MINISTERO DELLA SALUTE
Istituto Superiore di Sanità
Centro Nazionale Trapianti

WHO Collaborating Centre
On Vigilance and Surveillance for
Human Cells, Tissues and Organs

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Prot. 447/CNT2017

Alla cortese attenzione

Centri Regionali di Riferimento

Membri CNT

Cari Colleghi,

a seguito delle tre consensus conference che si sono svolte a Torino, Palermo e Padova e in cui sono stati coinvolti, oltre al Collegio dei chirurghi del fegato, al comitato AISF e al CNT, anche i Centri Regionali, i rappresentanti della SIAARTI, alcuni esperti di metodologia, alcuni eticisti ed i rappresentanti delle grandi associazioni di pazienti trapiantati di fegato, è stato definito un nuovo di sistema allocativo che eliminasse le disomogeneità esistenti in Italia relativamente all'assegnazione del fegato.

Si è creato, pertanto, un sistema di punteggio unico per ogni paziente italiano in lista di attesa di trapianto di fegato, basato su un ranking di priorità, che prende il nome di "Italian Score for Organ allocation (ISO) in liver transplantation".

Basato sullo score MELD, l'ISO fornisce un criterio di priorità a tutte quelle condizioni cliniche considerate come "eccezioni al MELD" e agli epatocarcinomi, soprattutto quando insorti su uno stadio di cirrosi compensata. Il lavoro di predisposizione, organizzato dal Collegio dei Chirurghi del fegato, è stato descritto in una pubblicazione sull'American Journal of Transplantation (*American Journal of Transplantation 2015; XX: 1–10*).

Il Centro Nazionale Trapianti ha approvato il modello ISO durante la riunione del 7 luglio 2015 ed ha sollecitato i centri ad adeguarsi al nuovo sistema allocativo.

Il sistema è stato reso operativo dal 1 Gennaio 2016 nelle regioni Veneto e Sicilia e, da ottobre 2016, nella regione Emilia Romagna.

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Considerata l'importanza di avere un sistema di allocazione uniforme in tutta la nazione, il CNT ritiene opportuno che anche le altre regioni e, di conseguenza, tutti i Centri Trapianto si allineino a quanto essi stessi hanno proposto. A tale scopo, il CNT prevede che entro 1 Aprile 2017 tutta la rete si adegui a tale modello allocativo. Dopo tale data il modello ISO verrà considerato l'unico operativo a livello nazionale.

Si ricorda, inoltre, che il Centro Nazionale Trapianti, in quanto gestore del Sistema Informativo Trapianti, richiede che nel sistema SIT sia imputato un MELD omogeneo per tutte le regioni: vale a dire sia il MELD biochimico, sia il MELD ISO (Meld Biochimico + correzioni ISO Score).

I Centri regionali sono inviatati, a partire dal 1 aprile p.v. ad imputare, solo ed esclusivamente, il MELD biochimico e l'ISO score e a prendere contatto, per eventuali difficoltà, con i propri data warehouse.

Un cordiale saluto

Dr. Alessandro Nanni Costa
Direttore Centro Nazionale Trapianti

Di seguito **1)** Tabella di **attribuzione dell'ISO score a ECCEZIONI e HCC**; **2)** Tabella riassuntiva sulle **eccezioni al MELD** e i **3) Stratificazione dei pazienti affetti da epatocarcinoma (HCC)** individuati dal modello ISO. ***[Am J Transpl. 2015, XX, 1-10].***

1) Tabella di **attribuzione dell'ISO score a ECCEZIONI e HCC**

Table 4: Proposed and agreed national waiting list prioritization policies and geographical distribution of organ allocation for patients with or without HCC and those considered MELD exceptions.

Priority	PTS Category	Points	Allocation area
Super-Urgent	FHF, early reLT	(first come, first served)	Nationwide
Urgent	MELD >30	Biochemical MELD	Macro area
Urgent	EXCEPTIONS P1	30	Macro area
Standard	EXCEPTIONS P2	25 + 1/month	Region
Standard	Bioch MELD 15–29	Biochemical MELD	Region
Standard HCC Stratum 1	HCC: TT_{DR}-TT_{PR} (downstaged patients or partial responders to bridge therapies)	HCC-MELD[19] + extra points for time or MELD 22 at entry + extra points for time (at regional board's discretion)§ Cap at 29	Region
Standard HCC Stratum 2	HCC: TT_{FR} (first presentation or late recurrence)	HCC-MELD[19] Criteria for awarding extra points for longer waits and priority class migration on disease progression will be set regionally (regional board approval)#	Region
Standard HCC Stratum 3	HCC: $T0_C$–T1-$T0_L$ (complete responders or T1 tumors)	Biochemical MELD	Region
Standard	EXCEPTIONS P3	20 + 1 every 2 months	Region
Standard	EXCEPTIONS P4	15 + 1 every 2 months	Region

FAP, familial amyloidotic polyneuropathy; FHF, fulminant hepatic failure; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NET, neuroendocrine tumours; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.
§Choice between ''HCC MELD + extra points for longer waits'' or ''22 points at entry + extra points for longer waits'' will be decided on a regional basis.
#Points for disease progression while on the waiting list can be discussed and adjusted (fast vs. slow pace) according to pattern of response or progression within the transplantability criteria. Progression has to be assessed after optimal treatments within defined protocols.
P1 = Rendu–Osler–Weber, young adult hepatoblastoma, Kasabach–Merritt, late ''acute'' retransplant.
P2 = Hepato-pulmonary syndrome, porto-pulmonary hypertension, late ''chronic'' retransplant, refractory hydrothorax, hepatorenal syndrome, previous severe infections.
P3 = Refractory ascites, FAP, Wilson's with initial neurological symptoms and well-compensated cirrhosis, NET metastases, hemangioendothelioma.
P4 = Complicated adenomatosis, polycystic disease, PSC or PBC with intractable pruritus.

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2) Tabella riassuntiva sulle **eccezioni al MELD**

Table 2: Agreed priority strata for MELD exceptions and corresponding organ-sharing areas

Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber
	Hepatoblastoma (young adult)
	Hemangioma (if Kasabach Merritt syndrome)
	Acute late ReLT
	FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome
	PPH
	Refractory hydrothorax
	Chronic late ReLT
	Hepato-renal syndrome (if not automatically equated to MELD)
	Previous severe infections
P3 (Sharing at regional level)	Refractory ascites
	FAP
	Wilson's (with compensated cirrhosis and initial neurological symptoms)
	NET metastases
	Hemangioendotheliomas
P4 (Sharing at regional level)	PSC or PBC with intractable pruritus
	Polycystic disease
	Complicated adenoma
	Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy
	Fibrolamellar HCC
	Liver adenomatosis (not complicated)
	Hilar cholangiocarcinoma
	CRC metastases

CRC, colorectal cancer; FAP, familial amyloidotic polyneuropathy; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NET, neuroendocrine tumours; PBC, primary biliary cirrhosis; PPH, portopulmonary hypertension; PSC, primary sclerosing cholangitis.

3) Stratificazione dei pazienti affetti da epatocarcinoma (HCC)

Table 3: Staging and prioritization of HCC patients for LT: Proposed new patient stratification

Category of transplantable (T) HCC	Priority according to HCC dropout models	Priority according to transplant benefit principle	Priority based on patient's/physician's expectations
$T0_C$ No residual tumor after curative treatment of a T-HCC	Very low Very low risk of dropout in cured HCC	Low Transplant benefit depending on lab-MELD only	Low Patients with no tumor should not be transplanted
$T0_L$ No residual tumor after loco-regional embolo-therapies for a TT-HCC	Low-intermediate Low risk of dropout in cured HCC	Low Transplant benefit depending on HCC-MELD	Intermediate The patient was transplantable but can now be put on hold because the tumor seems to be cured.
$T0_{NT}$** No residual tumor after treatment of an NT (nontransplantable) HCC	Not applicable NT HCC should not be listed, as in cases of no HCC in low MELD patients	Low Transplant benefit depending on lab-MELD only	Low The patient was not transplantable and has now been cured by other means.
T1 Single HCC ≤2cm (very early HCC)	Low Low risk of dropout in very early HCC	Low Low benefit in presence of alternative nontransplant treatments	Low No need to transplant someone who can be treated by other means
TT_{FR}* Any transplantable TT-HCC at presentation or recurrent HCC >2 years after curative treatment for a T-HCC (late recurrence)	Intermediate Demonstrated increase of dropout risk over time and across T2-HCC substages	Intermediate Benefit depending on true feasibility of alternative nontransplant treatments	High This is the patient with the best posttransplant survival (utility)
TT_{PR} Partial response to bridge therapy (cycle of multimodal therapy)	Intermediate-high Risk of selection of biologically aggressive clones with increased proliferative activity	High Failure of a bridge therapy with no residual therapeutic alternative	High Patients still with good posttransplant expected utility and high need for OLT
TT_{DR} TT-HCC after downstaging or recurrent HCC <2 years after curative treatment of any HCC (early recurrence)	Intermediate-high High dropout risk over time and across HCC substages	High Benefit depending on absence of feasible alternatives among nontransplant treatments	High Transplant is a chance to be offered before it is too late.

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.
*TT-HCC: any HCC meeting transplantability criteria (either conventional or expanded criteria, after donor rate and dynamics of waiting list considerations, in agreement with regional/national allocation rules).
**NT-HCC: Nontransplantable HCC: any other conditions not within the T-HCC definitions and/or any conditions of extrahepatic tumor spread and/or macrovascular invasion. Early or late recurrence: Recurrence within or beyond 24 months after previous complete treatment. Type of response to bridging therapy: Complete or partial response, stable or progressive disease according to the mRECIST.

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