 0%
ARID1A/B 12% 20% 14%
KMT2D 3% 9% 10%
CREBBP 0% 5% 5%
IDH1/2 6% 0% 2%
SMARCA4 5% 2% 3%
ARID2 3% 5% 3%
KMT2C 5% 4% 11%
BRD7 3% 4% 0%
Gene
iCluster1 iCluster2 iCluster3
% Altered cases
Inactivated Activated
Activation
Inhibition

Radiomics ve Genomics

Küçük HCC

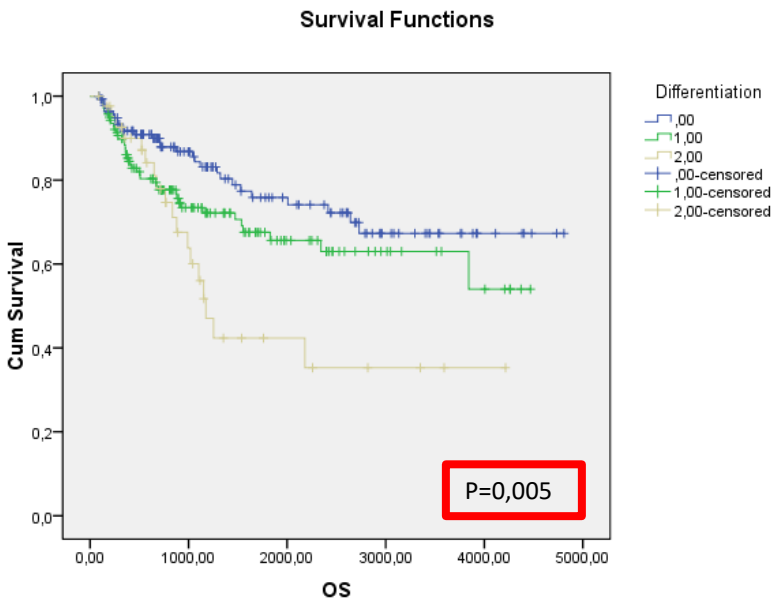
Agresif HCC

Tx öncesi kötü diferansiyasyon saptanması?

Diferansiyasyon – Rekürrens ilişkisi

Hastalıksız Sağkalım Analiz Tablosu

Parametreler	p	Hazard ratio	% 95 CI
Kötü diferansiasyon	0,016*	3,27	1,25-8,55



- Multivariate analizde kötü diferansiyasyon olması, rekürrens riskini 3,2 kat arttırmaktaydı
- Milan içi grupta kötü diferansiyasyon olan 9 hastanın sadece 1'inde nüks saptandı. Bu hastaların 5 yıllık sağkalımı %85 idi.
  - (ETC ve Hangzhou kriterleri, bu hastaları dışlamaktaydı)
- Kötü diferansiye olanlarda 5 yıllık OS %42

Tx öncesi kötü diferansiyasyon saptanması?

- **Biyopsi**
- **PET CT ?**
- **LRT yanıt ??**

Biyopsi

- **Rutin biyopsi yapmıyoruz**
  - **LRT yapılacak hastalarda aynı seansta Bx (+)**
- **Tümör heterojenitesi**
- **Tümör ekimi riski**
- **Genişletilmiş Malatya kriterleri ile differansiasyon bakılmaksızın**

  5 yıllık DFS %78,8 elde edilmiştir.

PET CT ve diferansiyasyon

- Tx öncesi PET CT çekilen 77 hastanın PET sonuçları explant patoloji verileri ile karşılaştırıldı

- ROC analizinde, TümörSUVmax/KcSUVmn >2,0 anlamlı bulundu

- Diferansiyasyon

	Kötü dif (+)	p
TmSUVmax/KcSUVmn >2 TmSUVmax/KcSUVmn ≤2	%55 %13	0,006*

- Mikrovasküler invazyon

	Micro.İnv(+)	p
TmSUVmax/KcSUVmn >2 TmSUVmax/KcSUVmn ≤2	%34 %7	0,008*

PET / CT’de Hilar LAP (+)

Makroskopik portal ven tümör trombüsü

Macrovascular Invasion Is Not an Absolute Contraindication for Living Donor Liver Transplantation

Kwang-Woong Lee,[1] Suk-Won Suh,[1] YoungRok Choi,[1] Jaehong Jeong,[1] Nam-Joon Yi,[1] Hyeyoung Kim,[1] Kyung Chul Yoon,[1] Suk Kyun Hong,[1] Hyo-Sin Kim,[1] Kyung-Bun Lee,[2] and Kyung-Suk Suh[1]

Departments of [1]Surgery and [2]Pathology, Seoul National University College of Medicine, Seoul, South Korea

The indication of liver transplantation (LT) for the treatment of advanced hepatocellular carcinoma (HCC) is expanding. However, portal vein tumor thrombus (PVTT) has been still accepted as an absolute contraindication. We experienced an unexpectedly good prognosis in selected patients. Therefore, we tried to identify the prognostic factors after LT for HCC with major PVTT. Among 282 patients who underwent living donor liver transplantation (LDLT) for HCC from January 2009 to December 2013, 11 (3.9%) patients with major PVTT that was preoperatively diagnosed were investigated. The 1-, 3-, and 5-year recurrence-free survival rates were 63.6%, 45.5%, and 45.5%, respectively, and all recurrent cases showed intrahepatic and extrahepatic recurrence. The 1-, 3-, and 5-year overall survival rates were 72.7%, 63.6%, and 63.6%, respectively, and 2 patients with delayed recurrence survived approximately 5 years after LT. Main portal vein (PV) invasion ($P<0.01$), high alpha-fetoprotein × protein induced by vitamin K absence/antagonist-II (AP) score (≥20,000; $P<0.01$), high standardized uptake value (SUV) ratio (tumor/background liver) in positron emission tomography (≥2.1; $P<0.01$), and a large original tumor (≥7 cm; $P=0.03$) were significant risk factors for recurrence. In conclusion, if the PVTT has not expanded to the main PV and the AP score is not high, we can consider LDLT as a curative treatment option.

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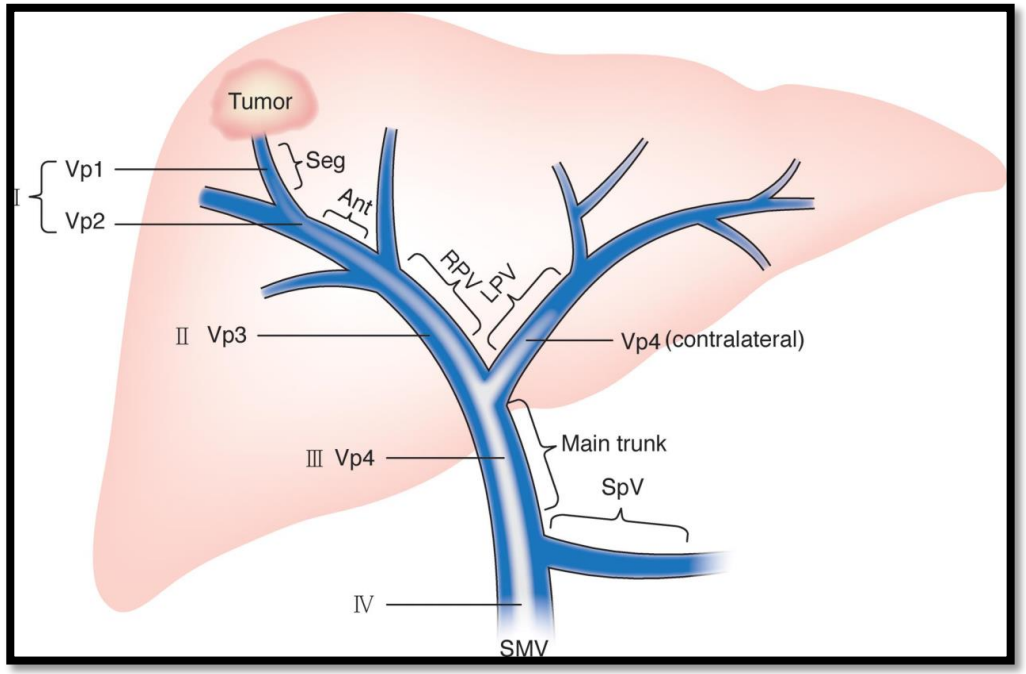

- **Segmental PVTT**
- **Düşük AP skoru**
  - **AFP x PIVKA-II < 20.000**
- **5 yıl OS %63**

Makroskopik portal ven tümör trombüsü

The Clinical Outcomes of Patients with Portal Vein Tumor Thrombi After Living Donor Liver Transplantation

Ho Joong Choi,[1] Dong Goo Kim,[1] Gun Hyung Na,[1] Tae Ho Hong,[1] Si Hyun Bae,[2] Young Kyoung You,[1] Jong Young Choi,[2] and Seung Kew Yoon[2]

[1]Department of Surgery; [2]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

The purpose of this study was to evaluate the feasibility of living donor liver transplantation for treatment of patients with hepatocellular carcinoma and segmental portal vein tumor thrombus (PVTT) below the second-order branch. Between January 2005 and December 2015, we retrospectively analyzed 242 patients in a control group (n = 184), a microvascular invasion (MVI) group (n = 24), and a PVTT group (n = 34). To assess the risks associated with PVTT, we evaluated recurrence, the disease-free survival (DFS) rate, the overall survival (OS) rate, and various other factors based on the characteristics of patients and tumors. Of the 242 patients, 5-year DFS and OS rates were 79.5% and 70.7%. A total of 34 (14.0%) patients had PVTT, of whom 7 had lobar PVTT in first-order branches. The control, MVI, and PVTT groups significantly differed in terms of tumor morphology (maximal and total diameters) and biology (alpha-fetoprotein [AFP] and protein induced by vitamin K absence or antagonist II). The control, MVI, and PVTT groups significantly differed in terms of the recurrence, DFS, and OS rates. Especially, lobar PVTT reduced the 5-year DFS and OS rates to dismal and 14.3%, respectively, but segmental PVTT was associated with favorable 5-year DFS and OS rates (63.9% and 50.3%, respectively). We found no statistically significant difference in the DFS and OS rates of patients with MVI alone and segmental PVTT alone. In patients in the segmental PVTT group with AFP levels of <100 ng/mL, the 5-year DFS and OS rates were 90.9% and 71.3%, respectively. In conclusion, a tumor thrombus in a lobar portal vein remains a contraindication to liver transplantation. However, a segmental PVTT is acceptable, especially when the AFP level is <100 ng/mL.

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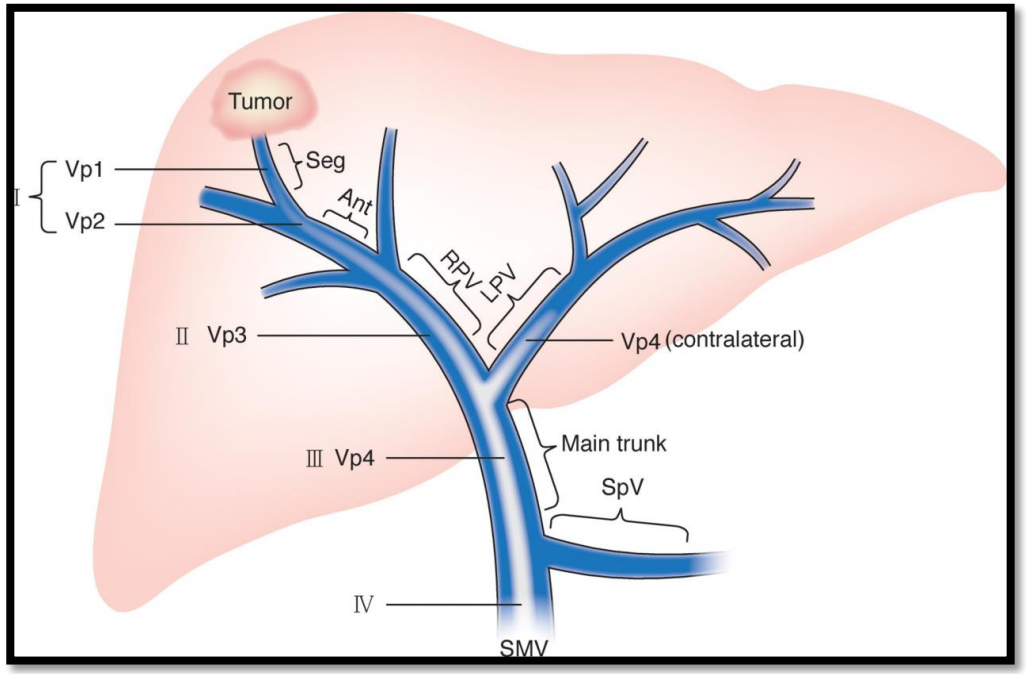

- **Segmental PVTT**
- **AFP < 100 ng/mL**
- **5 yıl OS %71.3**

Makroskopik portal ven tümör trombüsü

Original Clinical Science—Liver

Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

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Background. Median survival in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT) is 2–6 months; conventionally liver transplantation is contraindicated. **Methods.** We studied outcomes following living donor liver transplantation (LDLT) post-PVTT downstaging (DS) with stereotactic body radiotherapy (SBRT), and tumor ablation (with transarterial chemo- or radio-embolization). **Results.** Of 2348 consecutive LDLTs, 451 were for HCC, including 25 with PVTT (mainly Vp1-3) after successful DS and 20 with Vp1/2 PVTT without previous treatment. DS was attempted in 43, was successful in 27 (63%), and 25 underwent LDLT. Median alpha fetoprotein (AFP) at diagnosis and pre-LDLT were 78.1 ng/mL (3-58 200) and 55 ng/mL (2-7320), respectively. Mean DS to LDLT time was 10.2 weeks (5–16). Excluding 2 postoperative deaths, 1- and 5-year overall survival (OS) and recurrence-free survival (RFS) were 82%, 57%, and 77%, 51%, respectively, comparable to survival in 382 HCC patients without PVTT undergoing upfront LDLT (5-y OS 65%, $P = 0.06$; RFS 66%, $P = 0.33$, respectively). There was a trend toward better OS in DS+LDLT versus non-DS LDLT group (5-y OS/RFS—48%/40%). OS was significantly better than in HCC-PVTT patients receiving no intervention or palliative Sorafenib alone (1-y OS of 0%) or Sorafenib with TARE/SBRT (2-y OS of 17%) at our center during the study period. Initial AFP <400 ng/mL and AFP fall (initial minus pre-LDLT) >2000 ng/mL predicted better RFS; Grade III/IV predicted worse OS in DS patients. **Conclusions.** HCC patients with PVTT can achieve acceptable survival with LDLT after successful DS. Low initial AFP level, a significant drop in AFP with DS and low tumor grade, favorably influence survival in these patients.

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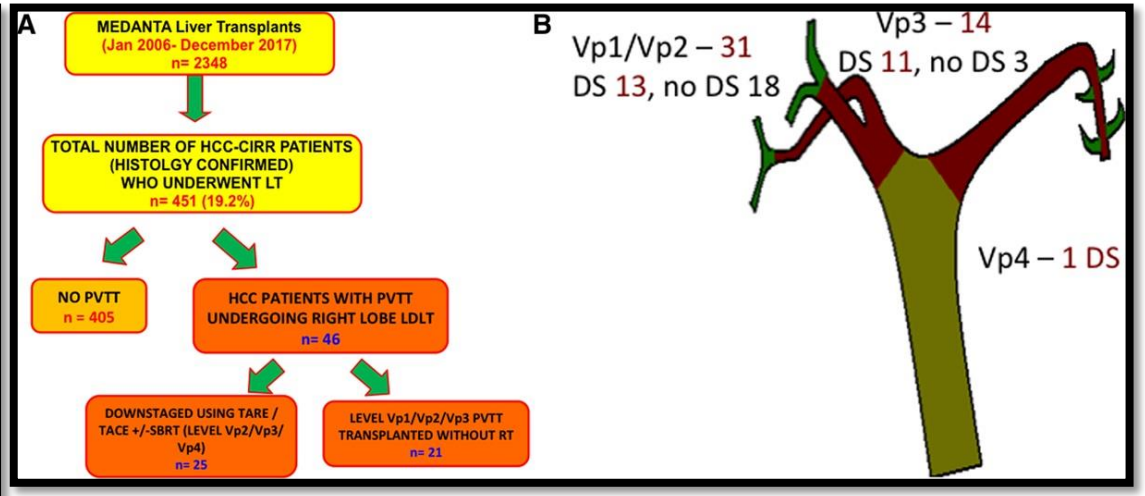

- TARE / SBRT ile downstage
- Yanıt olanlarda 5 yıl OS %57
- İlk AFP<400 olması
- İlk – preTx AFP farkı >2000 olması iyi prognoz

Makroskopik portal ven tümör trombüsü

ORIGINAL ARTICLE

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Deceased Donor Liver Transplantation After Radioembolization for Hepatocellular Carcinoma and Portal Vein Tumoral Thrombosis: A Pilot Study

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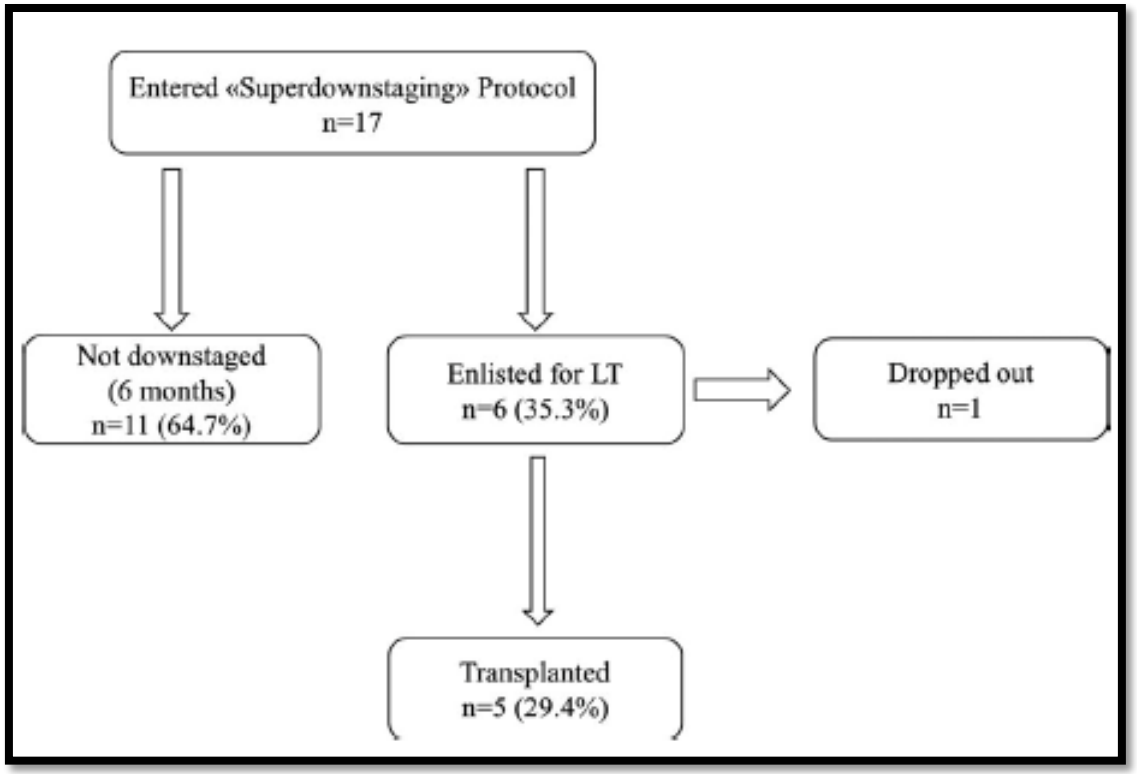

- **TARE ile downstage**
- **AFP<100**
- **Yanıt olanlarda 5 yıl OS %60**

Makroskopik portal ven tümör trombüsü

Transplant International

ORIGINAL ARTICLE

Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion – a multi-center retrospective cohort study

Michela Assalino[1], Sylvain Terraz[2], Michal Grat[3], Quirino Lai[4], Neeta Vachharajani[5], Enrico Gringeri[6], Marco Angelo Bongini[7], Laura Kulik[8], Parissa Tabrizian[9], Vatche Agopian[10], Neil Mehta[11], Raffaele Brustia[12], Giulio Cesare Vitali[1], Axel Andres[1,13], Thierry Berney[1,13], Vincenzo Mazzaferro[7], Philippe Compagnon[1,13], Pietro Majno[14], Umberto Cillo[6], William Chapman[5], Krzysztof Zieniewicz[3], Olivier Scatton[12] & Christian Toso[1,13]

- TACE, SIRT ve cerrahi
- AFP< 10
- 5 yıl OS %60 (DDLT)

groups with better outcomes. Medical records of 45 patients were retrospectively reviewed, and imaging was centrally assessed by an expert liver radiologist. In the 30 patients with validated diagnosis of macrovascular invasion, overall survival was 60% at 5 years. Pretransplant alpha-fetoprotein (AFP) value was significantly different between patients with and without recurrence ($P = 0.019$), and the optimal AFP cutoff was 10ng/ml (area under curve = 0.78). Recurrence rate was 11% in patients with pretransplant AFP < 10ng/ml. The number of viable nodules ($P = 0.008$), the presence of residual HCC ($P = 0.036$), and satellite nodules ($P = 0.001$) on the