
# Actitud a seguir ante la detección de una lesión focal inferior o igual a 2 cm. de tamaño en un paciente con cirrosis hepática

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# ACTITUD A SEGUIR ANTE LA DETECCIÓN DE UNA LESIÓN FOCAL INFERIOR O IGUAL A 2 CM DE TAMAÑO EN UN PACIENTE CON CIRROSIS HEPÁTICA

**MEMORIA TESIS DOCTORAL**

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**Memoria de tesis doctoral para optar al grado de Doctor en Medicina y Cirugía**

Barcelona, 2010


**UNIVERSIDAD DE BARCELONA**

**FACULTAD DE MEDICINA**

Departamento de Medicina

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CERTIFICA:

Que la Tesis Doctoral **"Actitud a seguir ante la detección de una lesión focal inferior o igual a 2 cm de tamaño en un paciente con cirrosis hepática"**, realizada por ALEJANDRO FORNER GONZÁLEZ y dirigida por el que suscribe, reúne las condiciones necesarias para su presentación y defensa ante el Tribunal correspondiente, para optar al grado de Doctor.

Lo que se hace constar a los efectos oportunos, en Barcelona a once de enero de 2010

Fdo.: Prof. Jordi Bruix

A Ana, por todo su apoyo

## AGRADECIMIENTOS

A mis padres, por todo el esfuerzo que han realizado por su familia. Indudablemente todos mis logros se los debo a ellos.

A mis hermanos Antonio, Elías y Fernando, por el apoyo y amor que he recibido de todos ellos durante toda mi vida.

A Ana, mi mujer, por todo su apoyo y comprensión a largo de todos estos años. A Lucía, mi princesa, y al hermanito que viene de camino; sois mi mayor tesoro.

A Jordi, director de esta tesis y mi mentor, por su amistad, apoyo y por todas las enseñanzas que he recibido.

A todos mis compañeros del BCLC: A Josep María por su ejemplo de trabajo, a Ramón, Luís, Conxita, Manel, Carmen y Jordi por su inestimable ayuda para la realización de todos estos estudios y su amistad, a Josep, Maribel y Marta por su apoyo, a mis compañeros de despacho, María, Carlos e Ingrid, por los buenos momentos que pasamos juntos, a Margarita, María, Diana y Natalia, que ya no están trabajando con nosotros pero os sigo recordando, y por último y no menos importante, a Nuria, por su cariño e inestimable ayuda para la realización de esta memoria.

A todos mis compañeros de residencia por todos los buenos momentos que hemos pasado juntos.

Al Instituto de Salud Carlos III y a la Fundación BBVA, por el apoyo económico imprescindible para la realización de este proyecto científico.

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# 1.-INTRODUCCIÓN

## 1.1.- Epidemiología

El carcinoma hepatocelular (CHC) es la neoplasia primaria de hígado más frecuente, la sexta neoplasia más incidente y la tercera causa de muerte por cáncer (1). Aunque su prevalencia es mayor en países en vías de desarrollo, se ha constatado que la incidencia está aumentando dramáticamente en países industrializados (2-4) y el desarrollo de CHC constituye actualmente la causa más frecuente de muerte en pacientes cirróticos (5). Por tanto, el CHC constituye un problema médico relevante y una de las áreas más importantes de conocimiento en Hepatología. Su distribución mundial es muy heterogénea y está estrechamente relacionada con la prevalencia variable de los diferentes factores de riesgo asociados al desarrollo de esta neoplasia. La incidencia es máxima en el Sudeste asiático y África Subsahariana. La mayor parte de casos en esa zona se hallan en relación con el virus de la hepatitis B (VHB) asociado o no con la exposición a aflatoxina y la incidencia excede 15 casos/100.000 hab/año. El sur de Europa, incluyendo España, presenta una incidencia intermedia, de 5-10 casos/100.000 hab/año, y finalmente, el norte de Europa y América tienen la menor incidencia, de aproximadamente 5 casos/100.000 hab/año (6). En ambas áreas juegan un papel predominante la infección por virus de la hepatitis C (VHC) y el alcoholismo. En España, el VHC constituye en el momento actual el principal factor de riesgo asociado a la aparición de CHC, y aunque los datos son heterogéneos dado que en muchas ocasiones las metástasis hepáticas son registradas como tumores hepáticos primarios, existen evidencias de que la incidencia de CHC ha aumentado en los últimos años (7, 8). En todas las áreas geográficas el riesgo de CHC varía según el grado de afectación hepática, siendo menor al 1% anual en pacientes con hepatitis crónica sin fibrosis significativa, incrementándose a 3-7% anual cuando el paciente desarrolla cirrosis (9). Una vez instaurada la cirrosis hepática, el riesgo de desarrollo de CHC persiste a pesar de obtener una respuesta viral persistente tras finalizar el tratamiento (10). Por tanto, cualquier enfermedad que pueda dar lugar a una cirrosis hepática (hemocromatosis hereditaria, cirrosis biliar primaria, hepatitis autoinmune) debe considerase un factor de riesgo para CHC. En los últimos años se ha demostrado que la diabetes mellitus (11) y otros factores asociados al síndrome metabólico como la obesidad o la dislipemia (12-15) se asocian a incremento de muerte relacionada con CHC.

La estrategia más eficaz para disminuir la mortalidad asociada a CHC es evitar la adquisición de factores de riesgo. La vacuna frente al VHB ha demostrado su eficiencia (16), mientras

que la infección por VHC, la ingesta de aflatoxina, el consumo de alcohol o el síndrome metabólico pueden prevenirse mediante campañas dirigidas a mejorar las condiciones sociosanitarias de los ciudadanos y promoción de hábitos de vida saludables. Si el factor de riesgo ya se ha adquirido, la única opción preventiva es evitar la progresión a cirrosis mediante la administración de tratamiento antiviral (17, 18) y el abandono de los hábitos que implican riesgo aumentado. Por tanto, la prevención primaria del CHC es la medida más eficaz.

### 1.2.- Técnicas de cribado

Una vez se ha desarrollada la enfermedad, la única estrategia disponible para disminuir la mortalidad asociada al CHC es diagnosticando esta neoplasia en una fase inicial, asintomática, cuando es posible aplicar tratamientos con intención curativa (19). Teniendo en cuenta que el CHC afecta en la mayoría de los casos a una población diana bien definida (pacientes afectos de cirrosis hepática), que la prueba de cribado (ecografía abdominal) tiene un rendimiento diagnóstico aceptable, que existe una estrategia de actuación bien definida ante un resultado positivo en la prueba de cribado, y que la aplicación de tratamiento en estadios iniciales claramente modifica la historia natural de la enfermedad, el cribado de CHC en pacientes cirróticos está justificado desde el punto de vista teórico (20). Además, un estudio aleatorizado realizado en China (21) y diversos estudios de cohortes (22-24) y estudios de coste eficacia (25-27) han demostrado que la instauración de programas de cribado en pacientes cirróticos es eficaz para disminuir la mortalidad del CHC, y en la actualidad se recomienda la realización de una ecografía abdominal (US) cada 6 meses (28-30).

Las técnicas de cribado de CHC pueden dividirse en radiológicas y serológicas. La prueba radiológica más usada es la ecografía abdominal. Se trata de una técnica no invasiva, aceptada por la población, con una sensibilidad de 60-80% y una especificidad superior al 90% para la detección precoz del CHC (31). Además, se dispone de una estrategia diagnóstica bien definida tras la detección de un nódulo sospechoso de CHC. Por tanto, la ecografía abdominal realizada por personal experto es actualmente la técnica de cribado más adecuada para la realización de detección precoz de CHC. Con objeto de asegurar el conocimiento y experiencia para efectuar cribado basado en ecografía, es fundamental

establecer programas de formación que certifiquen la capacitación para llevar a término esta actividad. La realización de tomografía computerizada (TC) como técnica de cribado debe desaconsejarse por el riesgo asociado a la irradiación (32) así como por motivos de coste-eficacia y menor disponibilidad. Este último aspecto también afecta a la resonancia magnética (RM).

Respecto a las pruebas serológicas, se disponen en la actualidad de multitud de marcadores tumorales. El más evaluado ha sido la alfa-feto-proteína (AFP), que hasta hace poco tiempo era la única herramienta disponible. Sin embargo, la AFP ha mostrado un bajo rendimiento diagnóstico dado que sus valores en muchos casos son normales en tumores iniciales y es bien sabido que los pacientes con cirrosis hepática pueden presentar elevaciones transitorias de AFP en ausencia de CHC. Análisis retrospectivos evaluando el rendimiento diagnóstico mediante curvas ROC han mostrado que el punto de corte óptimo para cribado se sitúa entre 16,9 y 20 ng/mL, ofreciendo una sensibilidad aproximada del 60% (33, 34). Sin embargo, cuando se consideran estudios prospectivos donde específicamente se evalúa el rendimiento diagnóstico de las pruebas de cribado, el valor diagnóstico de la AFP fue sensiblemente inferior (35). Además, no se dispone de ningún estudio que establezca qué incremento de AFP debe llevar a sospechar un CHC si la US es negativa. En este sentido, estudios en explantes demuestran que puede no existir CHC aunque la AFP supere 500 ng/mL (36). Por último, existe una correlación entre niveles de AFP y estadio tumoral, siendo la AFP simplemente un marcador de enfermedad avanzada. Por tanto, la AFP no es una herramienta de cribado eficaz y debe desaconsejarse su uso (37). Se han propuesto otros marcadores como la fracción de AFP ligada a lectina (38), des-gamma-carboxi protrombina (DGCP) (39) o el glypican-3 (40), pero presentan los mismos defectos que la AFP y en general no pueden competir con la fiabilidad de la US.

### 1.3.- Diagnóstico del CHC

En un paciente afecto de cirrosis hepática, la probabilidad de que un nódulo detectado mediante US sea un CHC es muy elevada, especialmente si su diámetro excede los 10 mm. Por tanto, ante la detección de un nódulo hepático, es recomendable realizar estudios complementarios para llegar a un diagnóstico concluyente.

El CHC presenta una vascularización predominantemente arterial (41), a diferencia del parénquima hepático en donde la vascularización es mixta: arterial y portal. Esto determina un patrón vascular específico caracterizado por una intensa captación de contraste en fase arterial, seguido de un lavado rápido del contraste en fase venosa portal o tardía (*washout* en la literatura anglosajona). Este patrón ha mostrado ser específico para el diagnóstico de CHC cuando se ha correlacionado con el análisis anatomopatológico de explantes o de piezas de resección quirúrgica (42). En la conferencia de consenso de la EASL (*European Association for the Study of the Liver*) celebrada en 2000 en Barcelona se propusieron unos criterios diagnósticos no invasivos basados en el patrón vascular detectado mediante pruebas de imagen dinámicas. De este modo, si un nódulo mayor de 2 cm sobre un hígado cirrótico presentaba una hipercaptación en fase arterial coincidente mediante 2 técnicas de imagen (28), el diagnóstico de CHC se consideraba establecido. En nódulos menores de 2 cm, se recomendaba basar el diagnóstico en la confirmación mediante biopsia. Estos criterios de imagen no invasivos han sido aplicados clínicamente con éxito y han demostrado su utilidad (43), particularmente para el diagnóstico de tumores avanzados. No obstante, la descripción de nódulos hipervasculares en hígados cirróticos sin diagnóstico final de CHC (p.ej. hemangioma atípico, colangiocarcinoma), llevó a refinar los criterios no invasivos (44, 45). En este sentido, el diagnóstico diferencial con el colangiocarcinoma es especialmente importante ya que se trata del segundo tumor primario más frecuente, su incidencia está aumentando, particularmente en pacientes afectos de cirrosis hepática por VHC, y el pronóstico y tratamiento es diferente al del CHC (46). Además, tras su publicación ningún grupo ha conseguido hasta la fecha validar de forma prospectiva estas recomendaciones.

Con estas premisas, recientemente se estableció en las guías de práctica clínica publicadas por la AASLD (*American Association for the Study of Liver Diseases*) (29) y aceptadas por un panel de expertos de la EASL, la necesidad de detectar lavado de contraste. Así, para registrar el patrón dinámico como específico de CHC debe detectarse hipervascularización en fase arterial seguido de lavado precoz en la fase venosa y de equilibrio. De acuerdo con estos nuevos criterios, es posible establecer el diagnóstico no invasivo de CHC si un nódulo en un hígado cirrótico muestra intensa captación de contraste en fase arterial seguido de lavado precoz en fase venosa en una técnica de imagen dinámica (ecografía con contraste, RM o TC con contraste).

En el caso de nódulos entre 1 y 2 cm, se recomienda la demostración de este patrón vascular específico de forma coincidente en dos pruebas de imagen con el fin de evitar posibles falsos diagnósticos positivos basados en una lectura equivocada de una única prueba de imagen. Si el patrón vascular no es típico o el nódulo no muestra captación de contraste, el diagnóstico concluyente de CHC debe basarse en anatomía patológica. Finalmente, en el caso de nódulos menores de 1 cm, dada la baja probabilidad de que sea de naturaleza maligna y la dificultad que supone su correcta caracterización, se recomienda realizar un seguimiento estrecho mediante una ecografía cada 3-6 meses con la finalidad de detectar su posible crecimiento, para entonces emplear los criterios anteriores (figura 1).

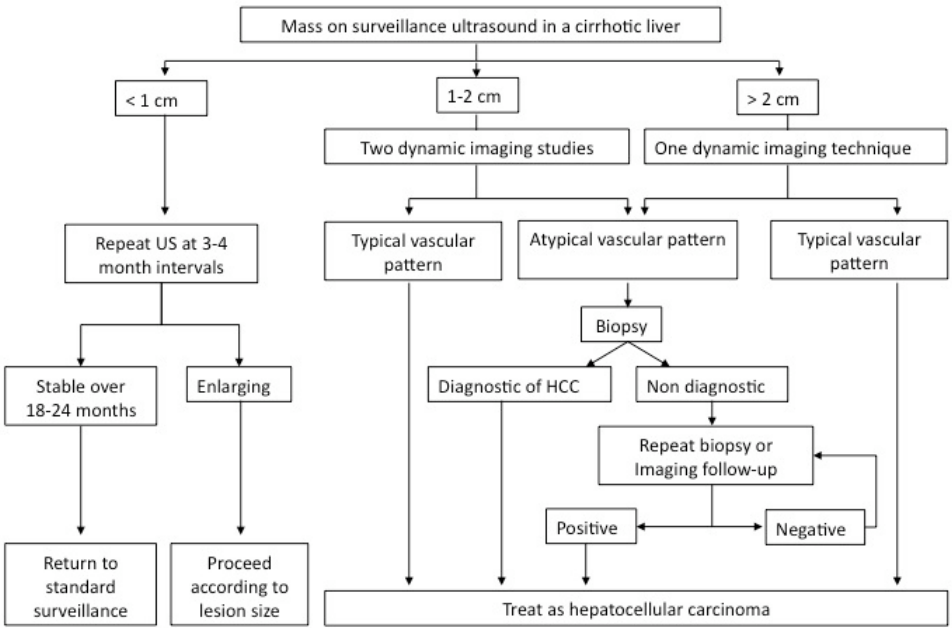


**Figura 1**: Algoritmo diagnóstico propuesto por la AASLD. Adaptado de Bruix et al (29)

En el caso de pacientes sin cirrosis establecida, la aplicación de estos criterios de imagen no es válida y es necesario la realización de una biopsia para obtener un diagnóstico concluyente. Estudios futuros deberán establecer si la detección de grasa o pseudocápsula o el comportamiento tras la administración de contrastes intracelulares pueden constituir criterios diagnósticos adicionales.

Tal como se ha comentado previamente, en un número no despreciable de casos, particularmente en aquellos nódulos menores de 2 cm, su correcta caracterización depende de la obtención de una biopsia. Sin embargo, la realización de una biopsia de un nódulo hepático en un paciente cirrótico no es siempre posible. En algunos casos, la presencia de ascitis o de

alteraciones severas de la coagulación contraindican este procedimiento y en otros casos, su localización en el hígado dificulta la accesibilidad para una punción percutánea. Además, el rendimiento diagnóstico de una biopsia en estos nódulos de pequeño tamaño no es óptimo, presentando una sensibilidad cercana al 70% (47). Ello puede estar en relación a un error de muestreo y a la dificultad de realizar un diagnóstico diferencial entre nódulos displásicos y CHC muy iniciales a partir del escaso material obtenido a través de una punción percutánea (41). Por tanto, ante una biopsia negativa no se puede descartar el diagnóstico de CHC y se debe valorar la necesidad de obtener una nueva biopsia.

Finalmente, el uso de AFP como herramienta diagnóstica presenta un rendimiento muy bajo (48). Diferentes neoplasias como el colangiocarcinoma o metástasis de origen gastrointestinal pueden presentar elevaciones de AFP (33, 49, 50). Por tanto, a pesar de encontrar unos niveles elevados de AFP (superior a 200 ng/mL), si la masa hepática no presenta un patrón vascular específico por imagen y el paciente es subsidiario de recibir tratamiento del CHC, se debe realizar una biopsia confirmatoria.

En los últimos años se ha producido un gran avance en el conocimiento de las vías moleculares que determinan la aparición de CHC (51, 52), lo que ha permitido evaluar técnicas de biología molecular que potencialmente ofrecerían nuevas herramientas diagnósticas. Se han propuesto diferentes firmas diagnósticas basadas en expresión génica y también tinciones inmunohistoquímicas que reflejarían esta diferente expresión a nivel proteico (53-55). Sin embargo, todos estos estudios han sido realizados sobre tumores obtenidos tras resección quirúrgica o trasplante hepático, limitando su aplicabilidad en las muestras obtenidas mediante punción percutánea. Aunque un estudio preliminar ha validado la utilidad de estos marcadores inmunohistoquímicos en muestras obtenidas mediante punción-biopsia (56), el diseño retrospectivo y la inclusión de CHC de gran tamaño impiden valorar su utilidad real en el diagnóstico precoz del CHC.

### 1.4.- Evaluación pronóstica y algoritmo terapéutico

Una vez confirmado el diagnóstico, es fundamental realizar una predicción pronóstica con el fin de facilitar la toma de decisiones. Tal como se ha discutido previamente, el CHC aparece en la mayoría de los casos sobre un hígado afecto de cirrosis hepática. Por tal motivo, en la evaluación pronóstica del paciente es necesario tener en cuenta no solo el estadio tumoral,

sino también el grado de reserva funcional. Asimismo, la evaluación del estado general del paciente ha demostrado ser clave en la valoración pronóstica y terapéutica.

En los últimos años se han propuesto múltiples sistemas pronóstico de estadiaje (57). El más usado en nuestro medio es el sistema BCLC (Barcelona Clinic Liver Cancer) (58), que tiene en cuenta el estadio tumoral, función hepática y el estado general, y asocia directamente el estadiaje con las diversas opciones terapéuticas. Este sistema pronóstico ha sido validado externamente, ha demostrado tener la mayor capacidad de estratificar los pacientes en diferentes grupos pronósticos (59, 60) y es el esquema recomendado por la AASLD y por el consejo de Salud Interterritorial del Ministerio de Sanidad de España (61). Divide a los pacientes en cuatro grupos pronósticos diferentes (figura 2):

1.4.1- *Estadio A (estadio inicial)*: Pacientes con tumor único o un máximo tres nódulos hasta 3 cm, con buena función hepática y ausencia de síntomas. En estos pacientes es posible obtener la curación de la enfermedad y la supervivencia esperada a los 5 años puede alcanzar el 70%. Los tratamientos con intención curativa disponibles son:

1.4.1.1.- Resección quirúrgica: La resección quirúrgica es la primera opción en aquellos tumores que aparecen sobre hígados no cirróticos. Lamentablemente, en la mayoría de los casos el paciente presenta una cirrosis hepática, lo que limita la aplicabilidad de esta estrategia terapéutica. Es indiscutible que la resección quirúrgica está contraindicada en pacientes con cirrosis descompensada o con pobre reserva funcional. En aquellos pacientes con enfermedad compensada, los mejores candidatos son aquellos con tumores únicos y ausencia de hipertensión portal clínicamente relevante (GPVH<10 mmHg) (62, 63). En pacientes bien seleccionados e intervenidos en centros con experiencia, la mortalidad perioperatoria debe ser inferior a 3% y la supervivencia a los 5 años debe ser del 70% (64). El principal inconveniente de la resección quirúrgica es la alta tasa de recidiva, que puede llegar al 70% a los 5 años. En la mayoría de los casos aparecen durante los primeros dos años de seguimiento, habitualmente en forma de enfermedad multifocal, y corresponden a metástasis intrahepáticas no detectadas previamente a la cirugía (64). Por este motivo, en nuestro medio se valora trasplante hepático antes de la aparición de la recidiva en aquellos pacientes en los que el análisis de la pieza resecada muestra invasión microvascular y/o nódulos satélites (65).

1.4.1.2.- Trasplante hepático: Esta opción terapéutica no solo consigue una eliminación radical del tumor hepático, sino también de la cirrosis hepática subyacente. Está

indicada en aquellos pacientes con escasa reserva funcional hepática y/o hipertensión portal significativa en los que no es factible realizar resección quirúrgica. Con la finalidad de evitar recurrencias de la enfermedad tras el trasplante, se limita el trasplante a aquellos pacientes con enfermedad limitada definida por los criterios de Milán: tumores únicos menores de 5 cm. o un máximo de tres nódulos menores de 3 cm., sin invasión vascular ni extrahepática (66). El uso de estos criterios restrictivos permite obtener tasas de recurrencia inferiores al 10% y la supervivencia a los 5 años debe ser superior del 70% (64). Sin embargo, en los últimos años el aumento significativo del tiempo en lista de espera ha condicionado una caída de la lista de espera (por progresión tumoral o fallecimiento durante el tiempo de espera) cercana al 20%, acompañada de una disminución de la supervivencia cuando se realiza un análisis por intención de tratamiento. Se han sugerido diversas estrategias para tratar de disminuir esta tasa de caída de la lista de espera. La primera estrategia sería aumentar el número de donantes, mediante la aceptación de donantes de alto riesgo (pe. donante añoso o de corazón parado), uso de trasplante dominó o split, o por último, el trasplante hepático de donante vivo (LDLT). Otra alternativa sería utilizar un sistema de priorización que permitiera transplantar antes a aquellos pacientes con alta probabilidad de progresión durante el tiempo en lista. La última opción sería la realización de tratamiento locorregional en lista, particularmente mediante ablación percutánea, que ha demostrado ser coste-efectiva cuando el tiempo en lista de espera supera los 6 meses (67).

1.4.1.3.- Ablación percutánea: Es el tratamiento de elección de aquellos pacientes en los que la cirugía no es factible y el trasplante hepático está contraindicado por patología asociada (29, 61). La ablación del tumor puede conseguirse mediante la inyección de sustancias químicas, frecuentemente etanol (PEI), o mediante modificación de la temperatura intratumoral, principalmente mediante radiofrecuencia (RFA). La eficacia de la ablación percutánea depende en gran medida del tamaño del nódulo, disminuyendo drásticamente su rendimiento en aquellas lesiones mayores de 3 cm. La RFA tiene mayor capacidad ablativa, y de acuerdo al resultado de diferentes meta-análisis, ofrece mayor beneficio en términos de supervivencia que la PEI (68, 69). Lamentablemente, la RFA no se puede aplicar en todas las lesiones debido a aspectos técnicos (p.ej. tumores subcapsulares o adyacentes al hilio hepático o a la vesícula biliar se asocian a un gran riesgo de complicaciones). Además, las técnicas ablativas, al igual que en la resección quirúrgica, presentan una alta tasa de recurrencias, cercanas al 40% a los 2 años (70).

1.4.2- *Estadio B (estadio intermedio):* Pacientes que exceden los límites del estadio A, sin invasión vascular ni extrahepática, con función hepática y estado general conservado. La supervivencia mediana sin tratamiento es de aproximadamente 16 meses (71). En este estadio, el único tratamiento que ha mostrado aumento de la supervivencia en dos ensayos clínicos (72, 73) y en un meta-análisis de datos acumulados (74) es la quimioembolización, obteniendo una supervivencia mediana superior a 20 meses. En los últimos años ha habido grandes avances en el campo de la quimioembolización. El más destacable es la aparición de las *drug eluting beads* (DEB), que permiten una embolización homogénea y calibrada junto con una liberación intratumoral retardada y selectiva del agente quimioterápico, obteniendo una respuestas radiológicas prometedoras (75).

1.4.3.- *Estadio C (estadio avanzado):* Son aquellos pacientes afectos de un CHC no subsidiario a tratamiento radical que presentan invasión vascular y/o extrahepática o con afectación leve del estado general. En estos casos, la supervivencia mediana era 6 meses y hasta recientemente no se disponía de ningún tratamiento eficaz, por lo que estos pacientes eran candidatos para participar en ensayos clínicos controlados y randomizados (RCT) para evaluar nuevas terapias. En los últimos años han aparecido agentes que bloquean selectivamente aquellas vías moleculares asociadas al inicio/progresión del CHC. De todos estos agentes actualmente en evaluación, el único que ha demostrado hasta la fecha eficacia en términos de supervivencia es sorafenib, un inhibidor multiquinasa con acción antiproliferativa y antiangiogénica con disponibilidad por vía oral (76, 77). Con el uso de sorafenib, la supervivencia mediana en pacientes bien seleccionados es de 11 meses. En la actualidad se están evaluando múltiples agentes moleculares, como agentes únicos o en combinación con sorafenib, por lo que es previsible que en los próximos años aparezcan grandes avances en el tratamiento de esta enfermedad.

1.4.4- *Estadio D (estadio terminal):* Corresponde a pacientes con gran carga tumoral, con disfunción hepática severa no candidatos a trasplante hepático o síntomas invalidantes. La supervivencia suele ser menor de 3 meses.

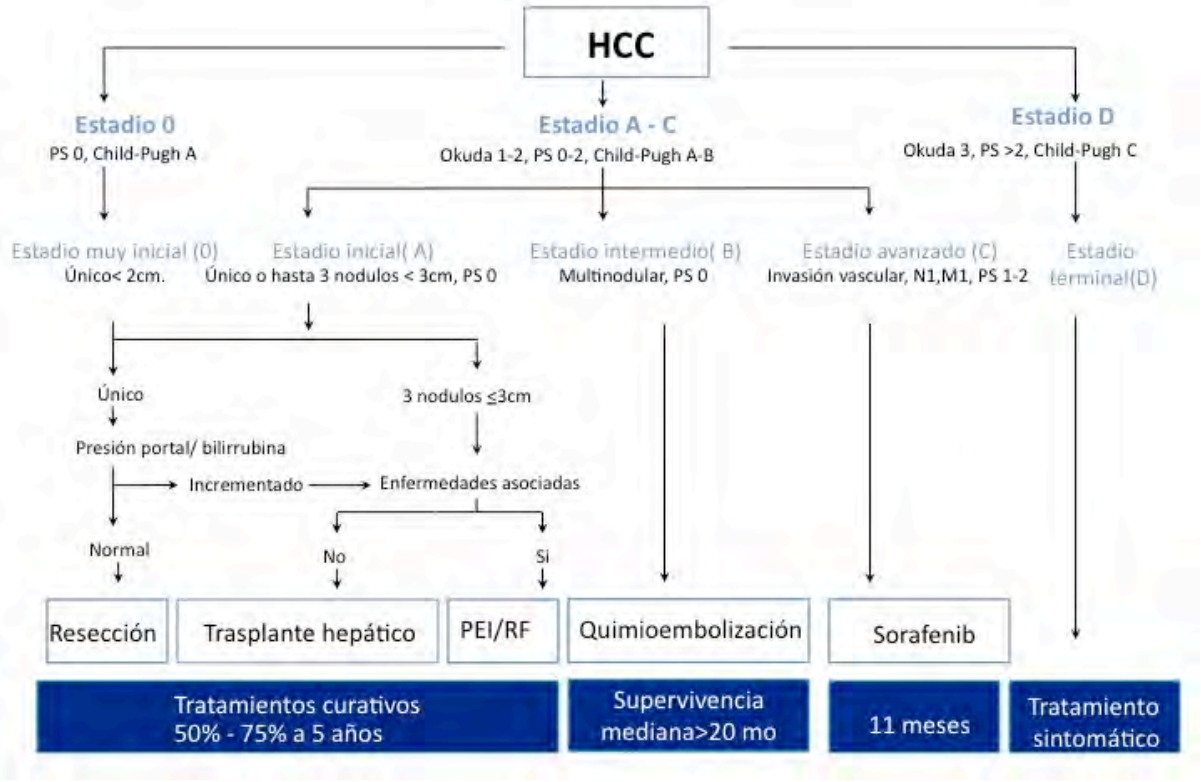


**Figura 2**: Sistema pronóstico BCLC (Barcelona Clínic Liver Cancer). Adaptado de Forner et al (61)

### 1.5.- Perspectivas de futuro

Los resultados positivos de sorafenib han constituido una prueba de concepto de que los agentes moleculares son potencialmente eficaces en esta neoplasia refractaria a otras terapias sistémicas, lo que unido al mejor conocimiento de las vías moleculares asociadas al inicio y progresión del tumor y al desarrollo de múltiples agentes moleculares, han determinado que en los últimos años se hayan iniciado una gran cantidad de ensayos clínicos que evalúan estos agentes en humanos. Conceptos clásicos en Oncología como la necesidad de disminuir carga tumoral para lograr impacto en la supervivencia se han demostrado obsoletos y deberán establecerse nuevos criterios de respuesta para detectar una posible eficacia que justifique la evaluación de un nuevo fármaco a gran escala en estudios fase 3. En este sentido, el sorafenib es capaz de aumentar de forma significativa la supervivencia sin apenas inducir respuesta radiológica convencional de acuerdo al cambio de tamaño de las lesiones. Asimismo, la simple medida del cambio del tamaño de las lesiones no es capaz de detectar la eficacia de

los diversos tratamientos disponibles en el CHC. En este sentido, los tratamientos locorregionales (ablación y quimioembolización) son altamente eficaces pero raramente consiguen disminuir el tamaño tumoral. Por este motivo, la EASL recomienda medir el porcentaje de necrosis (detectado como áreas intratumorales que no captan contraste) para evaluar la respuesta tras tratamiento. Además, posiblemente técnicas radiológicas avanzadas como la difusión o la perfusión sustituirán en un futuro a las medidas actuales aunque su validación será laboriosa. Obviamente, urge desarrollar biomarcadores que nos permitan identificar buenos candidatos a tratamiento o fracaso del tratamiento indicado, lo que nos permitiría aplicar un tratamiento personalizado *à la carte*.

Otro aspecto importante es el manejo de efectos secundarios. No cabe duda que estos agentes biológicos, a pesar de su mecanismo de acción específico sobre las células neoplásicas, no están exentos de efectos adversos. Además, no debemos olvidar que la mayoría de los pacientes afectos de CHC padecen una cirrosis hepática asociada, dificultando aún más el manejo de estos fármacos.

También habría que destacar el posible papel que en un futuro puedan tener las terapias génicas. En este sentido, en los últimos años ha habido una investigación activa sobre el rol de los microRNA (miRNA) en el desarrollo de neoplasias (78, 79) y su potencial aplicabilidad terapéutica en modelos animales (80).

# 2.- OBJETIVOS

La presente Tesis Doctoral va dirigida a profundizar en la utilidad de las técnicas de imagen dinámicas para el diagnóstico no invasivo del CHC y para la evaluación de la respuesta tumoral tras la realización de tratamiento locorregional.

Como se ha comentado previamente, una de las principales estrategias para disminuir la mortalidad asociada a CHC es diagnosticando la enfermedad en fases iniciales. Por este motivo se recomienda ofrecer la participación en programas de cribado a aquellos pacientes afectos de cirrosis hepática mediante la realización de una ecografía abdominal semestral (29, 61).

Tras la detección de una lesión mediante una ecografía abdominal, se recomienda realizar pruebas complementarias basadas en técnicas de imagen dinámicas (ecografía con contraste, TC abdominal y RM hepática) con la finalidad de caracterizar las diferentes lesiones identificadas mediante ecografía de cribado. La utilidad de las técnicas dinámicas de imagen se basan en la detección de un patrón vascular específico del CHC. Este comportamiento del contraste en el CHC se basa en la vascularización mayoritariamente arterial del CHC comparado con la vascularización mixta, arterial y portal, del parénquima hepático subyacente (41). Esto determina que el patrón vascular específico del CHC sea una intensa captación de contraste en fase arterial seguido de lavado de contraste en fase venosa. Este patrón ha mostrado ser específico para el diagnóstico de CHC cuando se ha correlacionado con el análisis anatomopatológico de explantes o de piezas de resección quirúrgica (42).

Inicialmente, la EASL sugirió reservar el diagnóstico no invasivo del CHC a aquellos nódulos mayores de 2 cm que exhibían captación de contraste en fase arterial en dos pruebas coincidentes (28). Estos criterios de imagen no invasivos han sido aplicados clínicamente con éxito y han demostrado su utilidad, particularmente para el diagnóstico de tumores avanzados (43). No obstante, en aquellas lesiones menores de 2 cm era imprescindible obtener una confirmación histológica y su aplicación en la práctica clínica demostró que existen otras lesiones frecuentes en el hígado cirrótico que pueden presentar hipervascularización arterial, como son el hemangioma hepático y el colangiocarcinoma (44, 45). Esto motivó la revisión y el refinamiento de estos criterios no invasivos del CHC. En primer lugar, se incluyó la necesidad de detectar lavado de contraste además de la hipervascularización en fase arterial. En segundo lugar, se consideró que era posible realizar el diagnóstico no invasivo de CHC en

nódulos entre 1 y 2 cm, siempre y cuando este patrón vascular específico fuera evidenciado en dos pruebas de imagen de forma coincidente. Evidentemente, en caso de ausencia de este patrón vascular específico, es necesario considerar la obtención de una biopsia para confirmación histológica (29).

Estas recomendaciones propuestas por la AASLD se basaban en estudios descriptivos que correlacionaban los hallazgos de las diferentes técnicas dinámicas con el análisis de explantes y en la opinión de expertos. Sin embargo, en el momento de su publicación no existía una validación prospectiva de estas recomendaciones, en particular en lesiones de pequeño tamaño, menores de 2 cm. El diagnóstico del CHC cuando no excede de 2 cm es de especial interés, ya que la probabilidad de invasión microvascular o satelitosis es muy baja en este estadio, por lo que el tratamiento del CHC mediante terapias radicales se asocia a la práctica curación de la enfermedad.

Asimismo, en los últimos años se ha evidenciado un aumento progresivo de la incidencia del colangiocarcinoma intrahepático (ICC), que es la segunda neoplasia primaria de hígado más frecuente. La cirrosis hepática, particularmente por VHC, constituye un conocido factor de riesgo para su desarrollo, y su tratamiento y pronóstico es diferentes al del CHC. Por tal motivo es imprescindible realizar un correcto diagnóstico diferencial entre el ICC y el CHC. Dado que el ICC puede aparecer como un tumor hipervascular en fase arterial (45, 81-83), es imprescindible analizar si la aplicación de los criterios no invasivos propuestos por la AASLD son capaces de diferenciar ambas enfermedades.

Por tanto, el primer objetivo era validar prospectivamente la utilidad de los criterios de imagen para el diagnostico no invasivo del CHC en aquellas lesiones inferiores a 2 cm, con especial énfasis en el diagnóstico diferencial con el colongiocarcinoma intrahepático.

Para poder responder esta hipótesis de trabajo se realizaron los siguientes estudios:

*Estudio 1:*

**Forner A**, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Bru C y Bruix J. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008 Jan 1;47(1):97-104.

*Estudio 2:*

Rimola J, **Forner A**, Reig M, Vilana R, Rodríguez de Lope C, Ayuso C y Bruix J. Cholangiocarcinoma in cirrhosis: Absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology. 2009;50(3):791-8.

La segunda parte del proyecto tenía por objetivo analizar la utilidad de las pruebas de imagen para la evaluación de la respuesta tumoral tras la realización de tratamiento locorregional.

La evaluación de la respuesta tumoral es fundamental en el tratamiento del cáncer ya que la obtención de una respuesta objetiva se considera una marcador subrogado de mejoría de supervivencia. En los últimos años se han desarrollado múltiples criterios que han permitido una evaluación uniforme de la respuesta tumoral. El sistema de evaluación de respuesta pionero fue propuesto por la OMS en 1979 (criterios WHO) (84). En el año 2000 se propusieron los criterios RECIST (*Response Evaluation Criteria In Solid Tumors*), que se basaban en la suma de los diámetros mayores de todas las lesiones dianas y la respuesta fue categorizada como: Respuesta completa (desaparición de todas las lesiones diana), respuesta parcial (al menos una disminución del 30% de la suma de diámetros de las lesiones diana), enfermedad progresiva (al menos un aumento del 20% de la suma de diámetros de las lesiones diana y/o aparición de nuevas lesiones y/o progresión inequívoca de las lesiones no diana) y enfermedad estable (ausencia de disminución o aumento de las lesiones que permitan definir respuesta o enfermedad progresiva) (85). A pesar del gran avance que supuso la aparición de los criterios RECIST, su aplicación en diferentes neoplasias no ha sido óptima (86). Además, con la aparición de los nuevos agentes moleculares con acción predominantemente citostática, la evaluación de la actividad mediante la medición de la

reducción del tamaño tumoral parece inadecuada. Por último, el criterio RECIST no tiene en cuenta cambios en la viabilidad del tumor que podrían estar asociados a respuesta tumoral. En este sentido, el objetivo de los tratamientos locorregionales en el CHC es obtener necrosis tumoral, independientemente de obtener reducción del tamaño del nódulo. Por tal motivo, un panel de expertos de la EASL acordó considerar la reducción del volumen de tumor viable (reconocido mediante áreas de ausencia de realce en técnicas de imagen dinámicas) como método para evaluar la respuesta local tras tratamiento locorregional del CHC (28). En este sentido, la mayoría de los autores que reportan resultados tras tratamiento locorregional tienen en cuenta esta recomendación (73, 75, 87-89).

Por tanto, el objetivo era comparar el grado de concordancia de la respuesta tumoral de los criterios RECIST comparado con las recomendaciones de la EASL en una cohorte de pacientes tratados con ablación percutánea (radiofrecuencia y alcoholización) y quimioembolización.

*Estudio 3:*

**Forner A**, Ayuso C, Varela M, Rimola J, Hessheimer AJ, Rodríguez de Lope C, Reig M, Bianchi L, Llovet JM y Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer. 2009 Feb 1;115(3):616-23.

# 3.- RESULTADOS

A continuación se adjunta copia de los artículos que componen la memoria de la presente tesis doctoral.

*Estudio 1:*

**Forner A**, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, Boix L, Sala M, Varela M, Llovet JM, Bru C y Bruix J. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: Prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008 Jan 1;47(1):97-104.

*Estudio 2:*

Rimola J, **Forner A**, Reig M, Vilana R, Rodríguez de Lope C, Ayuso C y Bruix J. Cholangiocarcinoma in cirrhosis: Absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. Hepatology. 2009;50(3):791-8.

*Estudio 3:*

**Forner A**, Ayuso C, Varela M, Rimola J, Hessheimer AJ, Rodríguez de Lope C, Reig M, Bianchi L, Llovet JM y Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? Cancer. 2009 Feb 1;115(3):616-23.

# Diagnosis of Hepatic Nodules 20 mm or Smaller in Cirrhosis: Prospective Validation of the Noninvasive Diagnostic Criteria for Hepatocellular Carcinoma

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**This study prospectively evaluates the accuracy of contrast-enhanced ultrasound (CEUS) and dynamic magnetic resonance imaging (MRI) for the diagnosis of nodules 20 mm or smaller detected during ultrasound (US) surveillance. We included 89 patients with cirrhosis [median age, 65 years; male 53, hepatitis C virus 68, Child-Pugh A 80] without prior hepatocellular carcinoma (HCC) in whom US detected a small solitary nodule (mean diameter, 14 mm). Hepatic MRI, CEUS, and fine-needle biopsy (gold standard) (FNB) were performed at baseline. Non-HCC cases were followed (median 23 months) by CEUS/3 months and MRI/6 months. FNB was repeated up to 3 times and on detection of change in aspect/size. Intense arterial contrast uptake followed by washout in the delayed/venous phase was registered as conclusive for HCC. Final diagnoses were: HCC (n = 60), cholangiocarcinoma (n = 1), and benign lesions (regenerative/dysplastic nodule, hemangioma, focal nodular hyperplasia) (n = 28). Sex, cirrhosis cause, liver function, and alpha-fetoprotein (AFP) levels were similar between HCC and non-HCC groups. HCC patients were older and their nodules significantly larger ($P < 0.0001$). First biopsy was positive in 42 of 60 HCC patients. Sensitivity, specificity, and positive and negative predictive values of conclusive profile were 61.7%, 96.6%, 97.4%, and 54.9%, for MRI, 51.7%, 93.1%, 93.9%, and 50.9%, for CEUS. Values for coincidental conclusive findings in both techniques were 33.3%, 100%, 100%, and 42%. Thus, diagnosis of HCC 20 mm or smaller can be established without a positive biopsy if both CEUS and MRI are conclusive. However, sensitivity of these noninvasive criteria is 33% and, as occurs with biopsy, absence of a conclusive pattern does not rule out malignancy. These results validate the American Association for the Study of Liver Disease (AASLD) guidelines.** (HEPATOLOGY 2008;47:97-104.)

Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and the third most frequent cause of death of cancer.[1] In more than 90% of the cases, HCC complicates liver cirrhosis, and in these patients HCC constitutes the leading cause of death.[2-6] HCC incidence at 5 years may exceed 25%,[5,7-9] and the sole approach to achieve long-term survival is to detect the tumor at an early stage when effective therapy can be applied. Accordingly, all guidelines recommend performing screening for HCC in those patients with cirrhosis who would be treated if diagnosed with this condition.[10,11] Screening is based on ultrasound (US), and unequivocal diagnosis of a US-detected nodule within a cirrhotic liver represents a major clinical challenge. Biopsy confirmation has several limitations. Location of the tumor, clotting disorders, and ascites may prevent needle insertion, and it is not free of risks (bleeding or seeding). Finally, it is flawed by false-negative results caused by sampling error or to the unfeasibility of confidently distinguishing between dysplastic changes and well-differentiated HCC. This raises the need of well-defined noninvasive criteria that would allow an accurate diagnosis based on the imaging characterization. This need is of paramount relevance in settings such as transplantation. False-positive diagnosis results in unfair priority granting to patients without HCC or, what is even worse, to indicate transplant in the absence of HCC.[12-14] The European

*Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; CEUS, contrast- enhanced ultrasound; FNB, fine-needle biopsy; FPR, false-positive rate; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound; VIBE, Volumetric Interpolated Breath-hold Examination.*

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*Received May 15, 2007; accepted August 6, 2007.*

*Supported in part by grants of the Instituto de Salud Carlos III (grant PI 05/150 and PI 06/132) and from NIH-NIDDK grant: 1R01DK076986-0. Alejandro Forner is partially supported by a grant of the Instituto de Salud Carlos III (PI 05/645) and a grant of the BBVA foundation. María Varela was supported by Fundación Científica de la Asociación Española de Ayuda contra el Cáncer, Spain. Josep M. Llovet is Professor of Research at Institut Català de Recerca Avancada (ICREA, IDIBAPS, Hospital Clinic).*

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*Published online in Wiley InterScience (www.interscience.wiley.com).*

*DOI 10.1002/hep.21966*

*Potential conflict of interest: Nothing to report.*

Association for the Study of Liver Diseases 2000 Conference proposed a set of criteria to establish HCC diagnosis in patients with cirrhosis.[10] These were based on the coincidental observation of a hypervascular arterial profile of the nodule by 2 dynamic imaging techniques. To reduce the risk of false-positive diagnosis in small nodules, the noninvasive criteria were restricted to tumors larger than 2 cm in a cirrhotic liver. Accordingly, below this cutoff a biopsy diagnosis was mandatory. These criteria have been widely applied and have been clinically useful in patients with large HCC. Thereby, their wrong implementation in noncirrhotic livers or by using single reports of isolated imaging techniques have brought disappointing results.[15] The same occurs if the diagnostic accuracy of noninvasive criteria is solely tested in patients with positive biopsy.[15] In practice, biopsy is just performed in patients with nondiagnostic imaging techniques, and hence, such a comparison is flawed. As said, the usefulness of the criteria based on detection of contrast uptake has been confirmed, and the sole concern relies on the potential anecdotal false-positive diagnosis that could be raised in small benign lesions such as atypical hemangioma.[16] Intense arterial uptake might be present in nodules other than HCC. Nodules larger than 2 cm are unlikely to be wrongly classified as HCC, but this risk has raised the need to refine the specific characteristics that a nodule within a cirrhotic liver should exhibit to establish HCC diagnosis. Several studies have shown that the characteristic HCC profile includes the intense arterial uptake but is followed by contrast washout in the delayed venous phase.[17] The recognition of the diagnostic value of contrast washout allowed the refinement of the criteria as reflected in the recent American Association for the Study of Liver Diseases (AASLD) guidelines[11] and in the unpublished consensus of the European Association for the Study of the Liver experts that met in 2005. According to these new criteria, it is possible to establish HCC diagnosis if a nodule within a cirrhotic liver exhibits intense arterial uptake followed by washout in the venous phase. Dynamic imaging techniques include contrast-enhanced ultrasound, computed tomography, and magnetic resonance imaging (MRI). In nodules larger than 2 cm, a single imaging technique would be enough. However, and trying again to prevent false-positive HCC diagnosis in tiny lesions, it was recommended that in nodules between 1 and 2 cm, the diagnosis should require the coincidental findings of 2 techniques. If these criteria are not met, biopsy diagnosis is recommended.

These criteria were derived from the results of several cohort studies with diagnostic confirmation by evolutionary findings or biopsy or explant correlations. However, they have never been prospectively validated, and this is especially relevant in small hepatic nodules detected during surveillance in cirrhosis. Accordingly, this study prospectively evaluates the accuracy of contrast-enhanced ultrasound (CEUS) and MRI for the diagnosis of solitary nodules of 20 mm or smaller detected during surveillance in patients with cirrhosis and, thus, validate the AASLD diagnostic algorithm.

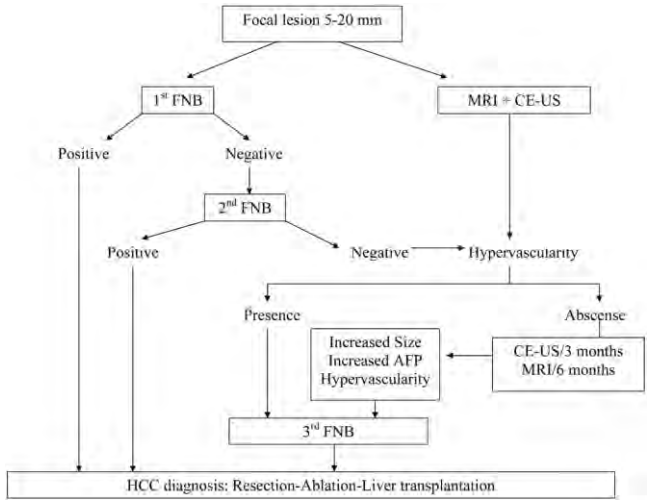


Fig. 1. Diagnostic algorithm followed in the study.

## Patients and Methods

Between November 2003 and August 2006, we prospectively included asymptomatic patients with Child-Pugh A-B cirrhosis with no history of HCC in whom a new solitary, well-defined, solid nodule between 5 and 20 mm was detected by screening ultrasound (US). Patients with poor liver function who would have undergone transplantation even without HCC diagnosis and those with significant comorbidities were excluded because no clinical decision/treatment would be indicated on HCC diagnosis. Patients with severe clotting alterations or contraindications to perform MRI, CEUS, or fine-needle biopsy were also excluded. The protocol was approved by the Ethics Committee for Clinical Research.

Figure 1 summarizes the diagnostic algorithm. On signing informed consent, we registered all demographic data and obtained a blood sample to determine liver, renal, and hematology parameters. Patients were examined by dynamic MRI and CEUS with second-generation contrast agent, and finally submitted to fine-needle biopsy (FNB). Biopsy result was considered the gold standard. If a conclusive diagnosis was not achieved, a second FNB was done. If the report was again negative for malignancy and did not raise a conclusive diagnosis, the policy was decided according to the imaging pattern. If any imaging technique evidenced arterial hypervascularization, a third

FNB was indicated. All the other cases and those with a third negative biopsy for malignancy were followed with CEUS every 3 months and MRI every 6 months. If growth or hypervascularization was detected, a new FNB was performed.

***MRI Imaging Technique.*** MRI was performed with a 1.5-T system (Symphony, Siemens Medical Systems, Erlangen, Germany) using a phased-array torso coil for signal detection. All patients underwent transverse T1-weighted and T2-weighted MRI and multiphasic contrast-enhanced dynamic 3-dimensional MRI of the whole liver with fat suppression. T1-weighted imaging included breath-hold in-phase gradient echo (100/5.24 TR/TE, 256 × 134 matrix, 70° flip angle) and out-of-phase gradient echo (100/2.38 TR/TE, 256 ×134 matrix, 70° flip angle). T2-weighted imaging included breath-hold haste (1100/116 TR/TE, 256 × 144 matrix). Dynamic MRI was performed with a 3-dimensional Volumetric Interpolated Breath-hold Examination (VIBE) sequence in axial plane by using the following parameters: 4.3/2, 25° flip angle, 256 × 106 matrix, slice thickness of 3 mm. Gadolinium (gadodiamide 0.5 mmol/L Ominscan-Amersham) was injected at a dose of 0.2 mL/kg at a rate of 2 mL/s. Bolus tracking technique was used to obtain arterial-phase images, approximately 20 seconds after contrast injection. Portal venous and delayed venous phase images were acquired 60 to 65 and 100 to 110 seconds thereafter. A breath-hold T1-weighted 2-dimensional gradient echo with fat suppression MRI (160/2.6 TR/TE, 256 × 115 matrix) was performed 5 minutes after contrast injection.

***CEUS Technique.*** US studies were performed using Sequoia 512 equipment (Acuson, Mountain View, CA). Baseline hepatic US was performed with a multifrequency 4C1 convex and 4V1 sectorial array probe to identify the target nodule. On identifying the lesion, CEUS was performed using the contrast coherent imaging (CCI, Siemens) with the 4C1 convex array probe. A low mechanical index (<0.2) was selected to avoid the microbubbles disruption. CEUS explorations were performed after the administration of 2.4 mL SonoVue (Bracco, Italy). This bolus was repeated if the first exploration was not evaluable. Enhancement patterns were studied during the vascular phase up to 3.5 minutes, including the arterial (0-49 seconds), portal (50-179 seconds), and late phase (>180 seconds).

***Fine-Needle Biopsy.*** FNB was performed using a 20-gauge spinal needle (Yale Spinal BD medical, NJ). Several back and forth passages were done after insertion of the needle. When technically feasible because of location and accessibility, a core-biopsy was performed using an 18-gauge needle-biopsy (Monopty; Bard Inc, Covington, UK). Specimens were routinely processed and stained with hematoxylin-eosin. Diagnosis of HCC was made according to the International Working Party criteria.[18]

***Image Interpretation.*** MRI studies were read by 2 radiologists experienced in imaging of the liver (C.A. and J.R.A.) who were unaware of the results of the biopsy. Nodular lesions were categorized as follows: (1) *conclusive HCC diagnosis*: nodules displaying intense contrast enhancement in the arterial phase and washout in 1 of the venous phases (portal or delayed), (2) *suggestive of HCC, but nonconclusive*: nodules showing enhancement during the hepatic arterial phase without washout; even if pseudocapsule of fatty content were demonstrated, lesions were still included in this category; (3) *dysplastic foci*: nodules with hyperintensity on T1-weighted images with isointensity/hypointensity during all 3 phases of dynamic study; (4) *regenerative nodules*: lesions only seen at delayed phases as low intensity; (5) *nonspecific hypervascular nodules*: contrast-enhanced nodules only seen during the arterial phase of the dynamic study, and (6) *hemangioma*: nodules with hyperintensity in T2-weighted images with centripetal contrast uptake after arterial phase that persists in delayed phases.

CEUS were performed by 3 expert radiologists (R.V., L.B., and C.B.). Explorations were recorded and blindly reviewed by at least 2 radiologists. Categorization of doubtful explorations was achieved by consensus. Lesions were defined as follows: (1) *conclusive HCC*: nodules showing intense contrast uptake during the arterial phase followed by washout in portal and/or venous phase; (2) *suggestive of HCC, but nonconclusive*: nodules showing early enhancement during the hepatic arterial phase without washout in venous phase; (3) *dysplastic/regenerative nodules*: nodules with no contrast enhancement during the 3 phases; and (4) *hemangioma*: early centripetal contrast uptake after arterial phase that persists in delayed phases.

***Categorization of the Results of Imaging Pattern for HCC Diagnosis.*** According to the previously depicted definitions, we stratified the findings of imaging techniques as hypovascular (no specific contrast enhancement of the nodule as compared with surrounding liver), suspicious (arterial hypervascularization regardless of washout), or conclusive (arterial hypervascularization followed by venous washout). Therefore, nodules classified as suspicious for HCC include those defined as conclusive and those categorized as suggestive but nonconclusive.

***Validation of the AASLD Criteria.*** Those nodules in which both CEUS and MRI depicted a conclusive pattern were classified as "AASLD criteria positive." Nodules not displaying this coincidental profile were classified as "AASLD criteria negative."

**Table 1. Patients' Characteristics Considering the Final Diagnosis**

| | All Patients | HCC Nodules | Non-HCC Nodules | Differences |
|---|---|---|---|---|
| **Number of patients** | 89 | 60 | 29 | |
| **Age median [range] (years)** | 65 [37–83] | 66.5 [37–83] | 60 [38–78] | $P = 0.032$ |
| **Male/female** | 53/36 | 37/23 | 16/13 | NS |
| **Child-Pugh A/B** | 80/9 | 52/8 | 28/1 | NS |
| **HCV/HBV/Ethanol/PBC/others** | 68/6/10/1/4 | 45/4/8/1/2 | 23/2/2/0/2 | NS |
| **AST median [range] (UI/L)** | 81 [25–322] | 82 [25–204] | 82 [26–322] | NS |
| **ALT median [range] (UI/L)** | 70 [16–537] | 65 [16–210] | 85.5 [21–537] | NS |
| **Prothrombin ratio median [range] (%)** | 78.5 [35–100] | 78 [35–100] | 80.5 [49–98] | NS |
| **Bilirubin median [range] (mg/dL)** | 1 [0.3–4.1] | 1 [0.3–4.1] | 0.7 [0.3–4.1] | NS |
| **Platelets median [range] ($10^9$/L)**1 | 04 [31–286] | 101 [32–286] | 139 [31–270] | NS |
| **Albumin median [range] (g/dL)** | 39 [26–48] | 39 [28–48] | 40 [29–46] | NS |
| **Baseline AFP median [range] (ng/mL)** | 8 [1–1154] | 8.5 [1–1154] | 5 [1–170] | NS |
| **Nodule size (mm):** | | | | |
| **<10** | 13 | 2 | 11 | |
| **10–15** | 44 | 29 | 15 | |
| **16–20** | 32 | 29 | 3 | $P < 0.0001$ |
| **Nodule pattern:** | | | | |
| **Hypoechoic** | 47 | 34 | 13 | |
| **Isoechoic** | 7 | 7 | 0 | |
| **Hyperechoic** | 35 | 19 | 16 | NS |
| **Halo: yes / no** | 29/60 | 26/34 | 3/26 | $P = 0.008$ |

Continuous variables expressed as a median/range and qualitative variables as total count.

***Statistical Analysis.*** Baseline characteristics of the patients are expressed as median and range or count and proportion. Comparison of patients with HCC and patients with non-HCC nodules was done by using the Student *t* test or the Mann-Whitney test for continuous variables and the chi-squared test/Fisher's exact test for categorical variables. A conventional *P* value = 0.05 was considered statistically significant. Calculations were done with the SPSS package (SPSS, Inc. 1989-1995, Chicago, IL).

## Results

A total of 89 patients with liver cirrhosis were included. Their characteristics are summarized in Table 1. Median age was 65 years; most had cirrhosis caused by hepatitis C virus infection (n = 68; 76.4%) with preserved liver function (Child-Pugh class A: 80). Median baseline alpha-fetoprotein (AFP) was 8 ng/mL (range, 1-1154) and was greater than 20 ng/mL in 23.2% of patients. Median size of the nodules was 14 mm (range, 7-20); 13 (14.6 %) were smaller than 10 mm, 44 (49.4 %) were 10-15 mm, and 32 (36 %) were 16-20 mm. Most nodules were hypoechoic (n = 47; 52.8%). Final diagnosis of the 89 nodules is summarized in Table 2: Sixty patients were diagnosed with HCC (67.4%), whereas 1 was diagnosed with cholangiocarcinoma (1.1%). Twenty-four lesions were classified as regenerative nodules/dysplastic nodules (27%). Three cases corresponded to hemangioma (3.4%) and 1 to focal nodular hyperplasia (1.1%). Patients with nonmalignant nodules were followed for a median of 23 months (range, 4-41) to ensure the benign nature of the nodule.

There were no significant differences between patients diagnosed with HCC and patients with non-HCC nod-

**Table 2. Final Diagnoses of the 89 Nodules**

| | | <10 mm | 11–15 mm | 16–20 mm | Total |
|---|---|---|---|---|---|
| **HCC nodules** | **HCC** | 2 | 29 | 29 | 60 |
| | **Well-differentiated** | 0 | 15 | 9 | 24 |
| | **Moderately differentiated** | 2 | 8 | 15 | 25 |
| | **Poorly differentiated** | 0 | 6 | 4 | 10 |
| | **Unknown degree** | 0 | 0 | 1 | 1 |
| **Non-HCC nodules** | **Cholangiocarcinoma** | 0 | 1 | 0 | 1 |
| | **Regenerative/dysplastic nodule** | 8 | 13 | 3 | 24 |
| | **Hemangioma** | 3 | 0 | 0 | 3 |
| | **Focal nodular hyperplasia** | 0 | 1 | 0 | 1 |
| **Total** | | 13 (14.6%) | 44 (49.4%) | 32 (36%) | 89 |

Size categorized as <10 mm; 10-15 mm, and 16-20 mm.

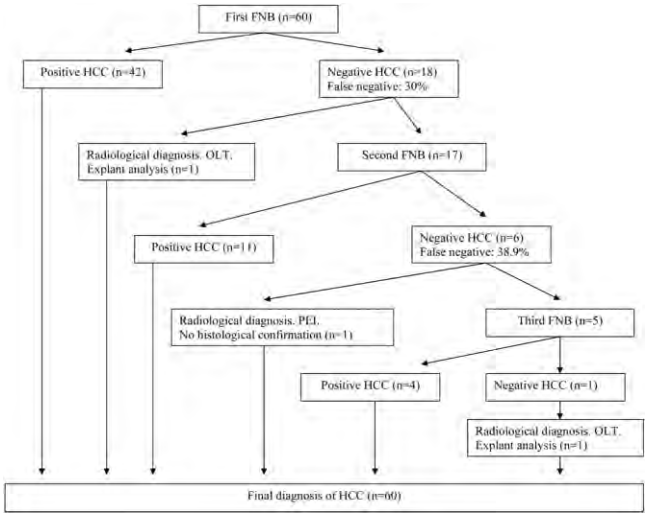


Fig. 2. Accuracy of FNB for HCC diagnosis.

ules in sex, etiology, Child-Pugh class, laboratory parameters, and presence of ascites. Patients with HCC were older (66.5 versus 60 years; $P < 0.05$). The median AFP of HCC patients was 8.5 (range, 1-1154) and 5 (range, 1-170) in the non-HCC cohort. AFP exceeded 20 ng/dL in 24% of the HCC patients, whereas this was registered in 21% of non-HCC patients (nonsignificant difference). There were no differences in the baseline US echogenicity of the nodules. However, 26 of the HCC exhibited a US halo, whereas this was observed in only 3 of the 29 non-HCC nodules ($P = 0.008$). In addition, HCC nodules were significantly larger than non-HCC: only 2 of 13 nodules smaller than 10 mm were diagnosed as HCC, whereas this was the case in 29 of the 32 nodules between 16 and 20 mm ($P < 0.0001$). Twenty-four (40%) of the HCCs were well differentiated, and 25 (42%) were moderately differentiated. In the single HCC case in which repeated biopsies were not diagnostic, the differentiation degree could not be registered. There was no significant association between tumor size and differentiation degree.

***Diagnostic Accuracy of FNB for HCC.*** The accuracy of FNB for HCC diagnosis is summarized in Fig. 2. FNB was not obtained in 5 patients because of confident diagnosis by imaging or technical issues related to proper definition of the nodules at the time of puncturing: all of them were diagnosed as non-HCC nodules (2 hemangiomas and 3 regenerative nodules, 4 of 5 smaller than 10 mm). Accordingly, 84 of the nodules underwent biopsies at least once. In 43 of them, a core-biopsy was obtained together with fine-needle aspiration. The first tissue sampling established the HCC diagnosis in 42 of the 60 cases with HCC. This represents a false-negative rate of 30% at first assessment. A second sampling was done in 17 of these 18 false-negatives, and it established the HCC diagnosis in 11 (61.6%). In 1 patient, the second FNB was not performed because of ascites and liver failure; both CEUS and MRI evidenced nodule growth beyond 2 cm with characteristic dynamic pattern (hypervascularization with washout). The explant analysis demonstrated a poorly differentiated HCC.

One of the 6 patients with 2 consecutive negative biopsies showed a significant growth of the nodule in the dome of the right lobe. Computed tomography and MRI were conclusive for HCC, and ablation was indicated. After initial success, the tumor recurred 9 months later, and diagnosis was thus secured. In 4 cases, HCC was diagnosed at the third biopsy. Median time between the first and third biopsy was 9.6 months (range, 3-23). In all of these cases the third biopsy was indicated because of nodule growth. The patient with 3 negative FNB exhibited nodule growth exceeding 2 cm. Imaging profile was diagnostic for HCC and was listed for transplantation with explant confirmation. There was no significant relationship between diagnostic accuracy of biopsy and nodule size or differentiation degree.

***CEUS and MRI.*** Table 3 summarizes the diagnostic accuracy of CEUS and MRI. CEUS was not evaluable in 3 nodules because of lung interposition; these 3 nodules were finally diagnosed as HCC.

Twenty-four of the 89 nodules were hypovascular by both techniques. Only 2 of the 24 (8.3%) hypovascular nodules were finally diagnosed of HCC, whereas 22 of 29 non-HCC nodules were hypovascular at CEUS and MRI.

Considering the suspicious criteria, CEUS detected 47 of 60 HCC (sensitivity = 78.3%). Four of the 29 non-HCC nodules were misdiagnosed as HCC [false-positive rate (FPR) = 13.8%; specificity = 86.2%]. At MRI, 51 of the 60 HCC were properly diagnosed (sensitivity =

**Table 3. Diagnosis Accuracy of CEUS and MRI**

| | | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value | Likelihood Ratio |
|---|---|---|---|---|---|---|
| **CEUS** | **Suspicious (n = 51)** | 78.3% | 86.2% | 92.2% | 71.4% | 5.682 |
| | **Conclusive (n = 33)** | 51.7% | 93.1% | 93.9% | 50.9% | 7.519 |
| **MRI** | **Suspicious (n = 54)** | 85% | 89.7% | 94.4% | 74.3% | 8.264 |
| | **Conclusive (n = 38)** | 61.7% | 96.6% | 97.4% | 54.9% | 18.182 |

Imaging diagnosis categorized as suspicious (arterial hypervascularization regardless of washout) or conclusive (arterial hypervascularization followed by venous washout). The nodules classified as suspicious include those defined as conclusive and those categorized as suggestive but nonconclusive of HCC.

**Table 4. Diagnosis Accuracy of Combined CEUS and MRI**

| | Sensitivity | Specificity | Positive Predictive Value | Negative Predictive Value |
|---|---|---|---|---|
| **CE-US suspicious MRI suspicious (n = 40)*** | 66.7% | 100% | 100% | 59.2% |
| **CE-US suspicious MRI conclusive (n = 29)†** | 48.3% | 100% | 100% | 48.3% |
| **CE-US conclusive MRI suspicious (n = 28)‡** | 46.7% | 100% | 100% | 47.5% |
| **CE-US conclusive MRI conclusive (n = 20)** | | | | |
| **AASLD criteria positive** | 33.3% | 100% | 100% | 42% |

Imaging diagnosis categorized as suspicious (arterial hypervascularization regardless of washout) or conclusive (arterial hypervascularization followed by venous washout). The nodules classified as suspicious include those defined as conclusive and those categorized as suggestive but nonconclusive of HCC.

*In 3 cases (1 nodule 10–15 mm and 2 nodules 16–20 mm), both techniques suggestive but inconclusive for HCC.

†Nine cases (1 nodule < 10 mm, 3 nodules 10–15 mm, and 5 nodules 16–20 mm); the CEUS was suggestive but inconclusive for HCC.

‡Eight cases (3 nodules 10–15 mm and 5 nodules 16–20 mm); the MRI was suggestive but inconclusive for HCC.

85%), whereas 3 of 29 non-HCC nodules were erroneously classified as HCC (FPR = 10.3%; specificity = 89.7%).

The application of conclusive criteria reduced sensitivity and increased specificity. CEUS accurately diagnosed 31 of the 60 HCC (sensitivity = 51.7%) with specificity raising to 93.9%. A false-positive HCC diagnosis was registered in a 14-mm cholangiocarcinoma and in a 16-mm angioma (FPR = 6.1%). MRI properly characterized both nodules and was able to accurately diagnose 37 of the 60 HCC nodules (sensitivity = 61.7%). There was a single false-positive HCC diagnosis at MRI that was registered in a 12-mm regenerative nodule. This nodule vanished during follow-up that currently goes beyond 30 months (FPR = 2.6%; specificity = 97.4%).

The diagnostic accuracy for HCC diagnosis increased in parallel with nodule size. Thereby, conclusive findings at MRI in nodules larger than 15 mm had a sensitivity of 76% with 100% specificity.

***Evaluation of AASLD Criteria.*** Combination of both techniques offers the best accuracy. Table 4 shows the sensitivity and specificity stratifying findings according to type of pattern by both techniques. The sensitivity of coincidental conclusive findings fitting into the AASLD definitions is markedly reduced (33.3%), but specificity reaches 100%. However, if both techniques would at least be suspicious (1 of them could be conclusive and the other not, or both suspicious), the sensitivity ranges between 46.7% and 48.3%. Because there are only 3 nodules with coincidental suggestive findings, the 100% specificity is not robust enough.

The results in nodules smaller than 10 mm are less informative for HCC diagnosis because only 2 of the 13 nodules were finally diagnosed as HCC. The AASLD guidelines recommend a wait-and-see policy in these very small nodules, and our data also support this aspect of the recommendations for HCC screening and diagnosis.

## Discussion

Confident diagnosis of cancer is a critical step before treatment indication. In most of the malignant diseases, diagnosis is based on biopsy sampling, but development of better imaging techniques and specific tumor markers have permitted establishment of the diagnosis of malignancy in the absence of pathology confirmation. These noninvasive diagnostic criteria are relevant for the management of patients with suspicion of HCC when the detected nodule is of small size. Early small HCC are usually composed of well-differentiated hepatocytes,[19] and this turns the confident diagnosis through examination of FNB samples into a pathology challenge. Their reading requires major expertise, and even so, it is usual to assume a high rate of false-negative reports. Accordingly, some unique studies where such false-negative results are not observed have not been reproduced elsewhere and should be looked at with caution.[20] Studies to evaluate the diagnostic capacity of imaging techniques offer limited information because they just include patients with already diagnosed HCC, either by imaging techniques or by biopsy. In that way, the population is biased by excluding those with nontypical imaging or negative biopsy. Such studies merely serve to validate the usefulness of any technique to establish vascularization[21] but provide no data about diagnostic sensitivity and specificity of any technique for the diagnosis of small nodules within a cirrhotic liver. This information is critical to establish reliable diagnostic criteria for HCC, and for this reason we designed this prospective investigation. It included small (≤2 cm) solitary nodules detected during follow-up US. These represent the target of screening programs. Larger nodules are easily diagnosed, and their treatment is less effective. Tumor growth beyond 2 to 3 cm is usually associated with microscopic vascular invasion/satellites, which are major predictors of recurrence after initial effective therapy.[22].

In our study, diagnosis was based on pathology even if this would require repeated biopsy. In addition, in pa-

tients without malignant diagnosis despite repeated biopsy we established an active follow-up policy to detect evolutionary changes such as growth or change in imaging pattern. If this would be observed, new biopsy procedures and intensive evaluation would be repeated. As a whole, the study aimed to define the nature of small nodules detected during screening in a cirrhotic liver and to evaluate the diagnostic accuracy of imaging techniques for small HCC, hence aiming to prospectively validate the noninvasive diagnostic criteria as recently proposed by AASLD.

We have recruited a cohort of patients with cirrhosis in whom a solitary nodule 2 cm or smaller was detected during US screening. The prevalence of HCC in our study was 67.4% (60/89), there being no previous prospective studies with similar design against which to compare this figure. Previous investigations have included all nodule sizes or just those nodules that show vascular uptake or those with positive biopsy. In our study, the sole criteria for selection was detection of a solitary nodule 2 cm or smaller, and this makes our investigation highly novel and unique. Patients were prospectively recruited on detection of a nodule between 5 and 20 mm on US screening, and the sole requirement to classify a nodule as a target was its recognition in at least 2 US views from different angles. If we would have recruited patients with multiple nodules, the prevalence of HCC might with have been higher and the same would have happened if the US detection of hepatic nodules had only registered those with a highly suspicious imaging appearance. The same would apply if cases had been selected because of an arterial blood flow pattern on baseline US-Doppler or immediately after CEUS. Clearly, detection of such small solitary nodules requires expert explorers, but this request for quality and expertise should be the case in any diagnostic intervention in patients. In addition to HCC nodules, we had 28 benign nodules (most of them classified as regenerative/dysplastic nodules, but also including 1 focal nodular hyperplasia and 3 angioma). Finally, we had a single case of cholangiocarcinoma, a neoplasm that while not as frequent as HCC may also appear in a cirrhotic liver.[23] In summary, our cohort offers a representative and large enough population to offer reliable data.

The study offers several relevant findings. The first of them is the low likelihood of nodules smaller than 10 mm being an HCC (only 2 of 13 nodules in our cohort) that together with the difficulty of obtaining an FNB in these tiny nodules reinforces the recommendation of close follow-up before initiating an active workup proposed by the AASLD. Secondly, as previously known, a first FNB is able to establish HCC in a major proportion of patients (70% in our series). However, in a relevant number, the diagnosis will require a second or third sampling, either at baseline or during follow-up when some evolutionary change reinforces the suspicion of malignancy. Tumor location and risk considerations prevented both approaches in all cases, and this stresses that the study reflects the difficulties of real clinical practice. Nevertheless, our most important result is that imaging techniques are accurate enough to establish diagnosis without requesting biopsy. Sensitivity and specificity figures are encouraging, but for HCC diagnosis the tool to be used in practice has to exhibit a 100% specificity to avoid false positives. This is why the AASLD criteria were developed, and in our study we unequivocally validate their value.

Our data show that the use of a single technique may raise the wrong diagnosis, and this affects both CEUS and MRI. Not surprisingly, if using only suspicious pattern (arterial contrast uptake regardless washout), the number of false positives (4 for CEUS and 3 for MRI in separate patients) is higher than when using the conclusive definitions (arterial uptake followed by washout). In this last scenario, we had 2 false positives for CEUS (one 14-mm cholangiocarcinoma and one 16-mm angioma) and 1 false positive for MRI (a regenerative nodule that experienced spontaneous necrosis and disappeared during follow-up). When both diagnostic techniques were used together and coincidental findings were requested, the false positives were eliminated. This indicates that even in experienced hands the reading of dynamic imaging techniques in tiny hepatic nodules is not easy, and as a consequence, the prudent guideline requirement to have coincidental findings to establish HCC diagnosis is worth being maintained. If false-positive diagnoses occur in experienced centers, the likelihood for such a mistake will surely be higher in nonreferral settings.[12] It could be argued that MRI specificity in nodules larger than 15 mm was 100%, and hence MRI could be enough in these larger nodules. The same could be argued for the detection of a suggestive pattern by 1 technique while the other was conclusive. The number of cases in each of these instances is limited and until further data are obtained it is advisable to remain on the safe side. The experience accumulated in the United Network for Organ Sharing shows that there is a major need to homogenize the diagnostic and staging criteria for HCC to avoid the misuse of organs.[12] Thus, before proposing a diagnostic policy that would be properly applied in a very limited number of sites, it is preferable to retain a cautious approach and recommend the current guidelines.

Obviously the application of stringent diagnostic criteria results in a limited sensitivity that implies that in up to 67% of the patients with HCC 2 cm or smaller the diagnosis will rely on a positive biopsy. Improvement in

the information offered by imaging techniques may allow the incorporation of new definitions and further reduce the need for biopsy, but these additional parameters are not available. The lack of sensitivity raises an important observation. Some authors have suggested that if a small nodule in a cirrhotic liver does not exhibit contrast uptake in the arterial phase, its malignant nature is ruled out and no additional explorations have to be performed. This concept has been proved wrong.[21] Such nodules may already be HCC, and patients may benefit from treatment leading to long-term cure, an option that might be gone with larger tumor size. If the suspicion of HCC is delayed until detection of arterial vascularization or further growth, the tumor stage is often more advanced. Pathology studies in HCC smaller than 20 mm in size have shown that the risk of microscopic vascular invasion and satellite nodules significantly increases when tumor size exceeds 2 cm and acquires the characteristic arterial blood supply.[19] Hence, the diagnosis of the very early HCC or carcinoma *in situ* entity that has the highest likelihood for cure with resection or ablation requires diagnosis before that afforded by the current capability of imaging techniques.[22] Obviously, diagnosing by biopsy and pathology reading of minute nodules will remain a challenge, and this has prompted several groups facing this problem to develop research programs to investigate new diagnostic tools based on immunostaining,[24] gene expression assessment,[25,26] or protein profiling.[27] Several promising results have been raised through the study of surgical samples, but no validation in biopsy tissues from small tumors is available, and this is where future research will have to focus.

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# Cholangiocarcinoma in Cirrhosis: Absence of Contrast Washout in Delayed Phases by Magnetic Resonance Imaging Avoids Misdiagnosis of Hepatocellular Carcinoma

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**This study assesses the magnetic resonance (MR) features of intrahepatic cholangiocarcinoma (ICC) in patients with cirrhosis with specific analysis of the contrast enhancement pattern. Cholangiocarcinoma may show increased contrast uptake in the arterial phase, and, if washout in the delayed venous phase were to be detected, the noninvasive diagnostic criteria proposed in the American Association for the Study of Liver Diseases guidelines would be refuted. We reviewed the MR findings of 25 patients with cirrhosis with 31 histologically confirmed ICC nodules. Signal intensity on basal T1-weighted and T2-weighted images and characteristics of enhancement after contrast administration on arterial, portal, and delayed phase were registered. Enhancement pattern was defined according to the behavior of the lesions in each phase, and dynamic pattern was described according to the progression of enhancement throughout the different phases. The most frequent pattern displayed by ICC was a progressive contrast uptake (80.6%). Stable contrast enhancement was registered in 19.4%. None of the ICCs showed a washout pattern, a profile that is specific for hepatocellular carcinoma (HCC). The ICC dynamic behavior differed significantly according to tumor size: progressive enhancement pattern was the most frequent (20 of 25 cases) in lesions larger than 20 mm, whereas the stable pattern was mainly identified in nodules smaller than 20 mm. The most characteristic MR contrast pattern in ICC in cirrhosis is a progressive contrast uptake throughout the different phases, whereas contrast washout at delayed phases is not observed. Because stable enhancement pattern without washout also can be registered in small HCC nodules, the evaluation of delayed phase is mandatory for a proper nodule characterization. If washout is not registered, a biopsy should be mandatory for diagnosis.** (HEPATOLOGY **2009;50:000-000.**)

The incidence of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) has experienced a marked increase in recent decades.[1,2] HCC appears mainly in the setting of cirrhosis, and this neoplasia has become the main cause of death in this population.[3] In addition, cirrhosis, mainly secondary to chronic infection with hepatitis C virus, has been recognized as an important risk factor for ICC development, and this association may be the cause of the increasing incidence of ICC in recent years.[4,5] It is critical to accurately distinguish both entities, because the prognosis and treatment are markedly different. In fact, patients diagnosed with liver cirrhosis are the target of early detection plans to diagnose HCC at an early stage, when it may be treated by effective options such as resection, transplantation, or percutaneous ablation.[6,7] Screening is done by imaging techniques, namely, ultrasound, and on detection of a suspicious nodule, the diagnosis may be established by biopsy or by imaging techniques.[6] These have to be highly specific to avoid false-positive results. Major information is available to characterize the HCC dynamic

*Abbreviations: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MR, magnetic resonance.*

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*Received March 17, 2009; accepted May 5, 2009.*

*This study has been performed within the cooperation framework established by the Transversal Cancer Action approved by the Council of Ministers on October 11, 2007 in accordance with the agreement between The Carlos III Health Institute (ISCIII), which is an autonomous entity currently belonging to the Ministry of Science and Innovation, and the Spanish Biomedical Research Network (CIBER) for the area of hepatic and digestive disorders. Supported in part by grants of the Instituto de Salud Carlos III (grant PI 06/132 and PI 08/0146). A.F. is partially supported by a grant of the Instituto de Salud Carlos III (PI 05/645). Maria Reig and Carlos Rodriguez de Lope are funded by a grant of the BBVA foundation.*

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*Published online in Wiley InterScience (www.interscience.wiley.com).*

*DOI 10.1002/hep.23071*

*Potential conflict of interest: Nothing to report.*

imaging pattern after contrast administration at ultrasound, computed tomography, and magnetic resonance: intense arterial uptake followed by washout in the venous phase by dynamic imaging techniques. This has allowed us to define noninvasive imaging criteria to diagnose HCC in the setting of liver cirrhosis.[6,8] However, as previously commented, HCC is not the sole malignancy that may appear in liver cirrhosis. ICC also may complicate cirrhosis, and in most centers it constitutes a contraindication for liver transplantation.[4,9] Several reports have described the imaging appearance of ICC by magnetic resonance (MR) in persons without cirrhosis[10-13] and suggest that in large tumors within a noncirrhotic liver the diagnostic challenge may not be relevant. Contrarily, on detection of a small nodule during screening in a patient with liver cirrhosis, the diagnostic difficulties may be higher. No previous studies have specifically reviewed the ICC MR findings in patients with cirrhosis, a specific population in whom portal hypertension and associated circulatory disturbances may induce a particular profile. Both HCC and ICC can have an increased arterial vascularization, and there is no information about the potential relationship between imaging profile and tumor size, and to which extent small arterialized ICCs may present washout in the venous/delayed phase. If this should occur, the American Association for the Study of Liver Diseases diagnostic criteria would be invalidated. Hence, data collected in series with advanced ICC will not serve to define the radiology pattern at early stages.[14]

The purpose of this study was to assess the MR features of ICC in the setting of cirrhosis, taking into account the nodule size and placing special emphasis on the enhancement pattern and the differential diagnosis with HCC.

## Patients and Methods

***Patients.*** We retrospectively reviewed the radiological images of all patients with ICC and cirrhosis consecutively registered in our institution between September 2001 and December 2008. The inclusion criteria were as follows: (1) pathology-confirmed diagnosis of ICC by percutaneous biopsy or surgical specimen analysis. Patients with mixed hepatocellular–cholangiocarcinoma were excluded; (2) patients with an abdominal MR performed at our institution following our standard protocol for focal hepatic lesion (see below); (3) patients with cirrhosis diagnosed by imaging (nodular or irregular liver surface and liver parenchyma heterogenicity with evidence of portal hypertension),[15-18] pathology, or clinical criteria.

***Image Acquisition.*** MR was performed in all patients with a 1.5-T MR system (Symphony, Siemens Medical Systems, Erlangen, Germany; and SIGNA CVi, General Electric Medical System, Milwaukee, WI), using a phased-array coil for signal detection. All patients underwent transverse T1-weighted in-phase and out-of-phase gradient echo, slice thickness of 5 mm, transverse T2-weighted breath-hold, slice thickness of 5 mm, and axial dynamic multiphasic contrast-enhanced three-dimensional image of the liver with fat suppression before and after gadolinium contrast administration (gadodiamide 0.5 mmol/L Ominscan-Amersham, Madrid, Spain), with a slice thickness of 2.5 to 3 mm. Arterial-phase images were acquired approximately 20 seconds after contrast injection. Portal venous and delayed-phase images were acquired 60-65 and 100-110 seconds thereafter. Finally, a T1-weighted gradient echo with fat suppression MR imaging was performed 5 minutes after contrast injection.

***Image Analysis.*** MR findings were retrospectively analyzed in consensus by two abdominal radiologists (J.R. and C.A.) with 5 and 20 years of experience in abdominal radiology, respectively. Each lesion was evaluated as following: size of the lesion, hepatic capsule retraction, and presence of satellite nodules and central scar.

The signal on pre-contrast T1-weighted and T2-weighted sequences was recorded. After endovenous contrast administration, the signal through each of the different phases was registered as follows: (1) globally hyperintense: increased signal, relative to the liver parenchyma, involving the totality of the lesion; (2) partially hyperintense: increased signal involving more than 25% of the lesion, except the central area, (3) peripherally hyperintense: increased signal limited to the periphery of the lesion, involving less than 25% of its area, resembling a rim-like pattern (Fig. 1).

Additionally, a dynamic pattern of enhancement was defined according to the analysis of the progression of endovenous contrast enhancement over the progressive different phases of the study, as follows: (1) stable, persistent contrast enhancement: the nodule enhancement remains invariable through the arterial and venous phases; (2) progressive contrast enhancement: the nodule enhances progressively over time, reaching maximal intensity in delayed phases; (3) washout: intense contrast uptake during the arterial phase followed by contrast washout in delayed phases (Figs. 2-4)

***Statistical Analysis.*** Data were analyzed on a by-lesion basis. Quantitative variables were expressed as median and range and categorically as count and proportions. Differences in signal intensity in baseline and postcontrast sequences and in dynamic enhancement pattern according to nodule size ($\leq$2 cm, 2-3 cm, and $>$3 cm) were evaluated by the chi-squared test/Fisher's exact test for categorical variables. A conventional $P$ value less

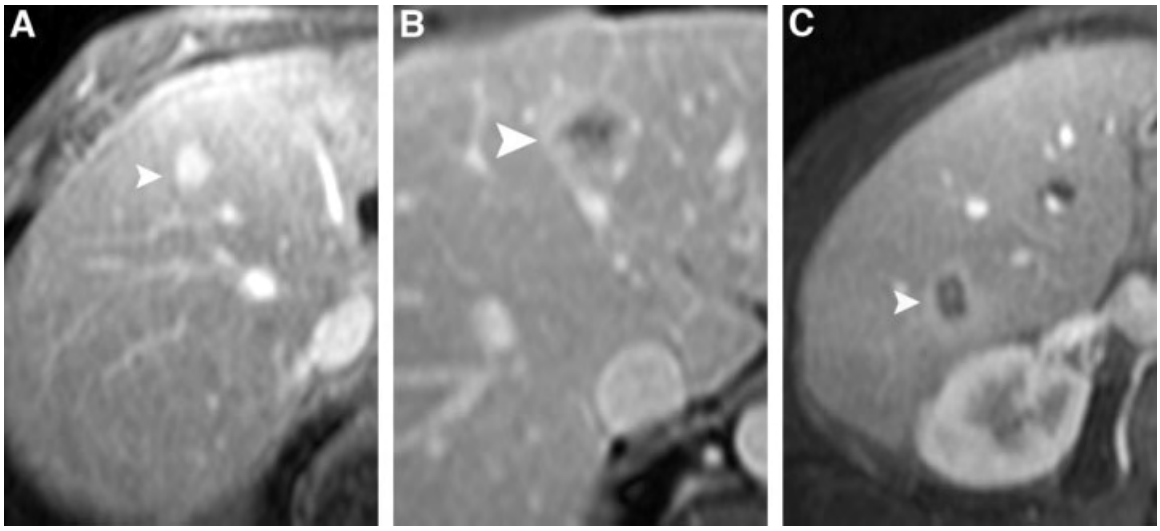


Fig. 1. Examples of enhancement of ICC (arrowheads) on T1 after intravenous contrast administration in each specific phase: (A) globally hyperintense, (B) partially hyperintense, and (C) peripherally hyperintense.

than 0.05 was considered significant. Calculations were done with SPSS package version 13 (SPSS Inc., Chicago, IL).

## Results

***Baseline Patient Characteristics.*** A total of 25 patients (17 men and 8 women; median age, 62; range, 49-79 years) met all the criteria to collect the ICC cohort. Twenty patients had uninodular ICC (80%); and five, multifocal (four patients had two nodules [16%], and one patient had three nodules [4%]). In the five cases with more than one nodule, all were located in a different segment and thus were not read as a peripheral satellite nodule.

Cirrhosis was confirmed by pathology assessment in 13 patients and by unequivocal clinical and imaging criteria in the remaining cases. Causes of liver cirrhosis included chronic hepatitis C virus infection (14 patients), alcohol abuse (six patients), hemochromatosis (one patient), chronic hepatitis C virus infection combined with alcohol abuse (two patients), and cryptogenetic (two patients). Child-Pugh class stage[19] at diagnosis was A (24 patients) and B (one patient). Final diagnosis of ICC was confirmed by resected specimen analysis in 13 patients and by ultrasonography-guided percutaneous liver biopsy in 12 patients. The main patient characteristics are summarized in Table 1.

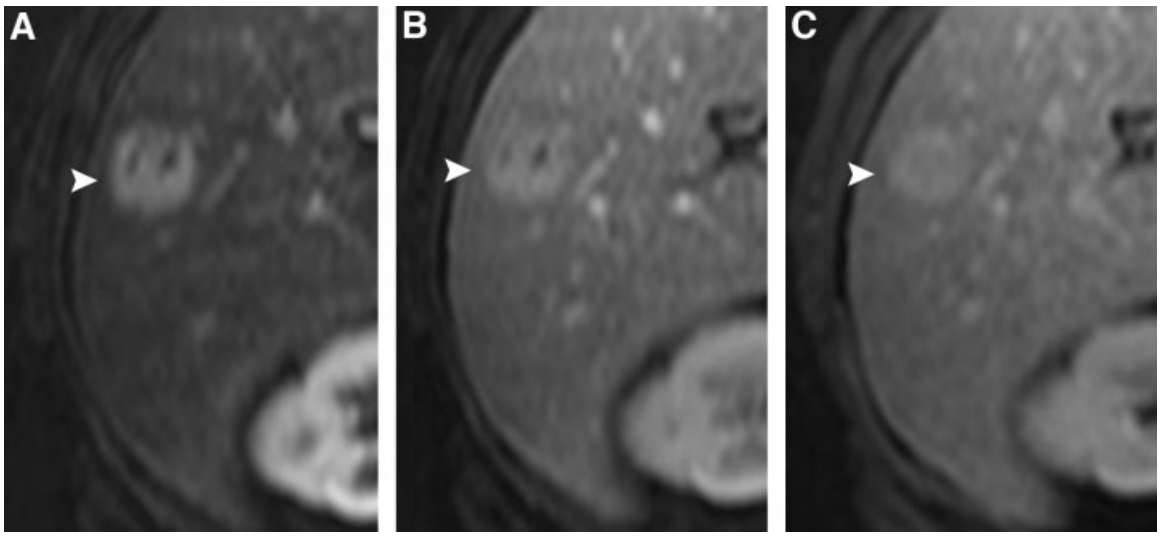


Fig. 2. A 57-year-old woman with intrahepatic cholangiocarcinoma in right lobe of the liver (arrowheads). MR 3D T1 GE in axial plane acquired on (A) arterial, (B) portal, and (C) delayed phases after intravenous contrast administration that shows progressive uptake of intravenous contrast until complete enhancement of the lesion.

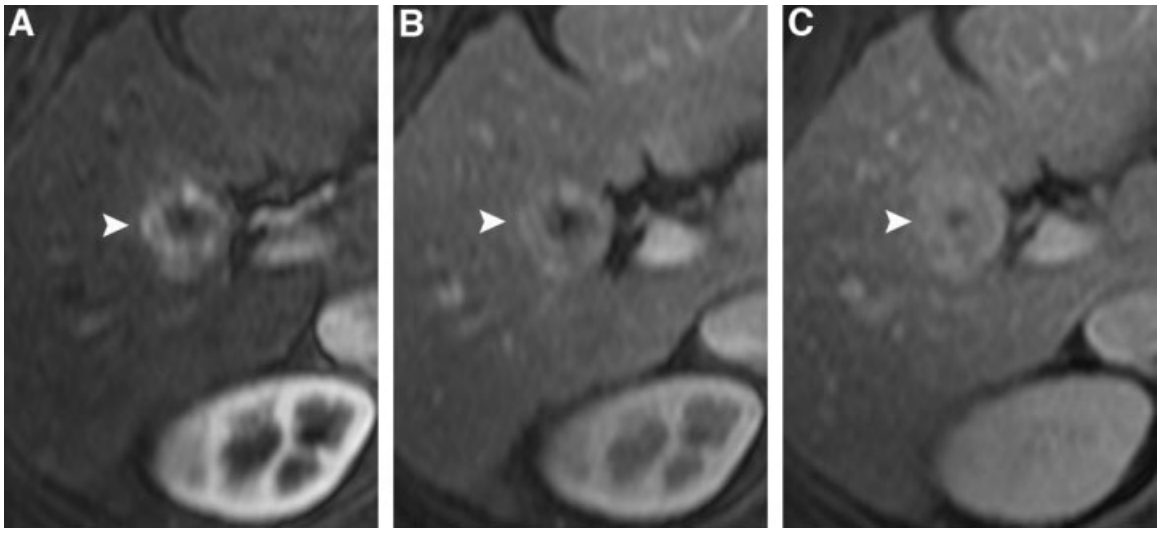


Fig. 3. A 53-year-old man with intrahepatic cholangiocarcinoma in right lobe of the liver (arrowheads). MR 3D T1 GE in axial plane acquired on (A) arterial, (B) portal, and (C) delayed phases after intravenous contrast administration that shows progressive uptake of intravenous contrast except in the central area of the tumor.

***Morphologic MR Features.*** A total of 31 nodules with histological diagnosis of ICC were analyzed, and the main characteristics are summarized in Tables 2 and 3. The median size was 25 mm (range, 13-87). In 9 of 31 cases (29%), the nodule was equal to or smaller than 2 cm; in 11 cases (35.5%), between 2 and 3 cm; and in the remaining 11 nodules (35.5%), the nodule size was larger than 3 cm. A tumor scar was present in seven nodules (22.6%), retraction of the hepatic capsule was seen in seven cases (22.6%), and satellites were demonstrated in eight cases (25.8%).

On T1-weighted sequences, 25 nodules (80.6 %) appeared as hypointense and the remaining six lesions (19.4%) as isointense. On T2-weighted images, 22 nodules (71%) appeared as hyperintense, three (9.7%) as heterogeneous mass with areas of different signal, five (16.1%) as isointense relative to the hepatic parenchyma, and one (3.2%) as hypointense. On arterial phase, 26 lesions (83.8%) were peripherally hyperintense, three nodules (9.7%) partially hyperintense, and two lesions (6.5%) were globally hyperintense. On portal venous phase, 19 lesions (61.3%) were partially hyperintense, 10

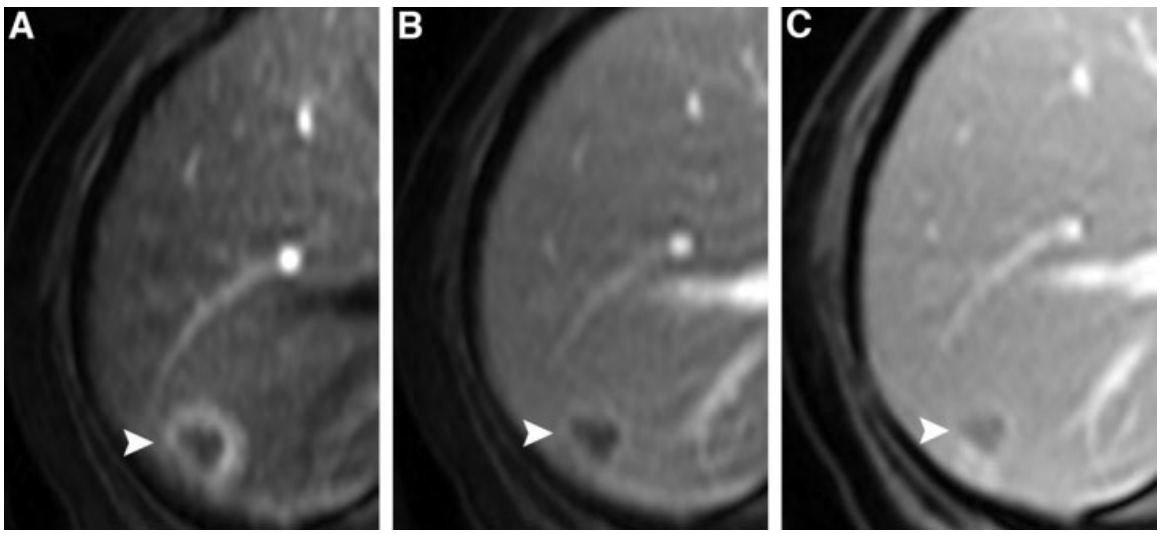


Fig. 4. Seventy-year-old woman with intrahepatic cholangiocarcinoma in right lobe of the liver (arrowheads). MR 3D T1 GE in axial plane acquired on (A) arterial, (B) portal, and (C) delayed phases after intravenous contrast administration that shows peripheral rimlike enhancement of the lesion stable during all phases of the dynamic study.

**Table 1. Main Patient and Tumor Characteristics**

| Characteristic | Value |
|---|---|
| Age median (range), (years) | 62 (49–79) |
| Male/female (n) | 17/8 |
| Cause (n): | |
| HCV | 14 |
| Ethanol | 6 |
| Hemochromatosis | 1 |
| HCV + ethanol | 2 |
| Cryptogenetic | 2 |
| Child-Pugh A/B (n) | 24/1 |
| AST median (range), (UI/L) | 48 (24–149) |
| ALT median (range), (UI/L) | 50 (15–167) |
| AP median (range), (UI/L) | 197 (121–846) |
| GGT median (range), (UI/L) | 65 (17–537) |
| Prothrombin ratio median (range), (%) | 90 (60–100) |
| Bilirubin median (range), (mg/dL) | 1 (0.5–17.5) |
| Platelets median (range), ($10^9$/L) | 152 (43–262) |
| Albumin median (range), (g/dL) | 42 (27–47) |
| Nodule size median (range), (mm) | 25 (13–87) |
| ≤20 mm (n) | 9 |
| 21–30 mm (n) | 11 |
| >20 mm (n) | 11 |
| Number of nodules: 1/2/3 (n) | 20/4/1 |

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HCV, hepatitis C virus.

lesions (32.3%) peripherally hyperintense, and two lesions (6.5%) were globally hyperintense. Finally, on delayed phase, 14 nodules (45.2%) appeared globally hyperintense; in 13 lesions (41.9%) the signal was partially hyperintense; and the remaining four nodules (12.9%) displayed a peripheral hyperintensity. None of the ICC nodules was isointense or hypointense compared with the surrounding liver parenchyma during the dynamic study.

***Patterns of Enhancement.*** Analysis of the vascular dynamic enhancement pattern throughout the different phases of the study showed that 25 lesions (80.6%) had a progressive contrast enhancement: in 12 nodules, the contrast uptake progressed until complete enhancement of the lesion, and in 13 lesions the contrast uptake progressed but a small central area remained unenhanced. The remaining six lesions (19.4%) showed a stable contrast enhancement during the dynamic study: four lesions displayed a stable, peripheral, rim-like contrast enhancement, and two lesions showed a global contrast enhancement during the dynamic study (Table 4).

***MR Findings According the Nodule Size.*** There were no significant differences in MR appearance of ICC on T1-weighted and T2-weighted sequences, presence of satellites, capsular retraction, or intralesional scar and on the arterial phase enhancement according to nodule size (≤2, 2-3, and >3 cm) (Table 3). However, the only two nodules globally hyperintense in arterial phase were smaller than 2 cm. In the portal phase, no nodule larger than 2 cm displayed global hyperintense signal, and in almost all nodules greater than 3 cm (10 cases, 90.9%), the nodule signal was partially hyperintense ($P = 0.03$). In the delayed phase, 13 of 20 nodules smaller than 3 cm (65%) showed a global enhancement compared with only one of 11 nodules (9.1%) larger than 3 cm ($P = 0.014$).

Taking into account the dynamic vascular pattern previously defined, 20 of 22 nodules (90.9%) larger than 2 cm displayed a progressive contrast enhancement compared with only five of nine (55.6%) nodules smaller than 2 cm. Contrarily, the stable pattern was more frequently identified in nodules smaller than 2 cm (four of nine nodules, 44.4%) than in larger nodules (2 of 22, 9.1%) ($P = 0.043$). Finally, the washout pattern was not identified in any patient. These differences related to size achieved statistical significance ($P = 0.001$).

## Discussion

Our findings provide valuable information for the accurate diagnosis of small hepatic nodules detected in patients with cirrhosis. Screening of this population is advocated to detect HCC at an early stage. However, not all nodules arising within a cirrhotic liver are malignant, nor are they always an HCC. It is well known that cirrhosis is a risk factor for ICC, and hence, this entity should be taken into consideration because the clinical management is sharply different, and thus, the need to distinguish between the two is not trivial.[4] Liver transplantation is an established treatment option for HCC, but it is not usually considered for ICC. In fact, in the current United Network for Organ Sharing criteria for liver allocation, clear-cut diagnostic criteria for HCC are demanded to be enlisted for transplantation and receive priority points.[4]

The results of our study show that the imaging profile of ICC in the setting of cirrhosis is characterized in most cases by a progressive enhancement after contrast administration. Interestingly, the extent of enhancement is related to tumor size. Hence, in small (≤3 cm) ICCs, the enhancement affects the whole tumor mass, whereas in large (>3 cm) ICCs, the uptake is incomplete, resembling the classic findings of ICCs in the noncirrhotic population.[14] A stable enhancement pattern is mostly seen in ICCs smaller than 2 cm. Thereby, 50% of those small ICC nodules exhibit hypersignal in all phases and the other 50% show peripheral enhancement. The first pattern may be observed in a small proportion of small HCCs,[8] and if radiologists are not aware of this potential similarity between ICC and HCC, risk is present of false HCC diagnosis.

Progressive contrast enhancement along the different phases of the dynamic study also may be seen in hemangiomas. However, in this entity, the contrast enhance-

**Table 2. MRI Characteristics of ICC at Baseline and After Intravenous Contrast Enhancement in Arterial, Portal, and Delayed Phase, and Vascular Dynamic Enhancement Pattern Defined According to the Analysis of the Progression of Intravenous Contrast Enhancement Throughout the Progressive Different Phases of the Study**

| Id | Age | Size | T1-w | T2-w | Scar | Satellites | Capsular Retraction | Arterial Phase Enhancement | Portal Phase Enhancement | Delayed Phase Enhancement | Dynamic Pattern |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 74 | 19 | Hypo | Iso | No | No | No | Globally hyper | Globally hyper | Globally hyper | Stable |
| 2 | 64 | 28 | Hypo | Iso | Yes | Yes | No | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 3 | 58 | 70 | Hypo | Hyper | No | Yes | Yes | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 4 | 79 | 45 | Hypo | Heterog | Yes | No | Yes | Partially hyper | Partially hyper | Partially hyper | Progressive |
| 5 | 63 | 67 | Hypo | Hyper | Yes | Yes | Yes | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 6 | 54 | 87 | Hypo | Hyper | No | No | No | Partially hyper | Partially hyper | Partially hyper | Progressive |
| 7 | 71 | 44 | Hypo | Hyper | No | Yes | Yes | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 8 | 61 | 30 | Iso | Hyper | No | No | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 9 | 64 | 25 | Hypo | Hyper | No | No | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| | | 14 | Hypo | Hyper | No | Yes | Yes | Peripherally hyper | Peripherally hyper | Globally hyper | Progressive |
| 10 | 69 | 51 | Hypo | Heterog | Yes | No | No | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| | | 20 | Hypo | Hyper | No | Yes | No | Peripherally hyper | Peripherally Hyper | Peripherally hyper | Stable |
| | | 15 | Hypo | Hyper | No | No | No | Peripherally hyper | Peripherally hyper | Peripherally hyper | Stable |
| 11 | 49 | 24 | Hypo | Hyper | Yes | No | Yes | Peripherally hyper | Peripherally hyper | Peripherally hyper | Stable |
| 12 | 63 | 24 | Hypo | Heterog | No | No | No | Peripherally hyper | Peripherally hyper | Globally hyper | Progressive |
| | | 16 | Hypo | Hyper | No | Yes | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 13 | 53 | 36 | Hypo | Hyper | Yes | No | No | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 14 | 77 | 23 | Iso | Hyper | No | Yes | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 15 | 56 | 15 | Hypo | Hyper | No | No | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 16 | 62 | 13 | Iso | Iso | No | No | No | Globally hyper | Globally hyper | Globally hyper | Stable |
| | | 20 | Iso | Hyper | No | No | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 17 | 59 | 29 | Hypo | Hyper | No | No | Yes | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 18 | 49 | 25 | Hypo | Hypo | Yes | No | No | Peripherally hyper | Peripherally hyper | Partially hyper | Progressive |
| 19 | 51 | 28 | Hypo | Hyper | No | No | No | Peripherally hyper | Peripherally hyper | Partially hyper | Progressive |
| 20 | 57 | 22 | Hypo | Hyper | No | No | No | Peripherally hyper | Peripherally hyper | Globally hyper | Progressive |
| 21 | 78 | 34 | Hypo | Hyper | No | No | No | Peripherally hyper | Partially hyper | Globally hyper | Progressive |
| 22 | 57 | 24 | Hypo | Hyper | No | No | No | Partially hyper | Partially hyper | Globally hyper | Progressive |
| 23 | 61 | 35 | Iso | Iso | No | No | No | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| | | 20 | Iso | Iso | No | No | No | Peripherally hyper | Peripherally hyper | Partially hyper | Progressive |
| 24 | 68 | 38 | Hypo | Hyper | No | No | No | Peripherally hyper | Partially hyper | Partially hyper | Progressive |
| 25 | 66 | 35 | Hypo | Hyper | No | No | No | Peripherally hyper | Peripherally hyper | Peripherally hyper | Stable |

Hypo, hypointense relative to the liver parenchyma; Hyper, hyperintense relative to the liver parenchyma; Iso, isointense relative to the liver parenchyma; Heterog, heterogeneity of the signal of the lesion.

ment starts with a characteristic peripheral nodular enhancement, opposite of the rim-like peripheral enhancement of ICC, which precludes its misdiagnosis as ICC.[20]

Our findings reinforce the need to define the enhancement pattern of any lesion by registering the findings of all dynamic phases after contrast administration. This is key if the aim is to confidently distinguish HCCs from other lesions in cirrhotic liver. Thereby, none of our ICCs displayed contrast washout at delayed phases, a characteristic that is specific to HCC and is the backbone of the noninvasive diagnostic criteria as proposed in the American Association for the Study of Liver Diseases guidelines that have been recently validated.[6,8] The observation of the complete contrast uptake in small nodules within a cirrhotic liver could raise the diagnosis of HCC if there is no awareness of the fact that small ICCS can display this profile that also may be observed in some early HCCs.

Our findings and data from other authors in patients without cirrhosis show that a progressive enhancement pattern is highly suggestive of ICC.[11,12,21] However, this pattern overlaps with that which may be observed in HCC nodules.[8] Accordingly, its identification in the setting of cirrhosis cannot allow a definitive ICC diagnosis by MR imaging. Therefore, if the nodule exhibits a progressive contrast enhancement and absence of washout in delayed phases, independently of its size, biopsy of the lesion should be considered mandatory. Obviously, ICC is highly likely,[10-14] but an HCC cannot be discarded. Alpha-fetoprotein will be of no value in this diagnostic effort, because it can be increased in both entities. Similarly, there is no reason to use tumor growth as diagnostic criteria. Both ICC and HCC will exhibit growth as this finding corresponds to malignant entities.

Finally, the characteristic rim-like pattern was only demonstrated in four nodules of 35 mm, 24 mm, 20 mm, and 15 mm. This peripheral rim enhancement may be misread as washout in delayed phases by inexpert radiologists. In our series, the lesions that displayed a peripheral rim-like enhancement in delayed phase showed the same

**Table 3. Analysis of Differences in ICC Group in the Basal, Specific Contrast Enhancement in Each Phase and Vascular Dynamic Enhancement Pattern According to Nodule Size**

| | Total (n = 31) | < 20 mm (n = 9) | 21–30 mm (n = 11) | >30 mm (n = 11) | P |
|---|---|---|---|---|---|
| T1-weighted | | | | | |
| Hypointense, n (%) | 25 (80.6%) | 6 (66.7%) | 9 (81.8%) | 10 (90.9%) | NS |
| Isointense, n (%) | 6 (19.4%) | 3 (33.3%) | 2 (18.2%) | 1 (9.1%) | |
| T2-weighted | | | | | |
| Hyperintense, n (%) | 22 (71%) | 6 (66.7%) | 8 (72.7%) | 8 (72.7%) | NS |
| Isointense, n (%) | 5 (16.1%) | 3 (30.3%) | 1 (9.1%) | 1 (9.1%) | |
| Heterogeneous, n (%) | 3 (9.7%) | 0 (0%) | 1 (9.1%) | 2 (18.2%) | |
| Hypointense, n (%) | 1 (3.2 %) | 0 (0%) | 1 (9.1%) | 0 (0%) | |
| Satellites | | | | | |
| Yes, n (%) | 8 (25.8%) | 3 (33.3%) | 2 (18.2%) | 3 (27.3%) | NS |
| No, n (%) | 23 (74.2%) | 6 (66.7%) | 9 (81.8%) | 8 (72.7%) | |
| Intralesional scar | | | | | |
| Yes, n (%) | 7 (22.6%) | 0 (0%) | 3 (27.3%) | 4 (36.4%) | NS |
| No, n (%) | 24 (77.4%) | 9 (100%) | 8 (72.7%) | 7 (63.6%) | |
| Capsular retraction | | | | | |
| Yes, n (%) | 7 (22.6%) | 1 (11.1%) | 2 (18.2%) | 4 (36.4%) | NS |
| No, n (%) | 24 (77.4%) | 8 (88.9%) | 9 (81.8%) | 7 (63.6%) | |
| Signal in arterial phase | | | | | |
| Globally hyperintense, n (%) | 2 (6.5%) | 2 (22.2%) | 0 (0%) | 0 (0%) | NS |
| Partially hyperintense, n (%) | 3 (9.7%) | 0 (0%) | 1 (9.1%) | 2 (18.2%) | |
| Peripherally hyperintense, n (%) | 26 (83.8%) | 7 (77.8%) | 10 (90.9%) | 9 (81.8%) | |
| Signal in portal phase | | | | | |
| Globally hyperintense, n (%) | 2 (6.5%) | 2 (22.2%) | 0 (0%) | 0 (0%) | 0.03 |
| Partially hyperintense, n (%) | 19 (61.3%) | 3 (33.3%) | 6 (54.5%) | 10 (90.9%) | |
| Peripherally hyperintense, n (%) | 10 (32.2%) | 4 (44.5%) | 5 (45.4%) | 1 (9.1%) | |
| Signal in delayed phase | | | | | |
| Globally hyperintense, n (%) | 14 (45.2%) | 6 (66.7%) | 7 (63.6%) | 1 (9.1%) | 0.014 |
| Partially hyperintense, n (%) | 13 (41.9%) | 1 (11.1%) | 3 (27.3%) | 9 (81.8%) | |
| Peripherally hyperintense, n (%) | 4 (12.9%) | 2 (22.2%) | 1 (9.1%) | 1 (9.1%) | |
| Pattern of enhancement | | | | | |
| Progressive, n (%) | 25 (80.6%) | 5 (55.6%) | 10 (90.9%) | 10 (90.9%) | 0.04* |
| Stable, n (%) | 6 (19.4%) | 4 (44.4%) | 1 (9.1%) | 1 (9.1%) | |
| Washout, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | |

*Comparison between nodules ≤2 and ≥2 cm.

pattern in arterial phase. Moreover, ICC lesions that enhanced homogenously in arterial phase have the same pattern in delayed phase.

Although the pattern of ICC described in our study is well defined in patients without underlying liver disease,[4,10-14] there is limited information about the characteristics of ICC in patients with cirrhosis and, more importantly, when the tumor is detected at an earlier stage. To our knowledge, only Kim and collaborators have intentionally investigated the ICC features on dynamic computed tomography imaging in patients affected with cirrhosis.[22] Interestingly, Kim et al. indicated that a significant number of ICC nodules displayed washout, and this could be taken as a potential for a false-positive diagnosis of HCC if applying noninvasive criteria. However, in this study, the mean diameter of the tumors was larger, the imaging technique evaluated was computed tomography, and only arterial and portal phases were described, omitting the valuable information of the delayed phases.

**Table 4. Analysis of Differences of Dynamic Pattern of Enhancement of the ICC According to the Diameter**

| Pattern of Enhancement of ICC | Total (n = 31) | ≤ 20 mm (n = 9) | 21–30 mm (n = 11) | > 30 mm (n = 11) | P |
|---|---|---|---|---|---|
| Progressive, n (%) | 25 (80.6%) | 5 (55.6%) | 10 (90.9%) | 10 (90.9%) | 0.01 |
| Complete, n (%) | 12 (38.7%) | 4 (44.4%) | 7 (65.5%) | 1 (9.1%) | |
| Incomplete, n (%) | 13 (41.9%) | 1 (11.1%) | 3 (27.3%) | 9 (81.8%) | |
| Stable, n (%) | 6 (19.4%) | 4 (44.4%) | 1 (9.1%) | 1 (9.1%) | |
| Peripheral, rim-like, n (%) | 4 (12.9%) | 2 (22.2%) | 1 (9.1%) | 1 (9.1%) | |
| Complete, n (%) | 2 (6.5%) | 2 (22.2%) | 0 (0%) | 0 (0%) | |

The limitation to our study is the relative small number of reported patients. However, as we previously mentioned, this study analyzed the MR findings of ICC in patients with cirrhosis, and in most cases the nodules were smaller than 3 cm, when radiological diagnosis was a challenge.

In summary, our data provide information that should be of major help in the evaluation of small nodules detected during surveillance in patients with cirrhosis and properly establish an accurate imaging diagnosis. It is important to note that patients without cirrhosis have mostly advanced tumors.

Observation of a washout pattern is specific for HCC, but if this is not observed, a diagnostic biopsy should be considered the sole tool to ensure a conclusive diagnosis.

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Original Article

# Evaluation of Tumor Response After Locoregional Therapies in Hepatocellular Carcinoma

## Are Response Evaluation Criteria in Solid Tumors Reliable?

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**BACKGROUND:** Evaluation of response to treatment is a key aspect in cancer therapy. Response Evaluation Criteria in Solid Tumors (RECIST) are used in most oncology trials, but those criteria evaluate only unidimensional tumor measurements and disregard the extent of necrosis, which is the target of all effective locoregional therapies. Therefore, the European Association for the Study of the Liver (EASL) guidelines recommended that assessment of tumor response should incorporate the reduction in viable tumor burden. The current report provides an assessment of the agreement/concordance between both RECIST and the EASL guidelines for the evaluation of response to therapy. **METHODS:** The authors evaluated a cohort of 55 patients within prospective studies, including 24 patients with hepatocellular carcinoma who underwent transarterial chemoembolization (TACE) with drug eluting beads (DEB-TACE) and 31 patients who underwent percutaneous ablation (percutaneous ethanol injection [PEI]/radiofrequency [RF]). Triphasic helical computed tomography scans were performed at baseline, at 1 month, and at 3 months after procedure, and 2 independent radiologists evaluated tumor response. **RESULTS:** Evaluating response according to RECIST criteria, no patients achieved a complete response (CR), 21.8% of patients achieved a partial response (PR) (none in the PEI/RF group), 47.3% of patients had stable disease (SD), and 30.9% of patients had progressive disease (PD). When response was evaluated according to the EASL guidelines, 54.5% of patients achieved a CR, 27.3% of patients achieved a PR, 3.6% of patients had SD, and 14.5% had PD. The $\kappa$ coefficient was 0.193 (95% confidence interval, 0.0893-0.2967; $P < .0001$). **CONCLUSIONS:** RECIST missed all CRs and underestimated the extent of partial tumor response because of tissue necrosis, wrongly assessing the therapeutic efficacy of locoregional therapies. This evaluation should incorporate the reduction in viable tumor burden as recognized by nonenhanced areas on dynamic imaging studies. **Cancer 2009;115:616–23. © 2008 American Cancer Society.**

**KEY WORDS:** hepatocellular carcinoma, locoregional therapies, Response Evaluation Criteria in Solid Tumors, tumor response assessment.

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We thank Mrs. Diana Segarra for her editorial assistance.

**Received:** July 7, 2008; **Revised:** August 13, 2008; **Accepted:** August 15, 2008

**Published online:** December 30, 2008, © 2008 American Cancer Society

**DOI:** 10.1002/cncr.24050, www.interscience.wiley.com

**Evaluation** of response to treatment is a key aspect in cancer therapy, because objective response may become a surrogate marker of improved survival. Several criteria have been developed to allow a uniform response assessment,[1,2] including the World Health Organization (WHO), which published criteria for response evaluation that became the most commonly used by investigators around the world.[3,4] Nonetheless, in the subsequent years, several problems in terms of interpretation of these criteria appeared, leading to numerous modifications or clarifications and resulting in a situation in which response criteria no longer were comparable among research organizations. In this scenario, the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines were published by the National Cancer Institute in 2000 with the objective of unifying criteria of response assessment.[5] These rely on the measurement of the greatest dimension of all target lesions, and response is categorized as a complete response (CR) (the disappearance of all target lesions), a partial response (PR) (a decrease $\geq$30% in the sum of the greatest dimension of target lesions), progressive disease (PD) (an increase $\geq$20% in the sum of the greatest dimension of target lesions and/or the appearance of new lesions and/or unequivocal progression of existing nontarget lesions), and stable disease (SD) (not enough shrinkage nor sufficient increase to qualify as a PR or as PD, respectively).

Despite the improvement of RECIST compared with previous criteria, it has been demonstrated that their applicability in different neoplasms is less than optimal.[6] Since the publication of the RECIST criteria 7 years ago, several reports have been published regarding the low reliability of RECIST criteria in evaluating response in different types of tumors, such as prostate cancer,[7] malignant pleural mesothelioma,[8-10] nonsmall cell lung cancer,[11,12] gastrointestinal stromal tumor,[13,14] soft tissue sarcoma,[15] neuroendocrine tumors,[16] and disseminated pediatric malignancy.[17] In addition, with the advent of new drugs, most of which are cytostatic rather than cytotoxic, the assessment of activity by measuring tumor shrinkage may not be appropriate at all.[18-20] Finally, RECIST criteria do not take into account changes in tumor viability that may be associated with tumor response. In patients with hepatocellular carcinoma (HCC), the objective of all effective locoregional therapies (ablation and chemoembolization) is to obtain necrosis of the tumor, regardless of the shrinkage of the lesion. Even in if extensive tumor necrosis is achieved, this may not be paralleled by a reduction in the greatest dimension of the lesion. Therefore, in 2000, a panel of experts on HCC of the European Association for the Study of the Liver (EASL) agreed that estimating the reduction in viable tumor volume (recognized as nonenhanced areas using dynamic imaging techniques) should be considered the optimal method for assessing local response to treatment in patients with HCC.[21] Therefore, most authors reporting results of locoregional therapy for HCC evaluate tumor response according to this recommendation.[22-26]

The objective of this study was to compare the concordance/agreement of tumor response evaluated by RECIST criteria versus the EASL guidelines in a cohort of patients received the locoregional therapies frequently used in the setting of HCC: percutaneous ablation (by ethanol injection or radiofrequency) and transarterial chemoembolization (TACE).

## MATERIALS AND METHODS

The current study included 2 cohorts of patients who were selected from 2 prospective investigations assessing TACE with drug eluting beads (DEB-TACE) (24 patients) and percutaneous ablation (31 patients) performed by our group.[22,27] Both studies were approved by the ethics committee of our institution.

### *The DEB-TACE Cohort*

This cohort included 27 consecutive, asymptomatic patients with untreated, intermediate HCC and compensated Child-Pugh A cirrhosis without vascular invasion or extrahepatic spread (Barcelona Clinic Liver Cancer [BCLC] stage B) from February 2004 to May 2005. The patients received 2 treatments with DEB-TACE separated by 2 months except in 1 patient, who developed persistent, complete arterial obstruction during the first procedure, precluding a second treatment, and the assessment of response was not done in 3 patients (2 because of liver abscess and 1 because of arterial dissection).[22] The diameter of DEB ranged between 500 μm and 700 μm, and these beads were preloaded with doxorubicin adjusted for body surface and bilirubin (100 mg/m$^2$ in patients with bilirubin $<$1.5 mg/dL and 75 mg/m$^2$ in patients with bilirubin 1.5-3 mg/dL; maximum dose, 150 mg; median dose, 143 mg).

### The Percutaneous Ablation Cohort

This study included 42 patients and was designed to evaluate the use of contrast-enhanced ultrasound for assessing tumor response after percutaneous ethanol injection (PEI) or radiofrequency (RF) in patients with early HCC (BCLC stage A).[27] We included in this RECIST assessment the 31 patients who had basal and post-treatment computed tomography (CT) scans obtained with the same scan and within the period of time recommended by RECIST criteria.

### Assessment of Response

All patients underwent a multiphasic study (nonenhanced, arterial, portal and late venous phases) performed with a helical CT scanner (Somatom Plus 4; Siemens, Erlangen, Germany) with 120 mL of nonionic contrast agent. Slice collimation was 5 mm in the arterial and portal phases and 8 mm collimation in the other 2 phases, and the pitch was 1.5. Images were reconstructed at 5-mm or 8-mm intervals. CT scans were obtained within 1 month before treatment, 1 month after percutaneous ablation or the second DEB-TACE treatment, and 3 months after the last procedure. Tumor assessment was made using 5-mm interval, axial reconstructed images obtained during the arterial phase. Response was defined according to RECIST criteria[5] and the EASL recommendation using WHO criteria ad taking into account tumor necrosis recognized by nonenhanced areas. According these latter criteria, a CR was defined as the absence of enhanced tumor areas, reflecting complete tissue necrosis; a partial response (PR) was defined a decrease $>50\%$ of enhanced areas, reflecting partial tissue necrosis; PD was defined as an increase $>25\%$ in the size of $\geq 1$ measurable lesion(s) or the appearance of new lesions; and SD was defined as a tumor response between PR and PD.[21] The responses were evaluated blindly by 2 experienced abdominal radiologists (C.A. and J.R.); in case of a discrepancy in response assessment, the radiologists reviewed the images together, and a decision was reached by consensus.

### Statistical Analysis

The values for baseline patients characteristics were expressed as the mean $\pm$ standard deviation or the median and range, as appropriate. Comparisons between groups were done by using the Student *t* test or the Mann-Whitney test for continuous variables and the chi-square test or the Fisher exact test for categorical variables. Agreement between both tumor response criteria was assessed by $\kappa$ coefficient. A conventional *P* value of .05 was considered statistically significant. Calculations were done with the SPSS software package (SPSS, Inc., Chicago, Ill).

## RESULTS

In total, 55 patients were included in this study: Twenty-four patients received by DEB-TACE, and 31 patients underwent percutaneous ablation (14 by RF and 17 by PEI). Table 1 summarizes the main characteristics of these 2 cohorts. All patients were cirrhotic, and the majority of them were secondary to hepatitis C viral infection ($n = 39$ patients; 70.9%). The median age was 67 years (range, 41-79 years), and there was a predominance of men in both groups ($n = 38$ men; 69.1%). Liver function was preserved in both groups but was significantly better in the DEB-TACE group. This is because well preserved liver function is required in patients who are candidates for TACE. The median basal $\alpha$-fetoprotein level was 15 ng/mL, and there were no statistically significant differences between the 2 groups. The size and the number of nodules were significantly larger in the DEB-TACE group, as expected, and all patients in that group fit within the BCLC intermediate stage. Conversely, most patients in the PEI/RF group presented with a solitary foci, and the nodule size did not exceed 50 mm.

Tumor response was evaluated 1 month after treatment in all patients and at 3 months after the procedure in all of the 24 patients who received DEB-TACE and in 26 patients who underwent PEI/RF; this second CT scan evaluation was not performed in 5 patients: In 3 patients, a CR was not achieved by the percutaneous ablation, and retreatment was conducted; 1 patient who had a CR according to the EASL guidelines underwent liver transplantation 2 months after PEI, and the explant analysis confirmed complete necrosis of the tumor; and, finally, in 1 patient who achieved a CR according to the EASL guidelines, the follow-up assessment at 3 months was based on contrast-enhanced ultrasound, whereas a CT scan was delayed to 6 months later. At that time point, the response was classified again as complete.

**Table 1.** Main Patient Characteristics

| Characteristic | DEB-TACE Group, n=24 | PEI/RF Group, n=31 | Total, n=55 | *P* |
|---|---|---|---|---|
| Age: Median (range), y | 65.5 (51-79) | 69 (41-78) | 67 (41-79) | NS |
| No. of men/women | 19/5 | 19/12 | 38/17 | NS |
| No. with HCV/HBV/ethanol/others | 13/1/6/4 | 26/2/3/0 | 39/3/9/4 | NS |
| Child A/B disease, % of patients | 100/0 | 73/27 | 85/5 | .007 |
| Basal AFP, ng/mL | | | | |
| Median (range) | 26.5 (1-78,487) | 13 (1-1486) | 15 (1-78,487) | NS |
| <10 ng/mL, % | 42 | 35 | 38 | |
| 10-100 ng/mL, % | 37 | 55 | 47 | |
| >100 ng/mL, % | 21 | 10 | 15 | |
| AST, mean±SD UI/L | 81.3±53.9 | 89.1±70.5 | 85.7±63.3 | NS |
| ALT, mean±SD UI/L | 95.4±94.7 | 77.4±68.7 | 85.2±80.8 | .04 |
| Bilirubin, mean±SD mg/dL | 1±0.4 | 1.3±0.9 | 1.2±0.7 | NS |
| Alkaline phosphatase, mean±SD UI/L | 253.8±147.8 | 290±143.8 | 273.2±145.4 | NS |
| GGT, mean±SD UI/L | 152.7±105.4 | 98.3±81.9 | 193±96.3 | NS |
| Albumin, mean±SD UI/L | 40.4±4 | 37.4±4.6 | 38.8±4.5 | .02 |
| Prothrombin rate, mean±SD % | 84.1±7.5 | 78.4±14.9 | 80.8±12.3 | NS |
| Total nodule size: Median (range), mm | 66.5 (33-150) | 21 (14-52) | 34 (14-150) | <.001 |
| No. of nodules: Median (range) | 2 (1-8) | 1 (1-2) | 1 (1-8) | <.001 |

*DEB indicates drug-eluting beads; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection; RF, radiofrequency; SD, standard deviation; NS, nonsignificant; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

**Table 2.** Tumor Response Evaluated by European Association for the Study of the Liver Guidelines and Response Evaluation Criteria in Solid Tumors

| | No. of Patients (%) | | | | |
|---|---|---|---|---|---|
| Treatment | CR | PR | SD | PD | OR |
| **DEB-TACE** | | | | | |
| RECIST | 0 (0) | 12 (50) | 7 (29.2) | 5 (20.8) | 12 (50) |
| EASL | 7 (29.2) | 11 (45.8) | 1 (4.2) | 5 (20.8) | 18 (75) |
| **PEI/RF** | | | | | |
| RECIST | 0 (0) | 0 (0) | 19 (61.3) | 12 (38.7) | 0 (0) |
| EASL | 23 (74.2) | 4 (12.9) | 1 (3.2) | 3 (9.7) | 27 (87.1) |
| **Total** | | | | | |
| RECIST | 0 (0) | 12 (21.8) | 26 (47.3) | 17 (30.9) | 12 (21.8) |
| EASL | 30 (54.5) | 15 (27.3) | 2 (3.6) | 8 (14.5) | 45 (81.8) |

CR indicates complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, overall response; DEB, drug-eluting beads; TACE, transarterial chemoembolization; RECIST, Response Evaluation Criteria in Solid Tumors; EASL, European Association for the Study of the Liver; PEI, percutaneous ethanol injection; RF, radiofrequency.

Evaluation of tumor response is summarized in Table 2. According to EASL criteria, an objective response was achieved in 87.1%, 75%, and 81.8% of patients in the PEI/RF group, the DEB-TACE group, and the total cohort, respectively. Because of its curative capability, as expected, the CR rate was significantly greater in the PEI/RF group compared with the DEB-TACE group (74.2% vs 29.2%, respectively; $P = .009$). Conversely, according to RECIST criteria, the PEI/RF group did not achieve any objective response, SD was obtained by in only 19 patients (61.3%), and 12 patients (38.7%) had PD. In the DEB-TACE group, no CR was achieved, a PR was achieved by 12 patients (50%), 7 patients (29.2%) had SD, and 5 patients (20.8%) had PD. Therefore, although DEB-TACE is a locoregional therapy with no curative capacity, the objective response rate was significantly greater than that achieved with PEI/RF when RECIST criteria were considered (0% vs 50%, respectively; $P < .001$).

**Table 3.** Correlation of Tumor Response Evaluation Between European Association for the Study of the Liver Guidelines and Response Evaluation Criteria in Solid Tumors

| | RECIST Criteria | | | | | | |
|---|---|---|---|---|---|---|---|
| **EASL Guidelines** | **CR** | **PR** | **SD** | **PD** | **κ Coefficient** | **95% CI** | ***P*** |
| **DEB-TACE** | | | | | **0.301** | **0.0498-0.552** | **<.003** |
| CR | 0 | 6 | 1 | 0 | | | |
| PR | 0 | 6 | 5 | 0 | | | |
| SD | 0 | 0 | 1 | 0 | | | |
| PD | 0 | 0 | 0 | 5 | | | |
| **PEI/RF** | | | | | **0.0761** | **0.0042-0.1481** | **<.002** |
| CR | 0 | 0 | 17 | 6 | | | |
| PR | 0 | 0 | 1 | 3 | | | |
| SD | 0 | 0 | 1 | 0 | | | |
| PD | 0 | 0 | 0 | 3 | | | |
| **Total** | | | | | **0.193** | **0.0893-0.2967** | **<.0001** |
| CR | 0 | 6 | 18 | 6 | | | |
| PR | 0 | 6 | 6 | 3 | | | |
| SD | 0 | 0 | 2 | 0 | | | |
| PD | 0 | 0 | 0 | 8 | | | |

RECIST indicates Response Evaluation Criteria in Solid Tumors; EASL, European Association for the Study of the Liver; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; 95% CI, 95% confidence interval; DEB, drug-eluting beads; TACE, transarterial chemoembolization; PEI, percutaneous ethanol injection; RF, radiofrequency.

Table 3 summarizes the comparison of tumor response evaluation between the EASL and RECIST criteria. RECIST criteria, as discussed above, did not identify an objective response in any patient who underwent PEI/RF despite the curative potential of this procedure; and, paradoxically, among the 23 CRs that were identified by EASL criteria, RECIST classified the same responses as SD in 17 patients and PD in 6 patients. Similarly, the 4 PRs by that were identified by EASL criteria were classified as SD in 1 patient and PD in the remaining 3 patients. Finally, RECIST classified all responses that were categorized as PD by EASL criteria in the same category. The evident lack of a correlation between these tumor response criteria was reflected by κ coefficients of 0.301 (95% confidence interval [CI], 0.0498-0.552; $P < .003$), 0.0761 (95% CI, 0.0042-0.1481; $P = .002$), and 0.193 (95% CI, 0.0893-0.2967; $P < .001$) in the DEB-TACE group, the PEI/RF group, and both groups, respectively.

## DISCUSSION

The accurate evaluation of response to treatment is a key aspect in cancer therapy, because an objective response may become a surrogate marker of improved survival. Therefore, the development of reliable and reproducible criteria universally applicable to allow comparisons between different groups is mandatory. Thus, the National Cancer Institute developed RECIST; and, since its publication, it has been used commonly as a tool in oncology investigations. However, RECIST evaluates only unidimensional tumor measurements and disregards the extent of necrosis, which is the objective of all effective locoregional therapies widely used for HCC, including ablation and intra-arterial procedures like chemoembolization. In light of these findings, the Barcelona-2000 EASL clinical guidelines recommended that assessment of tumor response should be performed taking into account the reduction in viable tumor burden as recognized by nonenhanced areas by dynamic CT or magnetic resonance imaging studies,[21] and this criterion has been used widely by the majority of groups dealing with HCC.

To our knowledge, there are no prospective studies specifically aimed at comparing the EASL criteria versus RECIST in patients with HCC who received locoregional treatments. However, several studies have established an association between complete necrosis of the tumor and survival. We recently evaluated the outcome predictors in

a cohort of 282 patients with early HCC who underwent percutaneous ablation in a single center. An initial CR was achieved by 192 patients and was maintained until the end of follow-up by 80 patients. In that study, a multivariate analysis of the predictors of survival clearly demonstrated that initially achieving complete tumor necrosis was associated with significantly better survival (odds ratio, 1.83; 95% CI, 1.1-3.1; $P = .020$).[25] Those results were reproducible by an Italian study in a similar population.[28] Other studies have evaluated the response with both RECIST and EASL criteria after radioembolization with Yttrium-90. Sato et al[23] published their preliminary data evaluating tumor response after radioembolization with Yttrium-90 by using WHO criteria, RECIST, and EASL criteria and reported objective tumor response rates of 24%, 31%, and 71%, respectively. In addition, WHO criteria and RECIST detected no CRs, whereas 10% of patients achieved a CR according to EASL criteria. Furthermore, the same group recently analyzed tumor responses in 76 HCC lesions that were treated by Yttrium-90 using RECIST, the WHO criteria, the size of necrosis, and RECIST combined with necrosis. The tumor response rate was 23% according to RECIST, 26% according to WHO criteria, 57% according to necrosis criteria, and 59% according to the combined criteria; in addition, response was detected earlier according to necrosis criteria compared with the use of size criteria alone. For these reasons, those authors concluded that the use of combined size and necrosis criteria might lead to a more accurate assessment of response to Yttrium-90 radioembolization than size criteria alone.[29]

In our study, RECIST criteria missed all CRs obtained by tumor necrosis and underestimated the extent of partial tumor response because of tissue necrosis. This finding was particularly relevant for patients who received percutaneous ablation. These therapies have curative capability, and they constitute 1 of the most commonly used treatments in HCC, particularly in those countries where liver transplantation is not feasible. Ablation repeatedly has produced high CR rates (>90%) if necrosis is taken into account.[30-32] However, if RECIST were used, then the rate of initial objective response would be near 0%. Thus, its established efficacy would be neglected.

Similar conclusions were reached when assessing transarterial procedures. The objective of these treatments is to achieve ischemic necrosis of the tumors, which is associated with increase in survival.[26,33,34] Therefore, it seems reasonable to evaluate response by measuring the extent of tumor necrosis instead of the mere measurement of size by unidimensional or bidimensional systems. Again, RECIST criteria underestimate tumor response to these treatments, and its use should be discouraged in this setting.

Finally, with the advent of biologic therapies, additional concerns about the reliability of RECIST criteria will emerge. Several promising molecules implicated in cancer cell signaling currently are under phase 2/3 evaluation. The majority of these treatments have demonstrated cytostatic, rather than cytotoxic, properties, so that shrinkage of the tumor after treatment is not expected, and RECIST would not detect the potential efficacy of these promising approaches.[18,19] This is true for bevacizumab in metastatic colorectal cancer,[35] erlotinib in nonsmall cell lung cancer,[36] temsirolimus in renal cancer,[37] and, more recently, sorafenib in liver cancer, the sole systemic agent that unequivocally has improved survival in patients with HCC.[38] Because of the finding that most of these agents act through the inhibition of neoangiogenesis, the assessment of necrosis could evaluate a potential tumor response more accurately, and it would prevent the rejection of a promising treatment because of an underestimation of its real antitumor activity.

In summary, the current analysis indicates that RECIST has no value in the assessment of tumor response after locoregional therapies in patients with HCC. Thus, RECIST should not be used, and this finding prompted us to recommend basing the evaluation of response on measurements of the reduction in viable tumor burden as recognized on dynamic imaging studies.[39]

## Conflict of Interest Disclosures

This action has been performed within the cooperation framework established by the Transversal Cancer Action approved by the Council of Ministers on October 11th 2007 in accordance with the agreement between The Carlos III Health Institute (ISCIII), which is an autonomous entity currently belonging to the Ministry of Science and Innovation, and the Spanish Biomedical Research Network (CIBER) for the area of hepatic and digestive disorders. Supported in part by a grant from the Carlos III Institute of Health (PI 06/132). Alejandro Forner is supported in part by a grant from the Carlos III Institute of Health

(PI 05/645) and from the BBVA Foundation; Maria Varela is supported by a grant from the Scientific Foundation of the Spanish Cancer Association; and Amelia J. Hessheimer, Carlos Rodriguez-Lope, and Maria Reig are supported by a grant from the BBVA Foundation.

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# 4.- DISCUSIÓN

*ESTUDIO 1*

La obtención de un diagnóstico concluyente es un paso fundamental en el manejo de cualquier neoplasia. En la mayoría de los escenarios, esto solo es posible mediante la obtención de una biopsia para confirmación histológica. El desarrollo de las técnicas de imagen y de marcadores tumorales específicos ha permitido poder establecer el diagnóstico de malignidad en ausencia de confirmación histológica. En el caso del CHC, el desarrollo de unos criterios de diagnóstico no invasivos ha supuesto un gran avance ya que la obtención de una biopsia hepática no está exenta de efectos adversos severos y no en pocos casos, su realización está imposibilitada por la localización del nódulo, presencia de ascitis o alteraciones severas de la coagulación. Además, la interpretación diagnóstica del material diagnóstico obtenido mediante punción es compleja y no está exenta de una alta tasa de resultados falsos negativos (47).

Hasta la fecha, ningún estudio había validado los criterios diagnósticos no invasivos propuestos por la AASLD. Los estudios que evalúan el rendimiento diagnóstico de las técnicas de imagen ofrecen una información limitada, ya que en muchos casos solo incluyen pacientes ya diagnosticados de CHC, excluyendo aquellos con imágenes no típicas o biopsias negativas (43). La única forma de evaluar de forma precisa el rendimiento diagnóstico de las diferentes técnicas de imagen para el diagnóstico no invasivo es mediante la realización de un estudio prospectivo incluyendo a aquellos pacientes con nódulos de nueva aparición detectados mediante ecografía de cribado. La inclusión de nódulos menores de 2 cm permite explorar la fiabilidad de las técnicas de imagen en el escenario más complejo. Además, el diagnóstico precoz del CHC idealmente se debería realizar en este estadio, cuando es posible aplicar tratamientos con alta probabilidad de curación (29, 61). Por último, en este tipo de estudios, el estándar de referencia debe ser la confirmación histológica y en aquellos casos con biopsias repetidamente negativas, es fundamental asegurar la ausencia de malignidad mediante un seguimiento adecuado. Estas consideraciones son las que se han tenido en cuenta a la hora de diseñar y realizar el estudio número 1 (90).

El primer resultado interesante fue que 60 de los 89 nódulos (67,4%) incluidos en el estudio fueron finalmente diagnosticados de CHC. Esta alta prevalencia de CHC en nódulos de nueva aparición detectados por ecografía de cribado ha sido corroborado por otro estudio prospectivo recientemente publicado realizado en Italia, en donde la prevalencia de malignidad fue del 66% (91). Si se hubieran incluido pacientes con nódulos de mayor tamaño

o lesiones multifocales, la prevalencia de CHC hubiera sido aún mayor. Por tanto, la aparición de un nódulo en una ecografía de cribado obliga a iniciar una estrategia diagnóstica sin dilación con la finalidad de llegar a un diagnóstico confirmatorio de malignidad dada la alta prevalencia de CHC. Cuando se hizo un análisis de acuerdo al tamaño de la lesión (<10 mm, 10-15 mm y 15-20 mm), se evidenció que sólo 2 de los 13 nódulos menores de 10 mm fueron finalmente diagnosticados de CHC. Este resultado, junto a la dificultad asociada a la obtención de una biopsia en estos nódulos infracentimétricos, valida la recomendación de la AASLD de realizar un seguimiento estrecho de estas lesiones y únicamente realizar exploraciones complementarias en caso de objetivar crecimiento de la lesión.

Otro resultado importante es que la punción-biopsia para el diagnóstico precoz del CHC se asocia con resultados falsos negativos; en nuestro estudio, la primera punción-biopsia ofreció una sensibilidad del 70%, por lo que en un 30% de los casos el diagnóstico se obtuvo mediante biopsias de repetición. Por tanto, un resultado inicial negativo no descarta el diagnóstico de CHC y se debe considerar la realización de una nueva biopsia o un seguimiento estrecho de la lesión. El aumento del rendimiento diagnóstico de la punción-biopsia para el diagnóstico del CHC en fases iniciales debe constituir una de las prioridades para la investigación en el área del diagnóstico de CHC. Estudios preliminares han evaluado la utilidad de técnicas de inmunohistoquímica (55, 56), expresión génica (53, 92) y proteómica (93), pero su aplicabilidad en la práctica clínica habitual aún no ha sido validada

Sin lugar a dudas, el resultado más importante de este estudio es que las técnicas de imagen dinámicas (en este caso, ecografía con contraste y RM) son útiles para poder establecer el diagnóstico de CHC sin precisar una biopsia. Nuestros resultados muestran que la ecografía con contraste y la RM presentan de forma aislada una excelente sensibilidad y especificidad, siempre y cuando se requiera hallar el patrón vascular específico de CHC. Sin embargo, el uso de una única técnica aislada puede dar lugar a falsos diagnósticos de CHC (un colangiocarcinoma de 14 mm y un angioma de 16 mm en el caso de la ecografía con contraste y un nódulo de regeneración de 12 mm en el caso de la RM). Cuando las dos técnicas de imagen fueron usadas conjuntamente, se eliminaron estos falsos diagnósticos positivos, obteniendo un 100% de especificidad. Evidentemente, la aplicación estricta de las recomendaciones de la AASLD se asoció a una baja sensibilidad; en nuestro estudio, a pesar de la amplia experiencia de nuestros radiólogos y el uso de técnicas de imagen de última

generación, la sensibilidad para diagnosticar de forma concluyente CHC en nódulos menores de 2 cm fue del 33%.

De las dos técnicas de imagen, la RM presenta mejor rendimiento diagnóstico. Además, si consideramos únicamente aquellos nódulos mayores de 15mm, la RM mostró un 100% de especificidad con una alta sensibilidad, por lo que se podría sugerir que en aquellos nódulos mayores de 15 mm, la demostración del patrón vascular específico del CHC mediante RM es suficiente para establecer el diagnóstico concluyente de CHC. Otros autores han demostrado que la RM aislada presenta una especificad del 100% (91), sugiriendo eliminar la necesidad de dos pruebas coincidentes positivas para establecer el diagnóstico de CHC. Indudablemente, en centros con amplia experiencia sería posible aplicar de forma exitosa esta sugerencia, pero habría que validar su utilidad en centros con menos experiencia. Por tanto, de momento es preferible mantener las actuales recomendaciones de confirmar el diagnóstico con dos pruebas coincidentes.

Por último, la ausencia de captación de contraste en fase arterial no descarta el diagnóstico de CHC. De hecho, muchos CHC muy iniciales aún no han desarrollado la extensa red de neoangiogénesis arterial responsable de la captación de contraste en fase arterial característica del CHC. Algunos autores han sugerido que si un nódulo pequeño en un hígado cirrótico no muestra hipercaptación arterial, se puede descartar su malignidad y no son necesarias exploraciones adicionales. Este concepto es claramente erróneo. Dado que el objetivo sería diagnosticar el CHC en este estadio inicial, si la sospecha de CHC se retrasa hasta la detección de captación de contraste en fase arterial, seguro que el estadio tumoral será más avanzado. Por tanto, ante esta situación es recomendable la obtención de una biopsia.

*ESTUDIO 2*

Los programas de cribado en pacientes afectos de cirrosis hepática tienen como objetivo diagnosticar el CHC en estadio inicial. Sin embargo, no todos los nódulos que aparecen sobre un hígado cirrótico son malignos, ni todas las lesiones malignas son CHC. Como hemos comentado anteriormente, la incidencia del colangiocarcinoma intrahepático (ICC) ha aumentado en los últimos años y es bien conocido que la cirrosis hepática, particularmente la secundaria a VHC, es un factor de riesgo para su desarrollo. Por tanto, el diagnóstico diferencial del CHC con el ICC es un problema médico relevante, ya que el manejo clínico y el pronóstico de ambas enfermedades es diferente. Por ejemplo, el trasplante hepático es una opción terapéutica aceptada en el CHC, pero raramente es considerado en el ICC. De hecho, los criterios actualmente aceptados en la UNOS (*United Network for Organ Sharing*) solicitan un diagnóstico concluyente de CHC para incluir a los pacientes en lista y para otorgarles prioridad en ella (46, 67, 94).

El hallazgo de un ICC de 16 mm con un patrón vascular idéntico al CHC en la ecografía con contraste cuestionó la utilidad de los criterios de imagen para el diagnóstico no invasivo del CHC. Por este motivo, decidimos realizar un análisis retrospectivo de todos los ICC diagnosticados en nuestra Unidad en pacientes afectos de cirrosis hepática con confirmación histológica, en los que se realizó una RM hepática dinámica usando el mismo protocolo de adquisición que en el estudio 1.

Este estudio mostró que el patrón vascular más frecuente del ICC en pacientes cirróticos es la captación progresiva de contraste a lo largo de todas las fases. Además, la extensión de la captación de contraste estuvo asociada al tamaño de la lesión. En este sentido, los nódulos menores de 3 cm presentaban una captación homogénea de la totalidad de la lesión, mientras en las lesiones de mayor tamaño, la captación de contraste es incompleta, similar a la descrita en pacientes no cirróticos (14). En el caso particular de nódulos menores de 2 cm, el patrón vascular típico fue una captación de contraste estable a lo largo de todas las fases; en la mitad de los casos esa captación fue homogénea, y en la otra mitad, la captación fue periférica, en anillo. En el primer caso, el patrón de captación en fase arterial es idéntico al del CHC (90), por lo que si el radiólogo no realiza una valoración exhaustiva, podría realizarse un falso diagnóstico de CHC.

La captación de contraste progresiva a lo largo de todas las fases también ha sido descrita en los hemangiomas. Sin embargo, en este caso la captación de contraste comienza con una captación nodular en la periferia; en cambio, en el ICC la captación es periférica en anillo, lo que permite el diagnóstico diferencial entre ambas entidades (95).

Los resultados de este estudio refuerzan la necesidad de definir el patrón de captación de cualquier lesión registrando los hallazgos en todas las fases tras la administración de contraste. En este sentido, ninguno de los ICC presentó lavado de contraste en fases tardías, hallazgo específico del CHC y clave para el diagnóstico no invasivo del CHC de acuerdo a las recomendaciones de la AASLD (29, 90). La simple identificación de una captación homogénea de contraste en nódulos pequeños sobre un hígado cirrótico podría conducir al diagnóstico de CHC si no se tiene en cuenta el hecho de que algunos ICC pequeños también pueden presentar este patrón vascular en fase arterial.

Al igual que otros autores, nuestras resultados muestran que la captación progresiva de contraste a lo largo de todas las fases es muy sugestivo de ICC (83, 96, 97). Sin embargo, este patrón también puede ser observado en nódulos CHC (90), por lo que la identificación de este patrón en un paciente cirrótico no permite el diagnóstico definitivo de ICC por RM. Lógicamente, el diagnóstico de ICC ante este patrón vascular es muy probable (81, 83, 97-99), pero no se puede descartar la presencia de un CHC. Por tanto, si un nódulo muestra una captación progresiva de contraste y ausencia de lavado en fases tardías, se debe recomendar la realización de una biopsia, independientemente del tamaño de la lesión.

Por último, merece la pena destacar que el característico patrón en anillo fue sólo demostrado en cuatro nódulos de 15, 20, 24 y 35 mm. Es importante mencionar que esta captación en anillo puede ser interpretada erróneamente como lavado de contraste por radiólogos inexpertos. En nuestra serie, aquellos nódulos que mostraban captación en anillo en fases tardías mostraron el mismo patrón en fase arterial.

*ESTUDIO 3*

Como hemos comentado anteriormente, la evaluación precisa de la respuesta a cualquier tratamiento es fundamental ya que la presencia de una respuesta objetiva puede constituir un marcador subrogado de mejoría de la supervivencia. Con la finalidad de crear unos criterios precisos, fiables y universales que permitieran la comparación entre diferentes grupos se instauraron los criterios RECIST (85), y desde su publicación se han convertido en los criterios más usados en la investigación clínica en el área de la Oncología. Sin embargo, los criterios RECIST solo evalúan el tamaño tumoral y no tienen en cuenta el grado de necrosis, que es el objetivo de los tratamientos locorregionales usados en el CHC.

Teniendo en cuenta este hecho, en las guías de práctica clínica de la EASL (28) se recomienda la evaluación de la respuesta mediante la cuantificación de la reducción del tejido viable identificado mediante las áreas intratumorales que no captan contraste en el estudio dinámico. En este sentido, múltiples estudios han demostrado la asociación entre la obtención de necrosis completa y aumento de la supervivencia tras tratamiento mediante ablación percutánea (89, 100) y radioembolización con Yttrium-90 (87, 101). Finalmente, un panel de expertos reunidos en una conferencia de consenso promovida por la AASLD confirmó la necesidad de cuantificar la respuesta de acuerdo al porcentaje de tejido necrótico (30), y este criterio de evaluación de respuesta es el más frecuentemente utilizado por los grupos con experiencia en el manejo del CHC. Con estas premisas, el objetivo de este estudio fue evaluar el grado de concordancia entre los criterios RECIST y los criterios EASL.

En nuestro estudio, los criterios RECIST no identificaron ninguna respuesta completa y subestimaron la presencia de respuesta parcial debido a necrosis tisular. Este hallazgo fue particularmente relevante en el caso de la ablación percutánea. Estas terapias tienen capacidad curativa y constituyen uno de los tratamientos más usados en el CHC, particularmente en aquellas áreas donde no existe disponibilidad de trasplante hepático. La ablación percutánea ha mostrado repetidamente una alta tasa de respuesta completa (>90%) si se tiene en cuenta el área de necrosis (70, 102, 103). Sin embargo, cuando se usaron los criterios RECIST, no se identificó ninguna respuesta objetiva. Por tanto, la indiscutible eficacia de los tratamientos ablativos está completamente infravalorada por los criterios RECIST.

Una conclusión similar fue obtenida tras la evaluación de los tratamientos transarteriales. Al igual que la ablación percutánea, el objetivo de los tratamientos transarteriales es obtener necrosis tumoral isquémica, lo que se asocia a aumento de supervivencia (72-74). De nuevo, los criterios RECIST subestimaron la respuesta objetiva de estos tratamientos, por lo que su uso también debería estar desaconsejado en este escenario.

Otros autores han comparado la respuesta tumoral tras radioembolización con Yttrium-90 mediante los criterios RECIST y EASL. En este sentido, Sato y colaboradores evaluaron la respuesta mediante los criterios WHO, RECIST y EASL; la respuesta objetiva fue de 24, 31 y 71%, respectivamente. Además, los criterios WHO y RECIST no detectaron ninguna respuesta completa, mientras que esta fue obtenida en un 10% de los casos de acuerdo a los criterios EASL. Además, este grupo ha evaluado la respuesta tumoral en 76 lesiones de CHC tratadas con radioembolización con Yttrium-90 mediante los criterios RECIST, WHO, tamaño de la necrosis y RECIST asociado con grado de necrosis. La respuesta tumoral fue de 23% y 26% de acuerdo a los criterios RECIST y WHO, respectivamente. En cambio, la respuesta objetiva fue de 57% de acuerdo al tamaño de la necrosis y 59% cuando se asoció RECIST con el grado de necrosis. Además, la respuesta fue detectada más precozmente cuando se consideró el grado de necrosis. Por tanto, la conclusión final de los autores fue que la evaluación de la reducción del tamaño tumoral asociado al grado de necrosis da lugar a una evaluación más precisa de la respuesta tumoral de la radioembolización con Yttrium-90 (101).

Por último, la aparición de las terapias biológicas pondrá en evidencia más aún las limitaciones de los criterios RECIST. La mayoría de estos tratamientos han mostrado acción citostática, por lo que no es esperable una reducción significativa del tamaño tumoral y los criterios RECIST no serán capaces de detectar la potencial eficacia de estos tratamientos prometedores (104, 105). Este es el caso del bevacizumab en el cáncer colorrectal metastático (106), erlotinib en el cáncer de pulmón de célula no pequeña (107), temsirolimus en el cáncer renal (108), y más recientemente, sorafenib en el CHC, que constituye hasta la fecha el único tratamiento que ha demostrado aumento de supervivencia en pacientes con CHC avanzado (76, 77). En este último caso, se identificó un claro aumento de la supervivencia en ausencia de respuesta objetiva de acuerdo a los criterios RECIST.

Debido a que la mayoría de estos agentes actúan a través de la inhibición de la neoangiogénesis, la evaluación de la necrosis sería desde el punto de vista teórico más útil

para detectar la potencial respuesta tumoral; esto podría prevenir la interrupción prematura de la evaluación de un agente prometedor debido a la subestimación de su actividad antitumoral real.

En resumen, nuestro análisis muestra que los criterios RECIST no tienen valor para la evaluación de la respuesta tumoral tras la aplicación de terapias locorregionales en pacientes afectos de CHC. La evaluación de la respuesta debería basarse en la medida de la reducción del tejido viable reconocido por técnicas dinámicas de imagen (30).

# 5.- CONCLUSIONES

Las conclusiones finales de los estudios que componen esta tesis Doctoral son:

1.- Los nódulos menores de 10 mm frecuentemente son CHC, por lo que se recomienda una actitud expectante, con un seguimiento estrecho para detectar un posible crecimiento. Se recomienda iniciar estudios complementarios adicionales cuando sobrepase los 10 mm de tamaño.

2.- El diagnóstico de CHC en nódulos menores de 20 mm puede establecerse sin necesidad de confirmación histológica si la ecografía con contraste y la resonancia magnética son concluyentes de CHC. Sin embargo, su sensibilidad es baja (33%).

3.- La ausencia de hipervascularización arterial no descarta el diagnóstico de CHC y se debe indicar la realización de una PAAF.

4.- Una PAAF negativa no descarta el diagnóstico de CHC. Ante un resultado inicial negativo hemos de plantearnos realizar una nueva PAAF.

5.- La captación de contraste específica del ICC en pacientes cirróticos en la RM es la captación progresiva de contraste a lo largo de las diferentes fases. En el caso de ICC pequeños, el patrón más frecuente fue el de captación estable de contraste en todas las fases.

6.- La ausencia de lavado de contraste en fases venosas tardías permite la clara diferenciación entre CHC e ICC, por lo que la valoración de la fase tardía es fundamental para la correcta caracterización de nódulos hepáticos en pacientes cirróticos.

7.- Estos resultados validan las recomendaciones propuestas por la AASLD para el diagnóstico no invasivo del carcinoma hepatocelular en pacientes con cirrosis hepática.

8.- Los criterios RECIST evalúan erróneamente la eficacia de los tratamientos locorregionales e infraestiman los beneficios de los tratamientos locorregionales.

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# 7.- ANEXO

Durante la realización de este proyecto científico para optar al título de Doctor en Medicina he participado en la publicación de los siguientes artículos:

Impact factor total (JCR 2008): 197,105

## 1.- TRABAJOS ORIGINALES:

1. Varela M, Real MI, Burrel M, **Forner A**, Sala M, Brunet M, Ayuso C, Castells L, Montaña X, Llovet JM, Bruix J. "Chemoembolization of hepatocellular carcinoma with drug eluting beads. Efficacy and doxorubicin pharmacokinetics". J Hepatol 2007; Mar;46(3):474-481.

2. JM. Llovet, S. Ricci, V. Mazzaferro, P. Hilgard, E. Gane, JF. Blanc, A. Cosme de Oliveira, A. Santoro, JL. Raoul, **A. Forner**, M. Schwartz, C. Porta, S. Zeuzem, L. Bolondi, TF. Greten, PR. Galle, JF. Seitz, I. Borbath, D. Häussinger, T. Giannaris, M. Shan, M. Moscovici, D. Voliotis y Jordi Bruix, for the SHARP Investigators Study Group. "Sorafenib in Advanced Hepatocellular Carcinoma". N Engl J Med 2008:359(4):378-390.

3. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Camerini T, Schiavo M, Mariani L, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, **Forner A**, de Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek, B and Pietro Majno. "Predicting Survival after Liver Transplantation in Patients with Hepatocellular Carcinoma beyond the Conventional Milan/UNOS Criteria". Lancet Oncol. 2009:10(1):35-43.

## 2.- EDITORIALES:

1. Varela M, **Forner A**, Bruix J. "Diagnosis and staging of hepatocellular carcinoma prior to transplantation: Expertise or failure". Liver Transpl. 2006;26;12(10):1445-1447.
2. **Forner A**, Bruix J. "Locoregional treatment for hepatocellular carcinoma: from clinical pioneering to robust clinical data changing standards of care". Hepatology 2008:47(1):5-6.
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8. **Forner A**, Trinchet JC. Transarterial therapies in HCC: Does embolization increase survival? J Hepatol. 2009;51:981-983.

**3.- REVISIONES:**

1. Sala M, **Forner A**, Varela M, Bruix J. "Prognostic prediction in patients with hepatocellular carcinoma". Semin Liver Dis 2005;25:171–180.
2. Sala M, **Forner A**, Varela M, Bruix J. "Diagnóstico y tratamiento del carcinoma hepatocelular de pequeño tamaño". Gastroenterol Hepatol 2005;28(supl 1): 20-26.
3. Sala M, Varela M, **Forner A**, Bruix J. "Diagnóstico temprano del cáncer de hígado" Gastroenterol Hepatol 2005;28(5):292-7.
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8. **Forner A**, Varela M. "Terapias curativas en el cáncer de Hígado". JANO. 2006;0;1620: 31-39.
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10. **Forner A**, Real MI, Varela M, Bruix J. "Transarterial chemoembolization for patients with hepatocellular carcinoma". Hepatology Research 2007;Sep;37 Suppl 2:S230-7.
11. Felipe V, Varela M, **Forner A**, Bruix J. "Trasplante hepático en el carcinoma hepatocelular; validez de los criterios de Milán". Gastroenterol Hepatol 2007;30(Supl 1): 78-81.
12. **Forner A**, Rodríguez de Lope C, Rimola J, Varela M. "Early diagnosis of primary liver cancer: Imaging vs genetics". Rev Esp Ap Digest 2008:100(7):423-429.
13. **Forner A,** Rodríguez de Lope C. "Tumores hepáticos benignos: Manejo del paciente com masa hepática detectada incidentalmente". Gastroenterología y Hepatología Continuada. Enero-febrero 2009;8(1):17-21.
14. Bouchard E, **Forner A**, Reig M, Bruix J. **"**New drugs for the treatment of hepatocellular carcinoma". Liver International. 2009 Jan;29 Suppl 1:148-58.

**4.- DOCUMENTOS DE CONSENSO:**

1. **Forner A**, Ayuso C, Real MI, Sastre J, Robles R, Sangro B, Varela M, de la Mata M, Fuster J, Buti M, Martí-Bonmatí L, Bru C, Tabernero J, Llovet JM, Bruix J. "Diagnóstico y tratamiento del carcinoma hepatocelular. Documento de consenso de la AEEH, SETH, SERAM, SERVEI y SEOM. MedClin(Barc).2009;132(7):272–287.

A continuación se adjunta a esta memoria una copia de los principales artículos de acuerdo a su relación con el proyecto de tesis doctoral o por su impacto.

ORIGINAL ARTICLE

# Sorafenib in Advanced Hepatocellular Carcinoma

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## ABSTRACT

### BACKGROUND

No effective systemic therapy exists for patients with advanced hepatocellular carcinoma. A preliminary study suggested that sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and Raf may be effective in hepatocellular carcinoma.

### METHODS

In this multicenter, phase 3, double-blind, placebo-controlled trial, we randomly assigned 602 patients with advanced hepatocellular carcinoma who had not received previous systemic treatment to receive either sorafenib (at a dose of 400 mg twice daily) or placebo. Primary outcomes were overall survival and the time to symptomatic progression. Secondary outcomes included the time to radiologic progression and safety.

### RESULTS

At the second planned interim analysis, 321 deaths had occurred, and the study was stopped. Median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; P<0.001). There was no significant difference between the two groups in the median time to symptomatic progression (4.1 months vs. 4.9 months, respectively, P=0.77). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group (P<0.001). Seven patients in the sorafenib group (2%) and two patients in the placebo group (1%) had a partial response; no patients had a complete response. Diarrhea, weight loss, hand–foot skin reaction, and hypophosphatemia were more frequent in the sorafenib group.

### CONCLUSIONS

In patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo. (ClinicalTrials.gov number, NCT00105443.)

*The affiliations of the authors and the names of the investigators in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) Investigators Study Group are listed in the Appendix. Address reprint requests to Dr. Llovet or Dr. Bruix at the Barcelona Clínic Liver Cancer Group, Liver Unit, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain, or at jmllovet@clinic.ub.es or jbruix@clinic.ub.es.

N Engl J Med 2008;359:378-90.

Hepatocellular carcinoma is a major health problem, accounting for more than 626,000 new cases per year worldwide.[1] The incidence of hepatocellular carcinoma is increasing in the United States and Europe, and it is the third highest cause of cancer-related death globally, behind only lung and stomach cancers.[1] In the West, the disease is diagnosed in 30 to 40% of all patients at early stages and is amenable to potentially curative treatments, such as surgical therapies (resection and liver transplantation) and locoregional procedures (radiofrequency ablation).[2] Five-year survival rates of up to 60 to 70% can be achieved in well-selected patients.[2] However, disease that is diagnosed at an advanced stage or with progression after locoregional therapy has a dismal prognosis, owing to the underlying liver disease and lack of effective treatment options.[2-4] No systemic therapy has improved survival in patients with advanced hepatocellular carcinoma.[5,6]

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals–Onyx Pharmaceuticals) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models.[7,8] It acts by inhibiting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor $\beta$ (PDGFR-$\beta$).[7,8] Cellular signaling that is mediated by the Raf-1 and vascular endothelial growth factor (VEGF) pathways has been implicated in the molecular pathogenesis of hepatocellular carcinoma,[9-12] providing a rationale for investigating sorafenib for this indication. In preclinical experiments, sorafenib had antiproliferative activity in liver-cancer cell lines, and it reduced tumor angiogenesis and tumor-cell signaling and increased tumor-cell apoptosis in a mouse xenograft model of human hepatocellular carcinoma.[13]

Results of an uncontrolled phase 2 study involving 137 patients with advanced hepatocellular carcinoma and Child–Pugh class A or B status indicated that single-agent sorafenib might have a beneficial therapeutic effect. Sorafenib treatment resulted in a median overall survival of 9.2 months and a median time to progression of 5.5 months (as assessed by independent radiologic evaluation).[14] On the basis of these data, we conducted a large phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma.

## METHODS

### PATIENTS

The study population consisted of patients with advanced-stage hepatocellular carcinoma, as confirmed by pathological analysis. None of the patients had received previous systemic therapy. Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies. The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less (Table A1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org),[15] Child–Pugh liver function class A (Table A2 in the Supplementary Appendix),[16,17] a life expectancy of 12 weeks or more, adequate hematologic function (platelet count, $\geq 60\times10^9$ per liter; hemoglobin, ≥8.5 g per deciliter; and prothrombin time international normalized ratio, ≤2.3; or prothrombin time, ≤6 seconds above control), adequate hepatic function (albumin, ≥2.8 g per deciliter; total bilirubin, ≤3 mg per deciliter [51.3 $\mu$mol per liter]; and alanine aminotransferase and aspartate aminotransferase, ≤5 times the upper limit of the normal range), and adequate renal function (serum creatinine, ≤1.5 times the upper limit of the normal range).

Patients were required to have at least one untreated target lesion that could be measured in one dimension, according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Table A3 in the Supplementary Appendix).[18] Concomitant antiviral systemic therapy was allowed. Patients were excluded if they had previously received molecularly targeted therapies or any other systemic treatment.

All patients provided written informed consent before enrollment in the study. The study was approved by the institutional review board or ethics committee at each center and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws.

### STUDY DESIGN

This multicenter, randomized, double-blind, placebo-controlled, phase 3 trial was conducted at 121 centers in 21 countries in Europe, North America, South America, and Australasia. All eligible patients were randomly assigned in a 1:1 ratio to receive continuous oral treatment with either 400 mg of sorafenib (consisting of two 200-mg tablets) twice daily or matching placebo (both sup-

plied by Bayer HealthCare Pharmaceuticals). Study randomization was centralized, and assignment to study groups was conducted by computer to achieve a balance between the two groups, with stratification before randomization according to region, ECOG performance status (a score of 0 vs. a score of 1 or 2), and the presence or absence of macroscopic vascular invasion (portal vein or branches) or extrahepatic spread.

Treatment interruptions and up to two dose reductions (first to 400 mg once daily and then to 400 mg every 2 days) were permitted for drug-related adverse effects (see Tables B1 and B2 in the Supplementary Appendix). If further dose reductions were required, patients were withdrawn from the study.

Treatment continued until the occurrence of both radiologic progression, as defined by RECIST,[18] and symptomatic progression, as defined by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) questionnaire (Table A4 in the Supplementary Appendix),[19] or the occurrence of either unacceptable adverse events or death. Crossover of patients in the placebo group to the sorafenib group was not permitted before the definitive overall analysis of survival.

The study was designed by Bayer HealthCare Pharmaceuticals in conjunction with the principal academic investigators. Data collection was performed by Covance. Axio Research performed the statistical analysis for the data and safety monitoring committee. Data were managed in parallel by the sponsor and the principal investigators. The academic investigators were responsible for the decision to publish the results of the study, had unrestricted access to the final data, and vouch for the completeness and accuracy of the data and data analyses.

### OUTCOMES AND ASSESSMENTS

The primary outcomes of the study were overall survival and the time to symptomatic progression. Overall survival was measured from the date of randomization until the date of death from any cause. The time to symptomatic progression was measured from the date of randomization until the first documented event of symptomatic progression. Symptomatic progression was defined as either a decrease of 4 or more points from the baseline score on patients' responses to the FHSI8 questionnaire, a change that was confirmed 3 weeks later (Table A4 in the Supplementary Appendix[19]), a deterioration in ECOG performance status to 4, or death.

Secondary outcomes included the time to radiologic progression, the disease-control rate, and safety. The time to radiologic progression was defined as the time from randomization to disease progression (according to RECIST) on the basis of independent radiologic review. Data from patients who died without tumor progression were censored. The disease-control rate was defined as the percentage of patients who had a best-response rating of complete response, partial response, or stable disease (according to RECIST) that was maintained for at least 28 days after the first demonstration of that rating on the basis of independent radiologic review. Safety was assessed in all patients receiving at least one dose of a study drug, with the use of version 3.0 of the National Cancer Institute's Common Terminology Criteria for adverse events.

Although treatment was administered in a continuous manner, for the purpose of data recording, the treatment period was divided into 6-week cycles. Tumor measurements were performed at screening, every 6 weeks during treatment (within 10 days before the end of each cycle), and at the end of treatment by computed tomography or magnetic resonance imaging. Patients visited the clinic every 3 weeks and at the end of treatment for assessment of compliance, safety, and determination of side effects. Compliance was assessed on the basis of pill counts and diary entries of patients. Safety assessments included documentation of adverse events, clinical laboratory tests (hematologic and biochemical analyses), physical examination, and measurement of vital signs. An end-of-treatment visit was made 21 to 35 days after the last dose of the study drug. The time to symptomatic progression was assessed at baseline, every 3 weeks during treatment, and at the end-of-treatment visit for patients who discontinued the study drug for reasons other than symptomatic progression.

### STATISTICAL ANALYSIS

The primary outcomes were assessed according to the intention-to-treat principle. For the primary analysis of overall survival and the time to symptomatic progression, we compared the two study groups using a one-sided overall alpha level of 0.02 or 0.005, respectively, thus maintaining the

overall type I error rate for the trial at a one-sided alpha level of 0.025. These analyses were performed with the use of log-rank tests, stratified according to region, ECOG performance status (a score of 0 vs. a score of 1 or 2), and the presence or absence of macroscopic vascular invasion (portal vein or branches) or extrahepatic spread. Two formal interim analyses after approximately 170 and 300 deaths had occurred and one final analysis were planned for the survival outcome. A single final analysis was planned for the outcome of the time to symptomatic progression. The O'Brien–Fleming spending function[20] was specified prospectively to ensure that the one-sided false positive rate was 0.02 or less for overall survival. A Cox proportional-hazards model was used to evaluate the interaction between baseline characteristics and the effect of sorafenib on overall survival.

We calculated the number of patients needed for the study on the basis of the primary outcome of overall survival, taking into account two interim analyses and one final analysis. Assuming a one-sided type I error of 0.02, a randomization ratio of 1:1 between the sorafenib group and the placebo group, and a median overall survival of 7 months in the placebo group, we estimated that with 424 deaths in the two groups combined, the study would have a power of 90% to detect a 40% increase in overall survival in the sorafenib group. On the basis of these calculations, we estimated we needed to enroll approximately 560 patients.

Formal analysis of the time to radiologic progression with the use of a stratified log-rank test was planned when approximately 227 progression events had occurred on the basis of RECIST. The required number of progression events was projected to occur by a prespecified cutoff date of May 12, 2006. Independent radiologic assessment was not continued after this date. We compared disease-control rates in the two study groups using the Cochran–Mantel–Haenszel test with a two-sided alpha level of 0.05. Adverse events were compared with the use of Fisher's exact test. All reported P values are two-sided.

## RESULTS

### PATIENTS

From March 10, 2005, to April 11, 2006, we screened 902 patients. Of these patients, 602 met the eligibility criteria and underwent randomization, with 299 patients assigned to the sorafenib group and 303 patients assigned to the placebo group. These patients were all included in the intention-to-treat analysis (Fig. 1). The remaining patients were excluded from the study during the screening period because they did not meet inclusion or exclusion criteria, withdrew their consent, had an adverse event, were lost to follow-up, or died. Among the 602 randomized patients, 297 received at least one dose of sorafenib and 302 received at least one dose of placebo; these 599 patients were included in the safety analysis.

There were no relevant differences between the two study groups with respect to demographic characteristics, the cause or severity of liver disease, previous antitumor therapy for hepatocellular carcinoma, prognostic characteristics, ECOG performance status, and tumor-staging criteria, according to the Barcelona Clinic Liver Cancer (BCLC) staging system (Table 1, and Table A5 in the Supplementary Appendix).[2,3] Most patients were recruited in Europe. Chronic hepatitis C virus infection was the predominant cause of liver disease, followed by alcohol consumption and chronic hepatitis B virus infection. The disease in 581 patients (97%) was rated as Child–Pugh class A at baseline, reflecting well-preserved liver function. No significant differences were observed between the sorafenib group and the placebo group with respect to mean baseline plasma levels of albumin, alkaline phosphatase, and total bilirubin. At baseline, 231 patients (38%) had macroscopic vascular invasion, and 309 (51%) had extrahepatic spread, with the most common extrahepatic sites being lymph nodes and lung. Approximately half the patients (305) presented with tumors that had not been previously treated, and locoregional therapy had failed in the remaining 297 patients.

### EFFFICACY

#### *Overall Survival*

We conducted the second planned interim analysis using a cutoff date of October 17, 2006, when 321 deaths had occurred (143 in the sorafenib group and 178 in the placebo group). Overall median survival was significantly longer in the sorafenib group than in the placebo group (10.7 months vs. 7.9 months; hazard ratio in the sorafenib group, 0.69; 95% confidence interval [CI], 0.55 to 0.87; P<0.001) (Table 2 and Fig. 2A). Survival rates at 1 year were 44% in the sorafenib group and 33% in the placebo group. This significant survival benefit represented a 31% relative

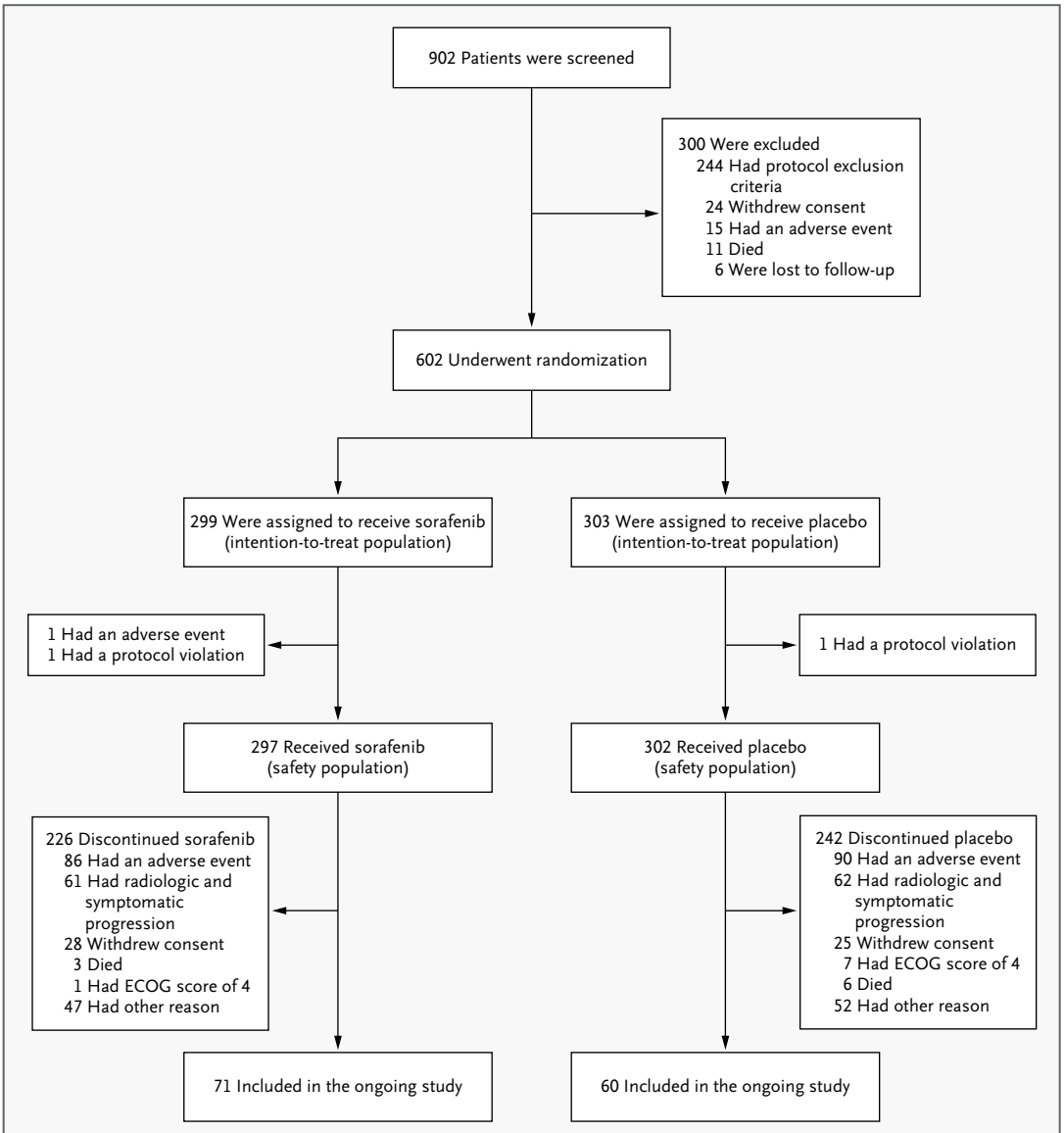



**Figure 1. Enrollment and Outcomes.**

ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 (fully active) to 5 (dead).

reduction in the risk of death. On the basis of these data and guided by the prespecified O'Brien–Fleming spending function[20] (which stipulates a one-sided nominal alpha level of 0.0077 for this interim analysis), the independent data and safety monitoring committee recommended that the trial be stopped in February 2007. The results reported here are considered final.

An exploratory multivariate analysis with the use of a Cox proportional-hazards model identified eight baseline characteristics that were prognostic indicators for overall survival: ECOG performance status, presence or absence of macroscopic vascular invasion, extent of tumor burden (defined as presence or absence of vascular invasion, extrahepatic spread, or both), Child–Pugh status, and median baseline levels of alpha-fetoprotein, albumin, alkaline phosphatase, and total bilirubin. After adjustment for these prognostic factors, the effect of sorafenib on overall survival remained significant (hazard ratio, 0.73; 95% CI, 0.58 to 0.92; P=0.004). A prespecified subgroup analysis

showed a survival benefit for sorafenib over placebo in most of the subgroups analyzed (Fig. 3).

### TIME TO SYMPTOMATIC PROGRESSION

The median time to symptomatic progression (which was defined as either a decrease of 4 or more points from the baseline score on the FHSI8 questionnaire or an ECOG status of 4 or death, whichever occurred first) did not differ significantly between the sorafenib group and the placebo group (4.1 and 4.9 months, respectively; hazard ratio, 1.08; 95% CI, 0.88 to 1.31; P=0.77) (Fig. 2B).

### TIME TO RADIOLOGIC PROGRESSION

By the cutoff date of May 12, 2006, radiologic progression had occurred in 263 patients (107 in the sorafenib group and 156 in the placebo group). On the basis of an independent review of radiologic data, the median time to progression was significantly longer in the sorafenib group than in the placebo group (5.5 vs. 2.8 months; hazard ratio, 0.58; 95% CI, 0.45 to 0.74; P<0.001) (Table 2 and Fig. 2C). The estimated rate of progression-free survival at 4 months was 62% in the sorafenib group and 42% in the placebo group.

### RESPONSE RATES AND DISEASE-CONTROL RATE

In the sorafenib group, 7 patients (2%) had a partial response and 211 (71%) had stable disease (according to RECIST), whereas in the placebo group, 2 patients (1%) had a partial response and 204 (67%) had stable disease (Table 2). There were no complete responses in either group. The disease-control rate was significantly higher in the sorafenib group than in the placebo group (43% vs. 32%, P=0.002) (Table 2).

### TREATMENT COMPLIANCE

At the October 17, 2006, cutoff date, 468 patients had discontinued treatment (226 in the sorafenib group and 242 in the placebo group) (Fig. 1). The most common reasons for discontinuation in both groups were adverse events (176 patients) and radiologic and symptomatic progression (123 patients). The median duration of treatment was 5.3 months (range, 0.2 to 16.1) in the sorafenib group and 4.3 months (range, 0.1 to 16.6) in the placebo group. Overall, 227 patients in the sorafenib group (76%) and 284 in the placebo group (94%) received more than 80% of the planned daily dose of the study drug.

### SAFETY

The overall incidence of treatment-related adverse events was 80% in the sorafenib group and 52% in the placebo group (Table 3). Adverse events that were reported for patients receiving sorafenib were predominantly grade 1 or 2 in severity and gastrointestinal, constitutional, or dermatologic in nature. Diarrhea, weight loss, hand–foot skin reaction, alopecia, anorexia, and voice changes occurred at a higher frequency in the sorafenib group than in the placebo group (P<0.001). Grade 3 drug-related adverse events included diarrhea (8% in the sorafenib group vs. 2% in the placebo group, P<0.001), hand–foot skin reaction (8% vs. <1%, P<0.001), hypertension (2% vs. <1%, P=0.28), and abdominal pain (2% vs. 1%, P=0.17); there were no grade 4 drug-related adverse events in any of these categories in either study group (Table 3). Grade 3 or 4 laboratory abnormalities occurred at similar frequencies in the two study groups, with the exception of grade 3 hypophosphatemia (11% in the sorafenib group vs. 2% in the placebo group, P<0.001) and grade 3 or 4 thrombocytopenia (4% in the sorafenib group vs. <1% in the placebo group, P=0.006).

The rate of discontinuation of the study drug due to adverse events was similar in the two study groups (38% vs. 37%). The most frequent adverse events leading to discontinuation of sorafenib treatment were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%). Dose reductions due to adverse events occurred in 26% of the patients in the sorafenib group and 7% of those in the placebo group, whereas dose interruptions due to adverse events occurred in 44% and 30% of the patients, respectively. The most frequent adverse events leading to dose reductions in the sorafenib group were diarrhea (8%), hand–foot skin reaction (5%), and rash or desquamation (3%). Drug-related adverse events leading to permanent treatment discontinuation occurred in 34 patients in the sorafenib group (11%) and 15 patients in the placebo group (5%).

The overall incidence of serious adverse events from any cause was similar in the two study groups: 52% (153 patients) in the sorafenib group and 54% (164 patients) in the placebo group. (In the Supplementary Appendix, adverse events and serious adverse events during treatment are described in Table C1 and Table C2, respectively.)

In the sorafenib group and the placebo group, the incidences of serious hepatobiliary adverse

**Table 1. Demographic and Baseline Characteristics of the Patients (Intention-to-Treat Population).***

| Variable | Sorafenib (N=299) | Placebo (N=303) |
|---|---|---|
| Age — yr | 64.9±11.2 | 66.3±10.2 |
| Sex — no. (%) | | |
| Male | 260 (87) | 264 (87) |
| Female | 39 (13) | 39 (13) |
| Region — no. (%) | | |
| Europe and Australasia | 263 (88) | 263 (87) |
| North America | 27 (9) | 29 (10) |
| Central and South America | 9 (3) | 11 (4) |
| Cause of disease — no. (%) | | |
| Hepatitis C only | 87 (29) | 82 (27) |
| Alcohol only | 79 (26) | 80 (26) |
| Hepatitis B only | 56 (19) | 55 (18) |
| Unknown | 49 (16) | 56 (19) |
| Other | 28 (9) | 29 (10) |
| ECOG performance status — no. (%)† | | |
| 0 | 161 (54) | 164 (54) |
| 1 | 114 (38) | 117 (39) |
| 2 | 24 (8) | 22 (7) |
| BCLC stage — no. (%)‡ | | |
| B (intermediate) | 54 (18) | 51 (17) |
| C (advanced) | 244 (82)§ | 252 (83) |
| Macroscopic vascular invasion — no. (%) | 108 (36) | 123 (41) |
| Extrahepatic spread — no. (%) | 159 (53) | 150 (50) |
| Lymph nodes | 89 (30) | 65 (21) |
| Lung | 67 (22) | 58 (19) |
| Macroscopic vascular invasion, extrahepatic spread, or both — no. (%) | | |
| Absent | 90 (30) | 91 (30) |
| Present | 209 (70) | 212 (70) |
| Child–Pugh class — no. (%)¶ | | |
| A | 284 (95) | 297 (98) |
| B | 14 (5) | 6 (2) |
| Biochemical analysis | | |
| Albumin — g/dl | | |
| Median | 3.9 | 4.0 |
| Range | 2.7–5.3 | 2.5–5.1 |
| Total bilirubin — mg/dl | | |
| Median | 0.7 | 0.7 |
| Range | 0.1–16.4 | 0.2–6.1 |
| Alpha-fetoprotein — ng/ml | | |
| Median | 44.3 | 99.0 |
| Range | 0–208×10$^4$ | 0–5×10$^5$ |

**Table 1. (Continued.)**

| Variable | Sorafenib (N = 299) | Placebo (N = 303) |
|---|---|---|
| Previous therapy — no. (%)‖ | | |
| Surgical resection | 57 (19) | 62 (20) |
| Locoregional therapy | | |
| Transarterial chemoembolization | 86 (29) | 90 (30) |
| Percutaneous ethanol injection | 28 (9) | 20 (7) |
| Radiofrequency ablation | 17 (6) | 12 (4) |
| Radiotherapy** | 13 (4) | 15 (5) |
| Systemic anticancer therapy | | |
| Hormonal therapy | 7 (2) | 8 (3) |
| Cytotoxic chemotherapy | 1 (<1) | 1 (<1) |
| Concomitant systemic antiviral therapy — no. (%) | 6 (2) | 2 (1) |

* Plus–minus values are means ±SD. None of the differences between the two study groups were significant (P≥0.05). To convert the values for bilirubin to micromoles per liter, multiply by 17.1. BCLC denotes Barcelona Clinic Liver Cancer staging system, and ECOG Eastern Cooperative Oncology Group.
† The ECOG performance status assesses the daily living abilities of the patient, on a scale ranging from 0 (fully active) to 5 (dead).[15]
‡ The BCLC system ranks hepatocellular carcinoma in five stages, ranging from 0 (very early stage) to D (terminal stage).[3]
§ One patient in the sorafenib group had a BCLC score of D and a Child–Pugh class of C.
¶ The Child–Pugh system evaluates the severity of liver disease, with patients divided into classes from A to C, with class C representing the worst prognosis.[16,17]
‖ Patients may have received more than one type of therapy. There was no significant difference between groups in the number of patients who had received previous palliative or curative therapy or previous adjuvant or neoadjuvant therapy (P≥0.05).
** Radiotherapy was applied to extrahepatic metastatic lesions in all patients except five in the sorafenib group and three in the placebo group.

events (11% and 9%, respectively), serious hemorrhagic events (9% and 13%), variceal bleeding (2% and 4%), renal failure (<1% and 3%), and cardiac ischemia or infarction (3% and 1%) were similar; the most common serious adverse events of any cause (aside from death) were liver dysfunction (7% and 5%, respectively), diarrhea (5% and 2%), and ascites (5% and 4%) (Table C2 in the Supplementary Appendix). Within 30 days after the final dose of the study drug, there were 13 deaths in the sorafenib group and 29 deaths in the placebo group that were not attributed to disease progression.

## DISCUSSION

In this trial, patients with advanced hepatocellular carcinoma who received sorafenib treatment had nearly a 3-month median survival benefit, as compared with those who received placebo. At the time the study was stopped, after the second prespecified interim analysis (conducted when 321 patients had died), patients in the sorafenib group had a median survival of 10.7 months, as compared with 7.9 months in the placebo group. The effect of sorafenib on overall survival remained significant after adjustment for baseline prognostic factors that were found to influence survival, thus supporting the primary analysis. The benefit of sorafenib was also consistent among all prespecified stratification groups, including patients with the worst prognosis, such as those with an ECOG performance status of 1 or 2 or with macroscopic vascular invasion or extrahepatic spread.

This study was designed to capture the benefits of a potentially efficacious drug while avoiding the confounding effect of deaths unrelated to cancer progression. Since hepatocellular carcinoma develops mainly in patients with cirrhosis, it was critical to select patients with well-preserved liver function (Child–Pugh class A).[16,17] If the trial had included patients with more advanced liver failure (Child–Pugh class B or C), deaths related to advanced liver disease might have masked any

**Table 2. Summary of Efficacy Measures.***

| Outcome | Sorafenib (N=299) | Placebo (N=303) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| Overall survival (mo) | | | 0.69 (0.55–0.87) | <0.001 |
| Median | 10.7 | 7.9 | | |
| 95% CI | 9.4–13.3 | 6.8–9.1 | | |
| 1-yr survival rate (%) | 44 | 33 | | 0.009 |
| Time to symptomatic progression (mo)† | | | 1.08 (0.88–1.31) | 0.77 |
| Median | 4.1 | 4.9 | | |
| 95% CI | 3.5–4.8 | 4.2–6.3 | | |
| Time to radiologic progression (mo) | | | 0.58 (0.45–0.74) | <0.001 |
| Median | 5.5 | 2.8 | | |
| 95% CI | 4.1–6.9 | 2.7–3.9 | | |
| Level of response (%)‡ | | | | |
| Complete | 0 | 0 | | NA |
| Partial | 2 | 1 | | 0.05 |
| Stable disease | 71 | 67 | | 0.17 |
| Disease-control rate (%)§ | 43 | 32 | | 0.002 |

* NA denotes not applicable.
† Symptomatic progression was defined as a decrease of 4 or more points from the baseline score on the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) questionnaire, deterioration to a score of 4 in Eastern Cooperative Oncology Group performance status, or death, whichever occurred first.[19] The scores were confirmed 3 weeks later at the next scheduled assessment.
‡ The level of response was measured according to RECIST (Response Evaluation Criteria in Solid Tumors)[18] by independent radiologic review.
§ The disease-control rate was the percentage of patients who had a best-response rating of complete or partial response or stable disease (according to RECIST) that was maintained for at least 28 days after the first demonstration of that rating on independent radiologic review.

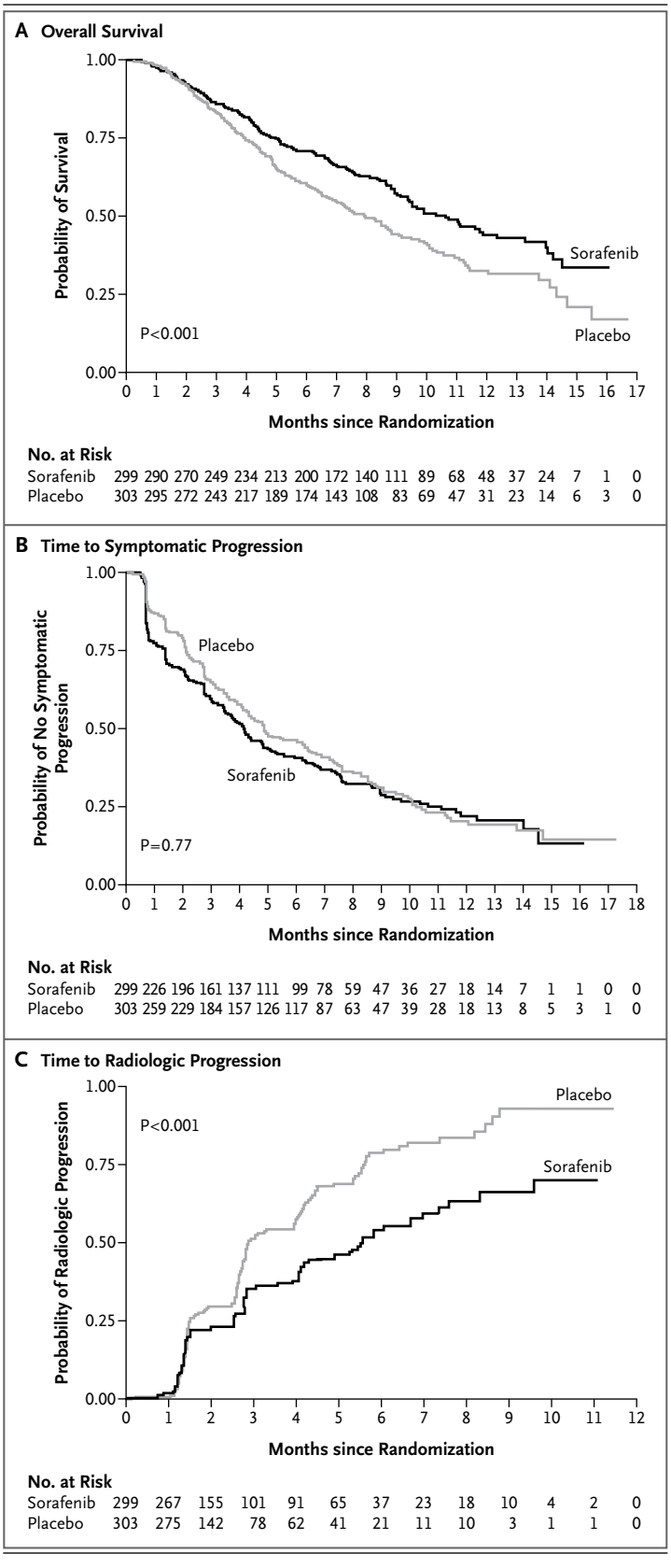
significant activity of sorafenib. Further data will be needed to confirm the safety and survival benefit of sorafenib in patients with poorer liver function. In addition, the choice of survival as a primary outcome was important, since other potential surrogate outcomes that are often used in oncology, such as progression-free survival, are considered to be suboptimal for the clinical evaluation of this cancer because of the confounding effect of the underlying cirrhosis. The absence of overlap in the confidence intervals between the groups that was observed for overall survival and the time to progression suggests that most of the patients receiving sorafenib had a delay in the progression of the disease that might have resulted in the prolongation of survival.

The second primary outcome, the time to symptomatic progression, did not differ significantly between the two groups. The FHSI8 questionnaire is a patient-oriented outcome instrument that might have been influenced by both the presence of symptoms related to the toxic effects of the drug and the effect of the response to tumor-related symptoms.[19] The lack of a significant difference in responses to the FHSI8 questionnaire might reflect the effect of the reporting of sorafenib's toxic effects by patients. In addition, the quality of life of these patients might have been affected by symptoms related to liver failure, which continued, regardless of whether the tumor stabilized or regressed.

Sorafenib simultaneously inhibits molecular components of the Raf–MEK–ERK signaling pathway, abrogating tumor growth and VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-$\beta$, thus inhibiting neoangiogenesis.[7] By targeting two key pathways that are reported to play an important role in the pathogenesis of hepatocellular carcinoma,[9-12] sorafenib is likely to delay disease progression; this might explain the observed survival benefit despite the low incidence of objective responses. Nonetheless, pharmacogenomic studies are under

**Figure 2. Kaplan–Meier Analysis of Overall Survival, the Time to Symptomatic Progression, and the Time to Radiologic Progression.**

Among 602 patients (of whom 299 received sorafenib and 303 received placebo), the median overall survival was 10.7 months in the sorafenib group, as compared with 7.9 months in the placebo group (hazard ratio for death in the sorafenib group, 0.69; 95% CI, 0.55 to 0.87) (Panel A). The median time to symptomatic progression was 4.1 months in the sorafenib group, as compared with 4.9 months in the placebo group (hazard ratio for progression in the sorafenib group, 1.08; 95% CI, 0.88 to 1.31) (Panel B). The median time to radiologic progression was 5.5 months in the sorafenib group, as compared with 2.8 months in the placebo group (hazard ratio for progression in the sorafenib group, 0.58; 95% CI, 0.45 to 0.74) (Panel C).




way to gain a further understanding of the drug's molecular mechanisms of action. In addition, the safety profile compares well with those of previously reported systemic therapies, such as the PIAF regimen (cisplatin, interferon, doxorubicin, and fluorouracil), which was associated with more severe complications than those observed with sorafenib.[21]

This trial shows that sorafenib improves overall survival by nearly 3 months in patients with advanced hepatocellular carcinoma. This finding is important, given the increasing incidence of the disease around the world[22] and the lack of efficacious therapeutic options in this setting.[2-6] Furthermore, no consistent survival benefits for anticancer agents in hepatocellular carcinoma have been recorded in approximately 100 randomized studies reported during the past 30 years,[2-6] including systemic and intraarterial chemotherapy (predominantly doxorubicin-based or platinum-based), various hormonal therapies (tamoxifen and antiandrogens), and immunotherapy (usually interferon alfa).[5,6,21] In some instances, such as studies of tamoxifen, encouraging data from underpowered initial studies[23,24] were not confirmed by subsequent large, well-designed, randomized studies.[3,6] Thus, scientific guidelines and regulatory agencies have not recommended or approved any drug for advanced hepatocellular carcinoma, representing a unique situation in the treatment of solid tumors and clearly an unmet medical need.[3,4]

Our finding that sorafenib, a multikinase inhibitor, has activity in hepatocellular carcinoma shows the potential of molecularly targeted therapies in this neoplasm. Other targeted agents that

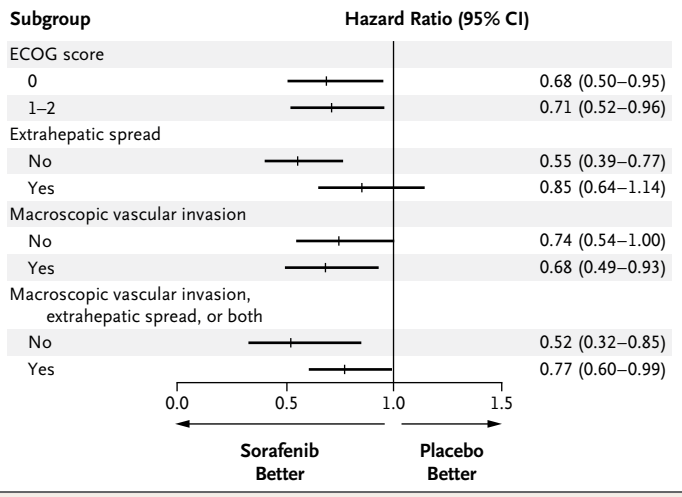



**Figure 3. Overall Survival of Selected Subgroups, According to Baseline Prognostic Factors.**

ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 (fully active) to 5 (dead).

have been evaluated in phase 2 clinical trials for the treatment of hepatocellular carcinoma include tyrosine kinase inhibitors of the epidermal growth factor receptor (erlotinib[25,26] and gefitinib[27]), a humanized monoclonal antibody against antivascular endothelial growth factor (bevacizumab[26,28,29]), and a multitargeted tyrosine kinase inhibitor (sunitinib[30,31]). Future studies should assess the benefits of combined molecular therapy, as compared with sorafenib alone.

The most frequent adverse events in this study were consistent with those observed in a previous phase 2 study involving patients with hepatocellular carcinoma[14] and in clinical trials of sorafenib in patients with advanced renal-cell carcinoma.[32,33] The adverse events that were more common in the sorafenib group (e.g., diarrhea, weight loss, and hand–foot skin reaction) were mainly mild to moderate in severity.[34] The two most relevant grade 3 drug-related adverse events were diarrhea and hand–foot skin reaction (both

**Table 3. Incidence of Drug-Related Adverse Events (Safety Population).***

| Adverse Event | Sorafenib (N=297) | | | Placebo (N=302) | | | P Value | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 or 4 |
| | percent | | | | | | | |
| Overall incidence | 80 | | | 52 | | | | |
| Constitutional symptoms | | | | | | | | |
| Fatigue | 22 | 3 | 1 | 16 | 3 | <1 | 0.07 | 1.00 |
| Weight loss | 9 | 2 | 0 | 1 | 0 | 0 | <0.001 | 0.03 |
| Dermatologic events | | | | | | | | |
| Alopecia | 14 | 0 | 0 | 2 | 0 | 0 | <0.001 | NA |
| Dry skin | 8 | 0 | 0 | 4 | 0 | 0 | 0.04 | NA |
| Hand–foot skin reaction | 21 | 8 | 0 | 3 | <1 | 0 | <0.001 | <0.001 |
| Pruritus | 8 | 0 | 0 | 7 | <1 | 0 | 0.65 | 1.0 |
| Rash or desquamation | 16 | 1 | 0 | 11 | 0 | 0 | 0.12 | 0.12 |
| Other | 5 | 1 | 0 | 1 | 0 | 0 | <0.001 | 0.12 |
| Gastrointestinal events | | | | | | | | |
| Anorexia | 14 | <1 | 0 | 3 | 1 | 0 | <0.001 | 1.00 |
| Diarrhea | 39 | 8 | 0 | 11 | 2 | 0 | <0.001 | <0.001 |
| Nausea | 11 | <1 | 0 | 8 | 1 | 0 | 0.16 | 0.62 |
| Vomiting | 5 | 1 | 0 | 3 | 1 | 0 | 0.14 | 0.68 |
| Voice changes | 6 | 0 | 0 | 1 | 0 | 0 | <0.001 | NA |
| Hypertension | 5 | 2 | 0 | 2 | 1 | 0 | 0.05 | 0.28 |
| Liver dysfunction | <1 | <1 | 0 | 0 | 0 | 0 | 0.50 | 0.50 |
| Abdominal pain not otherwise specified | 8 | 2 | 0 | 3 | 1 | 0 | 0.007 | 0.17 |
| Bleeding | 7 | 1 | 0 | 4 | 1 | <1 | 0.07 | 1.00 |

* Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 3.0), that occurred in at least 5% of patients in either study group. NA denotes not applicable.

of which occurred in 8% of patients in the sorafenib group). As has been previously observed in the treatment of renal-cell carcinoma,[33] sorafenib-associated adverse events led to dose reductions and interruptions in a subgroup of patients. Previous studies have raised caution about the risk of hemorrhagic and cardiac events in patients treated with sorafenib and other tyrosine kinase inhibitors.[12,34] This study did not identify an overall increase in the risk of bleeding, and the rates of variceal hemorrhage were similar in the two study groups, although the study may not have been large enough to accurately establish the incidence of uncommon adverse events.

In summary, this study showed that sorafenib prolonged median survival and the time to progression by nearly 3 months in patients with advanced hepatocellular carcinoma. Future studies are warranted to evaluate sorafenib as an adjuvant therapy after curative or locoregional therapies. Also needed are studies evaluating sorafenib in combination with other molecular targeted therapies and as a standard comparator, conducted according to recent guidelines for the design of clinical trials in hepatocellular carcinoma.[35]

Supported by Bayer HealthCare Pharmaceuticals–Onyx Pharmaceuticals.

Presented in part in abstract form at the annual meeting of the American Society of Clinical Oncology, Chicago, June 1–5, 2007.

Dr. Llovet reports receiving consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals, research grants from Exelixis, and consulting fees from Biocompatibles International and MDS Nordion; Drs. Mazzaferro, Santoro, and Schwartz, consulting fees from Bayer HealthCare Pharmaceuticals; Dr. Hilgard, lecture fees from Bayer HealthCare Pharmaceuticals and MDS Nordion; Dr. Gane, lecture fees from Novartis and GlaxoSmithKline; Dr. Raoul, consulting fees from Bayer HealthCare Pharmaceuticals and Biocompatibles and lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Forner, lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Porta, consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals; Drs. Zeuzem, Bolondi, and Galle, consulting and lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Greten, consulting and lecture fees from Bayer HealthCare Pharmaceuticals and lecture fees from Roche and Pfizer; Dr. Seitz, consulting fees from Sanofi-Aventis and Bayer HealthCare Pharmaceuticals; Dr. Borbath, consulting fees from Bayer HealthCare Pharmaceuticals and lecture fees from Novartis and Ipsen; Dr. Häussinger, lecture fees from Falk Foundation, Merz Pharma, and Roche; Mr. Giannaris and Drs. Shan, Moscovici, and Voliotis, being employees of Bayer HealthCare Pharmaceuticals; and Dr. Bruix, receiving consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals, consulting and lecture fees from Biocompatibles, consulting fees and research grants from Eisai, consulting fees from Bristol-Myers Squibb, AstraZeneca, and Pharmexa, and lecture fees from Bracco. No other potential conflict of interest relevant to this article was reported.

We thank the patients who participated in the study and their families, the members of the independent data and safety monitoring committee, Andrea Nadel of Bayer HealthCare Pharmaceuticals for data analysis, Noel Curtis of GeoMed for medical writing support, and Lila Adnane of Bayer HealthCare Pharmaceuticals for critical review of the manuscript.

## APPENDIX

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The following principal investigators enrolled patients in the SHARP trial: **Argentina:** M.G. Pallota, J.J. Zarba; **Australia:** M. Boyer, S. Riordan, A. Strickland, N. Tebbutt, B. Thomson; **Belgium:** I. Borbath, J. De Greve, J.-L. Van Laethem, W. Van Steenbergen, H. Van Vlierberghe; **Brazil:** C. Barrios, A. Cosme de Oliveira; **Bulgaria:** I. Kotzev, D. Takov, K. Tchernev; **Canada:** K. Burak, M. Ma, P. Metrakos, C. Olweny, M. Sherman; **Chile:** C. Gamargo Garate, J. Martinez-Castillo; **France:** M. Beaugrand, J. Bennouna, J.-F. Blanc, J.-P. Bronowicki, F. Degos, S. Dominguez, J.-D. Grange, P. Hillon, J.-L. Raoul, J.-F. Seitz; **Germany:** H. Blum, P. Buggisch, W. Caspary, M. Dollinger, P.R. Galle, G. Gerken, B. Göke, M. Gregor, T. Greten, D. Häussinger, J. Scherübl, M. Scheulen, R. Schmid, U. Spengler, R. Wiest, S. Zeuzem; **Greece:** C. Arvanitakis, G. Germanidis, I. Katsos; **Israel:** A. Figer, S. Stemmer; **Italy:** D. Amadori, L. Bolondi, F. Cognetti, A. Craxi, F. Farinati, C. Gridelli, A. Martoni, V. Mazzaferro, C. Porta, S. Ricci, A. Sangiovanni, A. Santoro, F. Trevisani; **Mexico:** L.E. Cisnero Garza; **New Zealand:** E. Gane, A. O'Donnell; **Peru:** J. Leon, A. Lozano; **Poland:** J. Jassem, G. Rydzewska, A. Szawlowski, P. Tomczak; **Romania:** F. Badulescu, L. Miron; **Russia:** V. Kubyshkin; **Spain:** J. Bruix, A. Forner, J. Bustamante Schneider, M. Diago, J.L. Montero Alvarez, S. Pascual, L. Ruíz del Arbol, B. Sangro, R. Solá, J. Tabernero; **Switzerland:** B. Muellhaupt, A. Roth; **United Kingdom:** T.R. Jeffry Evans, S. Falk, T. Meyer, H. Reeves, P. Ross; **United States:** A. Befeler, T. Boyer, C. Britten, T. Byrne, G. Garcia-Tsao, P. Gold, A. Goldenberg, D. Heuman, P. Kennedy, A. Koch, J.M. Llovet, J. Marrero, M. Schilsky, J. Schwartz, M. Schwartz.

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

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## 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.**

**Funding** **Specific funding was not used to do this study.**

## Introduction

Early-stage hepatocellular carcinoma is recognised as an excellent indication for liver transplantation. The size of the tumour, the number of tumours, and the presence of vascular invasion have been incorporated into the so-called Milan criteria, which predicts a low incidence of recurrence (about 10%) for transplant patients with a single tumour of 5 cm or less in size or with many tumours (up to a maximum of three, each 3 cm or less in size), and no macroscopic vascular invasion. Since the first prospective series done more than 10 years ago,[1,2] these criteria have been validated in several centres around the world, adopted as a prioritisation tool in the United Network of Organ Sharing (UNOS), and

Published **Online** December 4, 2008 DOI:10.1016/S1470-2045(08)70284-5

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incorporated in the Tumour Node Metastasis (TNM) and Barcelona Clinic Liver Cancer (BCLC) staging systems for hepatocellular carcinoma.[3–6]

In recent years, several studies have reported a good outcome for some patients transplanted outside these conventional criteria and the dichotomous yes/no nature of these criteria has been challenged for being too strict, because they exclude specific subgroups with meaningful, albeit lower, chances to benefit from transplantation. Furthermore, some patients might be excluded from transplantation as a result of the improvement in the accuracy of imaging techniques that enable the identification of very small lesions (<1 cm), which were undetectable a decade ago. Most of the studies on patients exceeding Milan criteria, however, are retrospective, with only a small number of patients, disease of variable severity, and short follow-up.[7–12] Overall, no precise information can be extracted from these studies, other than the further the distance from conventional limits, the higher the price in terms of malignant recurrences.[7]

The aim of the current study was to explore the area outside the conventional criteria for liver transplantation in hepatocellular carcinoma, by use of morphological (size of the largest tumour and number of tumours) and histological (microscopic vascular invasion) parameters in a large cohort of patients with adequate follow-up. The working postulation was that beyond the conventional eligibility criteria for transplantation for patients with hepatocellular carcinoma, a continuum in outcome probabilities could be identified linked to characteristics assessed in the TNM classification.[5]

## Methods

### Study background and data collection

The study design was presented during the International Liver Transplantation Society meeting held in Milan, Italy, in 2006 and a web-based survey of patients who received liver transplantation for hepatocellular carcinoma exceeding the Milan criteria was proposed. The website on which the survey can be completed (www.hcc-olt-metroticket.org) was built at the Clinical Trial Office of the National Cancer Institute of Milan, supported only by grants for investigator-initiated studies. The website was prepared according to the privacy and security regulations for sensitive data of both the European Union and the USA.

The **Metroticket Calculator** is available at http://www.hcc-olt-metroticket.org/calculator

After registration on the website, investigators from each centre were asked to enter data, with no restrictions for time of transplantation and tumour stage, of patients who underwent liver transplantation for hepatocellular carcinoma exceeding Milan criteria. The required dataset for each patient (table 1) was kept to a single-page form, to encourage maximum participation by as many centres as possible. Data on size of the main tumour, number of tumours, vascular invasion, grading, living donor versus cadaveric donor, year of transplantation, recurrence, and survival were based on the final pathology review of the explanted liver, and central review of pathology reports was not planned.

Patients who fell within conventional criteria could be entered on the database at the discretion of the investigators, because the database could also be used as a permanent registry for all patients who undergo transplant for hepatocellular carcinoma at each centre.

A professional website administrator and a data manager regularly checked the system and guaranteed security and privacy. Inconsistencies were corrected by contact with investigators in each centre. Data were analysed with approval by the local Institutional Review Board granted on the condition that all data was anonymised.

### Data presentation and study endpoints

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 TNM classification system: size of the largest tumour, number of tumours (morphology-related), and microvascular invasion (biology-related). Survival was chosen because it was considered to be the most reliable and unbiased endpoint in the research of hepatocellular carcinoma[13] and because of the assumption that in such a large patient population, causes of death other than tumour recurrence would not have been affected by the variables chosen for the study.

According to a previous proposal, data were plotted in a Cartesian plot, with size of the largest tumour on the X-axis and number of tumours on the Y-axis.[7]

Vascular invasion was included in the model as a biological variable rather than tumour grading because it was more consistently reported in the medical records and because of its lower interobserver variation compared with tumour grading.

The model was set up to give a mathematical function, which resulted in the prediction of survival after transplantation on the basis of the three covariates: size, number, and microvascular invasion. A by-product tool was the "Metroticket Calculator", a piece of software that is accessible online and which can calculate 3-year and 5-year overall survival probabilities, with confidence intervals, of a given patient on the basis of the characteristics of the hepatocellular carcinoma.

The secondary aim of this study was the identification of a subgroup of patients with hepatocellular carcinoma exceeding Milan criteria, who achieved a 5-year overall survival of at least 70%, which is similar to the outcome expected for patients who meet conventional criteria.[9–12]

### Statistical analyses

Overall survival was defined as the time interval between liver transplantation and death from any cause. Time was censored at the date of last follow-up assessment for patients who were still alive. Survival curves were estimated using the Kaplan-Meier method.

In the main analyses, size of the largest tumour, number of tumours, and presence or absence of microvascular invasion were entered into multiple Cox regression models, in this order, as covariates.[14] Tumour size and number were modelled as continuous variables by using three-knot restricted cubic splines,[15] together with size×number linear and non-linear interaction terms. Because data were sparse when tumour size was more than 150 mm or number of tumours was greater than 15, higher values were truncated at these thresholds. Microvascular invasion was modelled as a dummy variable (1/0, depending on whether it was present at post-transplant histological assessment). By backward selection, models were simplified on the basis of the Akaike Information Criterion.[16] The Cox proportional hazards assumption was checked by use of the smoothed plots of Schoenfeld residuals.[17] Cox model results were shown either by means of hazard ratio (HR) estimates, together with corresponding 95% CIs and Wald's test p values, or by graphical plots. The latter included log-relative hazard plots, showing the shape of the relation between the relative hazard of death and size or number of tumours, and contour plots showing the joint effect of the model covariates on survival probability.

The quality of the above Cox model was checked in several ways. First, for internal model validation, bootstrap resampling was applied to detect model overfitting.[18,19] Second, for checking the consistency of outcomes in the individual centres, we estimated the standardised mortality ratio (SMR), namely the ratio between the number of deaths noted and the number predicted by the Cox model in each centre. The SMRs were then fitted using the generalised linear mixed model with a Poisson response variable, and centre as a random factor.[19,20]

Finally, to assess whether the covariate effect on overall survival was mainly associated with the occurrence of tumour recurrence, we fitted Cox models that included recurrence as a time-dependent covariate, together with the prognostic score derived from the main Cox model analyses.

Although no formal sample-size calculation was made beforehand, the high number of deaths (more than 500) compared with the number of Cox model variables (five at most) implied that the "ten events per variable" rule was largely exceeded, thus implying sufficient accuracy and precision of regression estimates.[21]

Statistical tests were considered significant when the corresponding p value was less than 5%. SAS[22] and R[23] software were used to do the modelling and statistical calculations.

## Role of the funding source

This was an investigator-led study and no specific financial support was obtained. Investigators from the National Cancer Institute of Milan were partially funded by the Italian Association for Cancer Research (AIRC)

| | Number of patients (N=1556) | Milan criteria | | p value |
|---|---|---|---|---|
| | | Within (n=444) | Outside (n=1112) | |
| Transplant year, n (%) | | | | <0·0001 |
| 1984–90 | 53 (3·4) | 0 (0) | 53 (4·8) | |
| 1991–95 | 213 (13·7) | 54 (12·2) | 159 (14·3) | |
| 1996–2000 | 391 (25·1) | 93 (20·9) | 298 (26·8) | |
| 2001–06 | 899 (57·8) | 297 (66·9) | 602 (54·1) | |
| Transplant type, n (%) | | | | 0·006 |
| Cadaveric donor | 1404/1525 (92·1) | 421/443 (95·0) | 983/1082 (90·9) | |
| Living donor | 121/1525 (7·9) | 22/443 (5·0) | 99/1082 (9·1) | |
| Not available | 31 (··) | 1 (··) | 30 (··) | |
| Age, years | | | | 0·216 |
| Median (IQR) | 55 (50–60) | 55 (50–59) | 56 (50–61) | |
| Range | 10–75 | 30–69 | 10–75 | |
| Range of tumours, n (%) | | | | <0·0001 |
| 1 | 404 (26·0) | 257 (57·9) | 147 (13·2) | |
| 2–3 | 569 (36·6) | 187 (42·1) | 382 (34·4) | |
| 4–5 | 338 (21·7) | 0 (0) | 338 (30·4) | |
| 6–10 | 203 (13·0) | 0 (0) | 203 (18·3) | |
| >10 | 42 (2·7) | 0 (0) | 42 (3·8) | |
| Number of tumours | | | | <0·0001 |
| Median (IQR) | 3 (1–5) | 1 (1–2) | 4 (2–5) | |
| Range | 1–20 | 1–3 | 1–20 | |
| Maximum tumour size, mm | | | | <0·0001 |
| Median (IQR) | 35 (22–50) | 20 (15–30) | 40 (30–60) | |
| Range | 1–200 | 1–50 | 4–200 | |
| Grading, n (%) | | | | 0·003 |
| G1 | 284/1113 (25·5) | 50/197 (25·4) | 234/916 (25·5) | |
| G2 | 550/1113 (49·4) | 115/197 (58·4) | 435/916 (47·5) | |
| G3 | 279/1113 (25·1) | 32/197 (16·2) | 247/916 (27·0) | |
| Not available | 443 (··) | 247 (··) | 196 (··) | |
| Vascular invasion, n (%) | | | | <0·0001 |
| No | 977/1475 (66·2) | 361/405 (89·1) | 616/1070 (57·6) | |
| Yes | 498/1475 (33·8) | 44/405 (10·9) | 454/1070 (42·4) | |
| Not available | 81 (··) | 39 (··) | 42 (··) | |
| Follow-up, months | | | | ·· |
| Median (IQR) | 53 (25–95) | 47 (25–85) | 57 (25–97) | |
| Patient status, n | | | | ·· |
| Alive (with/without recurrence) | 60/904 | 8/327 | 52/577 | |
| Dead (with/without recurrence) | 251/341 | 11/98 | 240/243 | |
| Recurrence-free survival (95% CI), % | | | | <0·0001 |
| 5 years | 72·6 (69·6–75·3) | 94·5 (91·4–96·5) | 64·1 (60·3–67·6) | |
| 10 years | 68·2 (64·5–71·5) | 94·5 (91·4–96·5) | 58·1 (53·5–62·4) | |
| Overall survival (95% CI), % | | | | <0·0001 |
| 5 years | 59·1 (56·1–61·9) | 73·3 (68·2–77·7) | 53·6 (50·1–57·0) | |
| 10 years | 46·8 (43·0–50·5) | 69·6 (63·7–74·8) | 38·7 (34·2–43·1) | |
| Median overall survival (IQR), months | 95 (22–nr) | nr (46–nr) | 75 (18–nr) | |

IQR=interquartile range. nr=not reached.

***Table 1:*** **Main characteristics of patients with hepatocellular carcinoma undergoing liver transplantation**

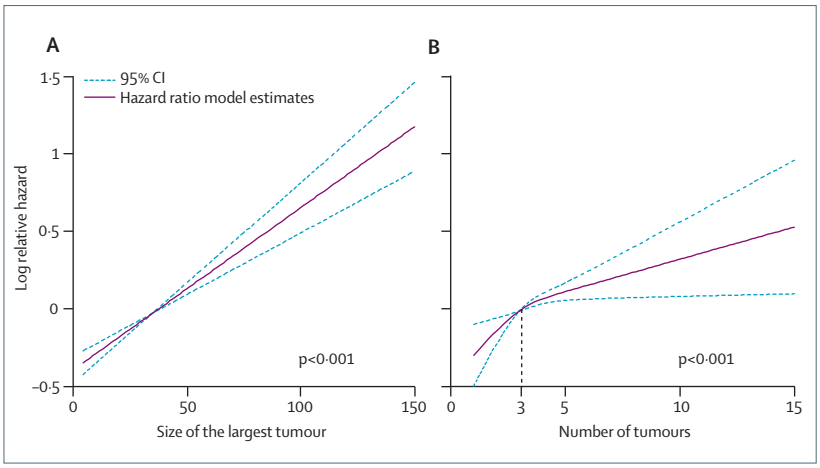


***Figure 1:*** **Log-relative risk of death related to size of the largest tumour (A) and number of tumours (B)**
(A) Number of tumours was fixed at three (median value of the number distribution). (B) Size was fixed at 35 mm. The increase in risk in patients with hepatocellular carcinoma is clearly related to the progressive increment of either the size or number with different patterns (see text).

| | HR (95% CI) | p value |
|---|---|---|
| Size of largest tumour (50 *vs* 22 mm) | | <0·001 |
| N=1 (1st quartile) | 1·38 (1·27–1·51) | |
| N=3 (median) | 1·34 (1·25–1·44) | |
| N=5 (3rd quartile) | 1·30 (1·20–1·40) | |
| Number of tumours (5 *vs* 1) | | <0·001 |
| S=22 mm (1st quartile) | 1·55 (1·23–1·97) | |
| S=35 mm (median) | 1·51 (1·21–1·88) | |
| S=50 mm (3rd quartile) | 1·46 (1·18–1·81) | |

Data derived from figure 1. HR=hazard ratio. N=number. S=size.

***Table 2:*** **Risk of death related to size of the largest tumour and number of tumours**

and the Oncology Research Funds of the Italian Ministry of Health. All authors were responsible for data collection and interpretation. V Mazzaferro, R Miceli, M Schiavo, L Mariani, and P Majno had full access to all data, and V Mazzaferro and P Majno had the final responsibility to submit for publication.

## Results

During the 10-month recruitment period, between June 25, 2006, and April 3, 2007, 36 liver-transplantation centres entered data on the website, with an overall data collection of 1556 patients who underwent liver transplantation for hepatocellular carcinoma: 1274 patients (81·9%) from 31 centres in Europe, 269 patients (17·3%) from four centres in America, and 13 patients (0·8%) from one centre in Asia. The study population included 1112 patients (71·5%) with hepatocellular carcinoma exceeding Milan criteria, and 444 patients (28·5%) not exceeding such criteria at post-transplant pathology review.

Characteristics of the collected series and cumulative data on overall survival are summarised in table 1.

More than 50% of patients with hepatocellular carcinoma exceeding conventional criteria (602 of 1112 patients) underwent transplant between 2001 and 2006. In the group of patients exceeding the criteria (n=1112), the median number of tumours was four (interquartile range [IQR] 2–5) and the median size of the tumours was 40 mm (30–60). 583 of 1112 patients (52·4%) had multifocal disease exceeding three nodules. These characteristics were significantly different to those of the group of patients with hepatocellular carcinoma adherent to Milan criteria (p<0·0001). With respect to histological surrogates of biological behaviour, hepatocellular carcinoma exceeding conventional criteria showed a significantly higher percentage of undifferentiated grade 3 tumours (p=0·003) and vascular invasion (p<0·0001) than hepatocellular carcinomas that fell within the Milan criteria. However, due to the high number of patients with missing data for tumour grading (443 of 1556 [28·5%]) a meaningful consideration of tumour grading in the survival model was precluded, whereas information on vascular invasion was available for most patients (1475 of 1556 [94·8%]) included in the database. In patients with hepatocellular carcinoma exceeding the Milan criteria, vascular invasion was present in 454 of the 1070 patients (42·4%) with data available versus 44 of 405 patients (10·9%) with hepatocellular carcinoma within the Milan criteria.

Overall median follow-up was 53 months (IQR 25–95), with a total number of 592 deaths from any cause (483 patients [81·6%] with hepatocellular carcinomas exceeding Milan criteria), and tumour recurrence was noted in 311 patients overall. This resulted in a significant difference in the observed 5-year overall survival: 53·6% (95% CI 50·1–57·0) for patients with hepatocellular carcinomas exceeding the Milan criteria versus 73·3% (68·2–77·7) for those with hepatocellular carcinomas within the Milan criteria (p<0·0001).

Results of Cox regression models, either based solely on the size of the largest tumour and number of tumours, or including microvascular invasion, are shown in figure 1 and table 2, and figure 2. These models, after applying a backward selection procedure, included a linear term for size, a cubic spline for number, and the linear-by-linear interaction size-by-number.

Because of the presence of interaction, the effect of size (or number) could not be represented separately, and thus is shown for different values of each of the two variables. Estimated HRs for the increase in the relative hazard of death associated with size or number progression were about 1·3 and 1·5, respectively (table 2). For example, patients with five tumours were estimated to have a risk 1·55-times higher than patients with one tumour of 22 mm in size (1st quartile of the size distribution; figure 1), or slightly lower at 1·46-times for a tumour of 50 mm in size (3rd quartile; figure 1 and table 2). Conversely, patients with a tumour of 50 mm in size were estimated to have about 1·38-times the risk of patients with a hepatocellular carcinoma of 22 mm in size, and this risk for a 50-mm

 Published online December 4, 2008 DOI:10.1016/S1470-2045(08)70284-5

versus 22-mm tumour did not change with an increasing number of tumours (table 2).

Although the effect of size was linear, the covariate number of tumours showed a non-linear behaviour in which the increment was sharp for up to three tumours and weak thereafter (figure 1). Incidentally, such a result supported the number of three tumours as the accepted cut-off for the criteria currently used for transplant candidacy.

A doubling in the hazard of death was associated with the presence of microvascular invasion. The median number of tumours in the subgroup of patients with hepatocellular carcinomas not showing microvascular invasion was two (IQR 1–4), whereas in the subgroup of patients with tumours presenting microvascular invasion the median number was three (2–5). The corresponding estimates for median tumour size were 30 mm for no microvascular invasion (20–45) and 45 mm for the presence of microvascular invasion (30–65 mm). Both differences were significant (p<0·0001).

Figure 2 shows 5-year overall survival estimates as a function of different values of size, number, and microvascular invasion. Contour lines connect points of equal probability, and are shown to aid with the clinical interpretation of the model. As a practical tool for individualised calculation of survival probability, a freely accessible software tool was developed, called the Metroticket Calculator (link to website noted earlier), which provides 3-year and 5-year survival estimates and 95% CIs for an individual patient on the basis of their tumour characteristics.

A search for combinations of tumour characteristics exceeding the Milan criteria, but resulting in an estimated 5-year overall survival of at least 70% generated a subgroup that, in the absence of microvascular invasion, fulfilled the so-called up-to-seven criteria, with seven being the result of the sum of size (in cm) and number of tumours for any given hepatocellular carcinoma. This includes all combinations of a given hepatocellular carcinoma from one nodule up to 6 cm in size (1+6=7) to many tumours fulfilling seven as the sum of the size plus number (ie, two tumours up to 5 cm in size, three tumours up to 4 cm in size, four tumours up to 3 cm in size, and five tumours up to 2 cm in size). The 5-year overall survival estimate for this subgroup of 283 patients was 71·2%, (95% CI 64·3–77·0), which was not significantly different from the 5-year overall survival for the 444 patients who had hepatocellular carcinomas within the Milan criteria, irrespective of microvascular invasion (figure 3; 73·3% (68·2–77·7). Patients exceeding the up-to-seven criteria, plus patients with microvascular invasion who were beyond the Milan criteria and within the up-to-seven criteria (829 patients), had a 48·1% (44·1–52·0) 5-year overall survival (p<0·001).

The occurrence of microvascular invasion at any size-and-number category was paralleled by a significant deterioration in patient outcome, both for overall survival and cumulative incidence of post-transplant recurrence (table 3). This was assessed in a uniform way, according to international guidelines.[4] Differences in survival in the identified prognostic categories were deemed significant regardless of graft origin (ie, deceased *vs* living donor).

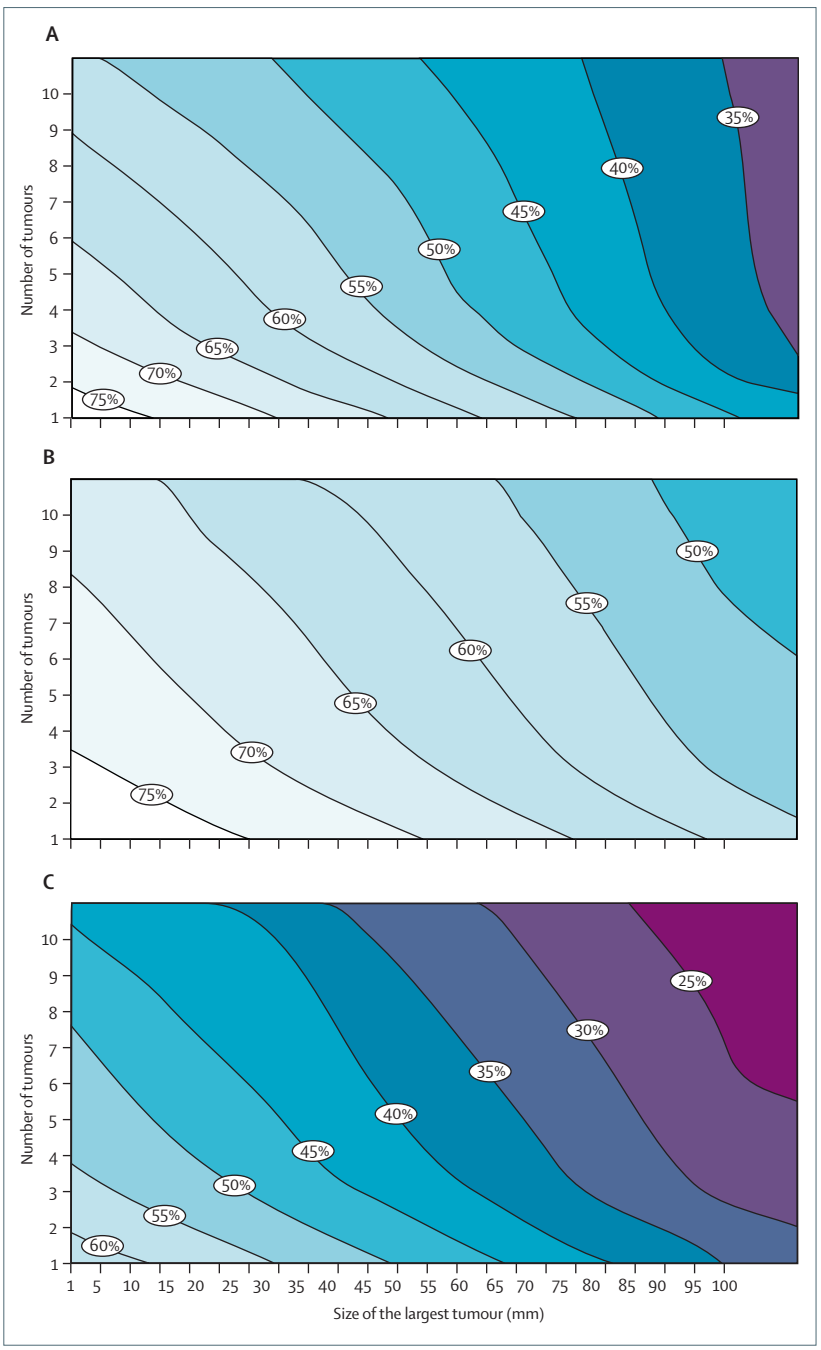


***Figure 2:*** **Contour plot of the 5-year overall-survival probability according to size of the largest tumour, number of tumours, and presence or absence of microvascular invasion**
(A) Survival estimates according to size and number, not considering microvascular invasion (median SE 4·2% [interquartile range 3·6–5·2]). (B,C) Survival estimates according to absence (B) or presence (C) of microvascular invasion. Presence of microvascular invasion approximately halves the survival predicted in the absence of the same variable: absent (6·3% [5·7–7·1]); present (3·7% [3·1–4·7]).



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A significant increase in the proportion of hepatocellular carcinomas with microvascular invasion was noted as the limit of the Milan criteria was moved to the up-to-seven criteria and beyond (31 of 187 [16·6% *vs* 95 of 324 [29·3%] *vs* 287 of 572 [50·2%], respectively; figure 4).

Although microvascular invasion was the strongest covariate affecting patient survival, high tumour grade (grade 3) significantly affected outcome (table 1) and significantly increased in prevalence from 16·0% (30 of 187) to 21·3% (69 of 324) to 30·6% (175 of 572), as tumour staging progressed from Milan criteria, to the up-to-seven category, and beyond (p<0·0001; figure 4). However, data on grading of hepatocellular carcinoma were not available in 443 of 1556 (28·5%) of the patients, preventing grade 3 from being included in the predictive survival model.

The prediction of tumour recurrence by the model paralleled patient survival, but was less precise because of a decreased accuracy of the data in terms of interval to recurrence and treatment efficacy on survival. As expected, due to the high number of events compared with the number of model parameters, and the use of a selection procedure that was not based on multiple testing, bootstrap validation showed that overfitting was negligible, and therefore no adjustment of Cox model estimates was needed. The effect of size-and-number covariates on overall survival, as summarised by the prognostic score in the main analysis, was almost totally abolished when tumour recurrence was included as a time-dependent covariate (regression coefficient b=0·08, SE=0·12, p=0·476). This shows that the prognostic effect of size-and-number on survival is mediated by the occurrence of tumour relapse. Results were less clear-cut when adding in the variable microvascular invasion, in that the regression coefficient associated with the prognostic score derived from this model differed significantly from zero (b=0·31, SE=0·09, p<0·0001). Thus, whether or not microvascular invasion affects survival independently of tumour recurrence, either directly, or by association with other factors, remains to be elucidated.

The model for checking the consistency of outcomes between the individual centres showed that between-centre variability, as estimated from the common random effect, was 22% (SE 8·3): a result indicating that some degree of variation exists, between centres, around an average SMR of 1·18, which indicates a negligible overestimation (<1%) of the model's general predicitive ability with respect to the observed mortality.

## Discussion

This study, based on an unprecedented sample size of 1112 patients with hepatocellular carcinomas that fell outside the conventional transplantation criteria, aimed to establish a model that is able to predict survival probabilities on the basis of objective tumour parameters—ie, size of the tumour, number of tumours, and microscopic vascular invasion. The model presented here represents the first large-scale attempt to stratify patients with hepatocellular carcinoma in a continuum of outcome probabilities: an important advance compared with the current dual yes/no approach of the Milan criteria or alternative criteria, which are considered by the transplant community as unduly restrictive.[8–12]

This model provides consistent data for estimates of outcome in most scenarios of liver transplantation for

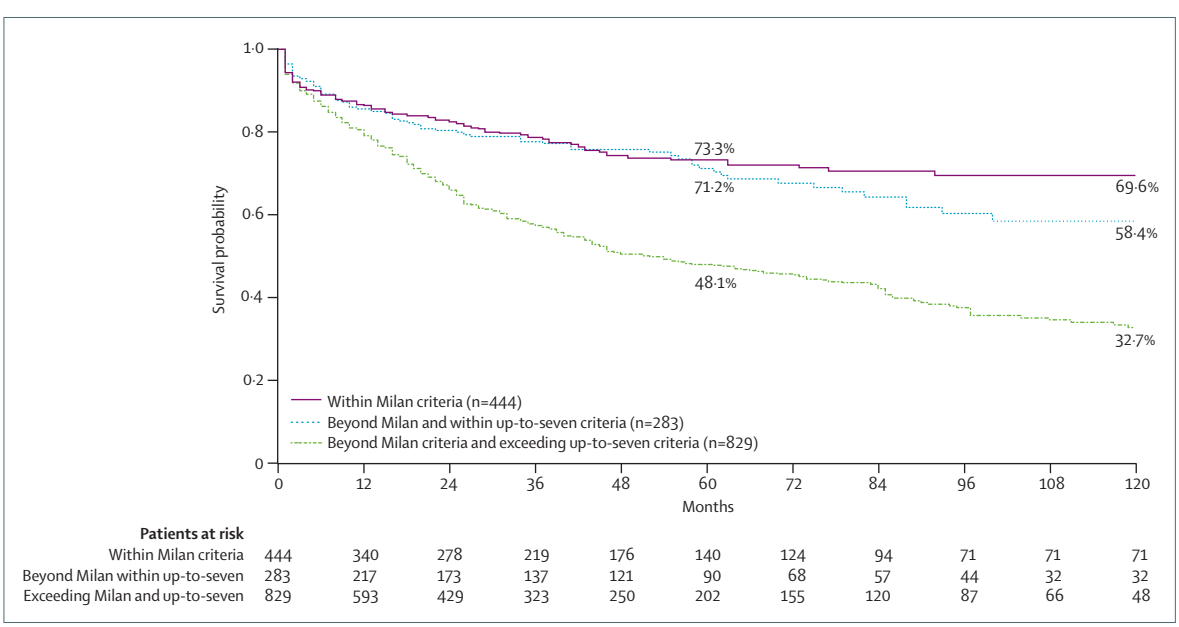


***Figure 3:*** **Up-to-seven criteria**
Kaplan-Meier overall survival curves of the three subgroups: within Milan criteria (n=444); beyond Milan and within up-to-seven criteria (n=283); and beyond Milan and exceeding up-to-seven criteria (n=829). Patients with hepatocellular carcinomas beyond Milan criteria, but within up-to-seven criteria had a similar survival compared with patients within Milan criteria. Patients beyond up-to-seven criteria had a significant deterioration in survival (p<0·001).

hepatocellular carcinoma and identifies three separate prognostic categories: a population fulfilling the so-called up-to-seven rule, in which preoperative assessment of the absence of microvascular invasion is crucial because, in its presence, the results are equivalent to transplantation within conventional criteria (figure 3); an intermediate group (5-year overall survival 50–65%), in which further refinement of prognostication is needed; and a group with characteristics of hepatocellular carcinoma that are associated with such a poor outcome (ie, survival below 50% at 5 years) that transplantation should be considered futile.

After more than a decade of excellent outcomes for liver transplantation for hepatocellular carcinoma with restrictive selection criteria, several expansions of the criteria have been suggested on the basis of post-transplant survival comparable to that achieved after application of the Milan criteria.[10] The lack of consensus on expanded indications has resulted in unreasonable heterogeneity in clinical practice, with some proposals expanded just beyond the borders of the conventional criteria, and others much more liberally dispersed from the conventional limits. In the current scenario, rather than debating whether the expanded criteria are better or worse than the Milan criteria, the fundamental question to be answered is whether expanded criteria can result in post-transplant survival that is considered acceptable to justify the use of a scarce resource.[24,25]

The advantages of an individualised forecast for patients with liver cancer who are proposed for transplant candidacy are self-evident in the frame of graft shortage and limited access to transplantation. However, further refinements of the model are desirable for other parameters that were not included in the present study, such as tumour progression with time, grading, aetiology of cirrhosis (eg, hepatitis B virus or hepatitis C virus), cause of death, response to pre-transplant treatments, alpha-fetoprotein concentrations, and genomic markers,[26–28] which have all been shown to predict outcomes in subgroups of hepatocellular carcinoma, independently from clinical variables.

A second potential limitation of the current model is that data on tumour characteristics were collected from postoperative histopathology reports. It is known that pre-transplant staging fails to predict the number of hepatocellular tumours at pathology in about 25–35% of patients, due to both understaging and overstaging.[29–31] If updated imaging techniques are used, inaccuracies in the pretransplant assessment should not concern the maximum size of the tumour.[32] As for the number of tumours, discrepancies between preoperative and postoperative investigations are currently decreasing with the improving quality of radiological imaging[29,30,32] and can be included in the model by considering alternative scenarios (ie, adding or subtracting one or two tumours in the outcome calculations). Incidentally, this study shows that the importance of the number of tumours decreases as the number increases (figures 1 and 2).

| | Milan (within)* | Milan (outside)† | |
|---|---|---|---|
| | | Within up-to-seven criteria | Exceeding up-to-seven criteria |
| **Microvascular invasion absent** | | | |
| Number of patients | 361 | 283 | 333 |
| Overall survival‡ (95% CI), % | | | |
| 3 years | 81·8 (77·1–85·7) | 77·7 (72·0–82·5) | 71·8 (66·2–76·7) |
| 5 years | 76·1 (70·6–80·7) | 71·2 (64·3–77·0) | 64·0 (57·7–69·5) |
| Crude cumulative incidence of recurrence (95% CI), % | | | |
| 3 years | 3·3 (1·8–6·0) | 4·8 (2·7–8·6) | 17·4 (13·5–22·5) |
| 5 years | 3·3 (1·8–6·0) | 9·1 (5·6–14·5) | 22·3 (17·7–28·0) |
| **Microvascular invasion present** | | | |
| Number of patients | 44 | 116 | 338 |
| Overall survival‡ (95% CI), % | | | |
| 3 years | 77·1 (60·2–87·5) | 60·2 (49·7–69·2) | 41·7 (35·8–47·5) |
| 5 years | 71·6 (51·8–84·4) | 47·4 (36·4–57·7) | 33·0 (27·2–38·9) |
| Crude cumulative incidence of recurrence (95% CI), % | | | |
| 3 years | 12·8 (5·6–29·6) | 31·3 (23·3–41·9) | 31·3 (23·3–41·9) |
| 5 years | 12·8 (5·6–29·6) | 39·9 (30·8–51·7) | 51·5 (45·8–57·8) |

*Data missing for 39 patients. †Data missing for 42 patients. ‡According to Kaplan-Meier analysis.

***Table 3:*** **Outcome of liver transplantation for hepatocellular carcinoma according to Milan criteria and up-to-seven criteria, in relation to microvascular invasion**

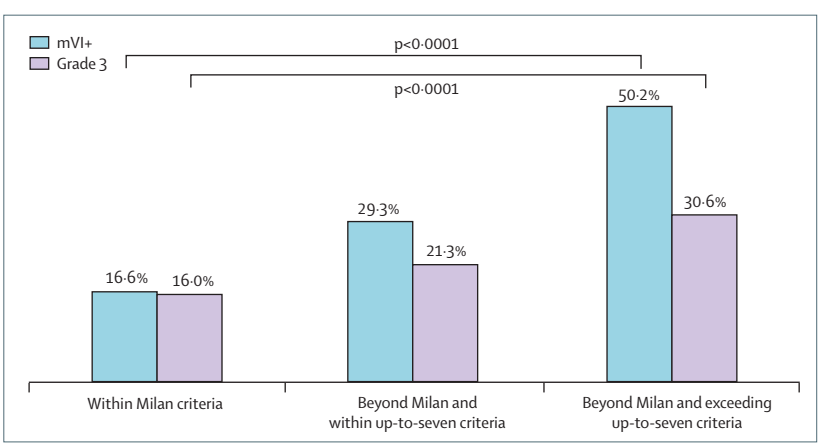


***Figure 4:*** **Correlation of microvascular invasion and poorly differentiated tumour (grade 3) in the identified size-and-number group categories**
In the 1083 patients for whom data on both microvascular invasion and tumour grading were available, a progressive increment of high-grade tumour pattern (grade 3) was noted, which tended to parallel the increase in size-and-number tumour characteristics and the incidence of microvascular invasion (mVI+). By contrast with the other analyses, this analysis included both the presence and absence of microvascular invasion in patients with hepatocellular carcinoma that fell within the up-to-seven criteria. Overall, the chances of detecting an mVI– tumour were significantly higher within the up-to-seven criteria compared with tumours exceeding the proposed limits (70·7% *vs* 49·8%).

For example, if one assumes, in the presented series, a 25% tumour understaging at preoperative imaging with respect to multinodular hepatocellular carcinoma, patients eventually falling within the up-to-seven criteria would have a decrement in 5-year survival from 71% to 65%, namely still within acceptable limits, should



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microvascular invasion be confirmed as absent. Such results are in keeping with previous findings[29] and could lead to future adjustments in the counting of tumours for prognostic scores, so that only hypervascular tumours greater than 10 mm in size are included, as per the definition of the Response Evaluation Criteria for Solid Tumours (RECIST).[33]

A limitation in the applicability of the model concerns the information on microvascular invasion, for which only a-priori probabilities or surrogate markers are available preoperatively (ie, alpha-fetoprotein concentrations, response to treatment, and differentiation grade on biopsy). However, microvascular invasion is strictly related to size-and-number covariates and tumour grading, and doubles the hazard of recurrence and death, whichever morphology-related criteria is considered (Milan, up-to-seven, and beyond up-to-seven; table 1 and figure 4). These uncertainties are represented in the confidence intervals of survival probabilities given by the model, and can be integrated in the decision process until future studies will detect reliable preoperative, non-invasive markers of microvascular invasion.

Despite the above-mentioned limitations, our model presents several advantages that are relevant in clinical practice. Above all, it offers individualised survival estimates for a range of tumour configurations and shows that different patients and tumour characteristics can result in the same expected survival (figure 2). Survival estimates, contrary to inclusion or exclusion criteria, allow a more subtle analysis of the benefits of transplantation, such as the estimation of incremental life expectancy as a function of age and of the availability of alternative treatments.[34] Individual survival estimates in patients with hepatocellular carcinoma beyond conventional criteria allow comparison with survival data after other controversial indications to transplantation (ie, hepatorenal syndrome or re-transplantation for hepatitis C infection) that compete with cancer for organ allocation,[35–38] and also allow the consideration of living donation, which, in general, accepts far more liberal patient criteria with deceased donations. In this respect, this study confirmed that post-transplant outcome is strictly dependent on tumour stage rather than graft origin (ie, deceased *vs* living donation).

A further advantage of our study is the robustness of the survival estimates, based on an unprecedented sample size and objective pathological data. This study shows that a group of patients with hepatocellular carcinoma with excellent outcome exists outside the conventional Milan criteria, with upper limits defined by the up-to-seven rule and in the absence of vascular invasion (figure 3). Such limits capture most of the alternative proposals of expansion of conventional criteria (ie, University of California, San Francisco; University of California, Los Angeles; and Tokyo criteria[10,39,40]) and could be the basis for a prospective multicentre investigation.

Finally, a computer-generated estimation of post-transplant prognosis, which takes into account pretransplant staging uncertainties of hepatocelluar carcinoma (ie, tumour number and vascular invasion), could favour an objective approach to the creation of policies and prioritisation for patients with cancer, and could aid clinical decisions according to different scenarios. In fact, clinical-pathological discrepancies, to some extent, depend on patient characteristics and local practices and expertise, and are predictable in individual patients (eg, quality of radiological imaging and range of variations in the pathology variables in clinical practice). The likelihood and the different importance of understaging hepatocellular carcinoma by size versus understaging by number of tumours, as clearly shown by this study (figures 1–3), should also be considered in any computer-generated predictive system.

Until pretransplant assessment of the biological behaviour of hepatocellular carcinoma becomes feasible using molecular techniques or well-tested clinical surrogates, the present model could offer a useful tool for addressing the need to balance patient's expectations and best use of the limited availability of donor organs.

#### Conflicts of interest

The authors declared no conflicts of interest.

#### Contributors

V Mazzaferro and P Majno were responsible for the conception and design of the study and for writing the final report. V Mazzaferro, J M Llovet, R Miceli, S Bhoori, M Schiavo, L Mariani, T Camerini, J Bruix, A K Burroughs, and P Majno were involved with the collection and interpretation of data. G L Grazi, L De Carlis, U Cillo, and M Rossi took part in the design of the study. The other authors participated in data management and manuscript review.

#### Acknowledgments

The study was endorsed by the International Liver Transplantation Society (ILTS), the European Liver and Intestine Transplantation Association (ELITA), and the International Liver Cancer Association (ILCA). The Metroticket Website and Calculator were designed by Claudio Jacomelli.

#### Metroticket Investigator Study Group

The following Principal Local Investigators enrolled patients in the Metroticket Project and are members of the study group: *Austria*—Ivo Graziadei, Wolfgang Vogel (University Hospital, Innsbruck); *Belgium*—Jan Lerut (University Hospital St Luc, Brussels); Valerio Lucidi (Erasme University Hospital, Brussels); Bernard de Hemptinne, Roberto Troisi (University Hospital Medical School, Ghent); *Brazil*—Ilka Boin, Luiz Leopardi (University Hospital of Campinas, Sao Paulo); *France*—Christian Cotsoglou, Jean Gugenheim, Antonio Iannelli, Aline Staccini (Hôpital Archet 2, Nice); Rene Adam (Villejuif Paul Brousse Hospital, Paris); Jacques Belghiti (Beaujon Hospital, Paris); *Germany*—Peter Neuhaus (University Hospital, Berlin); Alfred Koenigsrainer, Wolfgang Steurer (University Hospital, Tuebingen); *Italy*—Nicola Cautero, Andrea Risaliti (Ospedali Riuniti, Ancona); Luigi Lupo (Università di Bari, AO Policlinico Hospital, Bari); Michele Colledan, Massimo De Giorgio, Stefano Fagiuoli (Ospedali Riuniti Hospital, Bergamo); Gian Luca Grazi, Antonio Daniele Pinna, Matteo Ravaioli (Sant'Orsola Malpighi Hospital, Bologna); Carlo Battiston, Jorgelina Coppa, Enrico Regalia, Raffaele Romito (Istituto Nazionale Tumori, Milan); Luciano De Carlis, Alessandro Giacomoni, Jacopo Mangoni (Ospedale Niguarda Hospital, Milan); Umberto Maggi, Giorgio Rossi (Ospedale Maggiore Policlinico Hospital, Milan); Giorgio Enrico Gerunda, Michele Masetti, Roberto Montalti (University Hospital, Modena); Fulvio Calise, Oreste Cuomo, Enzo Scuderi (Cardarelli Hospital, Naples); Alessandro Bridda, Umberto Cillo, Alessandro Vitale (University Hospital, Padova); Giuseppe Tisone (Tor Vergata University

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www.thelancet.com/oncology **Published online December 4, 2008 DOI:10.1016/S1470-2045(08)70284-5**

Med Clin (Barc). 2009;**132(7)**:272–287

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Conferencia de consenso

# Diagnóstico y tratamiento del carcinoma hepatocelular

## Diagnosis and treatment of hepatocellular carcinoma

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INFORMACIÓN DEL ARTÍCULO

*Historia del artículo:*
Recibido el 21 de noviembre de 2008
Aceptado el 11 de diciembre de 2008

### Introducción

El carcinoma hepatocelular (CHC) es la neoplasia primaria de hígado más frecuente. Su incidencia se ha incrementado mundialmente y datos recientes indican que en España también se ha asistido a un aumento significativo de su detección. Es conocido que el CHC afecta de manera casi exclusiva a sujetos con enfermedad hepática crónica que han desarrollado una cirrosis hepática y, además, diversos estudios han constatado que la aparición de CHC es en la actualidad la causa de muerte más frecuente en esta población. Simultáneamente al reconocimiento de la relevancia clínica de esta neoplasia, se ha asistido al desarrollo de técnicas nuevas para el diagnóstico precoz del CHC y para su tratamiento eficaz en todos los estadios. Esta evolución positiva en la actitud diagnóstico-terapéutica de los sujetos con CHC ha dado lugar a un interés creciente en todos los aspectos relacionados con esta enfermedad; diversas sociedades científicas han elaborado guías de práctica clínica para orientar la toma de decisiones en sujetos con posible diagnóstico de CHC.

Con el objeto de revisar la situación actual de la epidemiología, el diagnóstico y el tratamiento del CHC, la Asociación Española para el Estudio del Hígado (AEEH) organizó una conferencia monotemática sobre CHC (Santander, mayo de 2008) y al mismo tiempo propuso la elaboración de un documento de consenso por parte de un panel de expertos. Con el objeto de conseguir una máxima aceptación y validez, se invitó a participar en la elaboración de este documento a la Sociedad Española de Trasplante Hepático (SETH), a la Sociedad Española de Radiología (SERAM), a la Sociedad Española de Radiología Médica Vascular e Intervencionista (SERVEI) y a la Sociedad Española de Oncología Médica (SEOM). De este modo, se integraban en esta propuesta todos los campos del conocimiento que participan en el diagnóstico y el tratamiento de esta neoplasia. En este sentido, una de las principales conclusiones del panel de expertos es la necesidad de que el diagnóstico y el tratamiento de estos sujetos se lleve a cabo en grupos multidisciplinarios asentados en centros de referencia y en los que participen todas las especialidades involucradas: hepatología y gastroenterología, radiología (incluida

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0025-7753/$ - see front matter 
doi:10.1016/j.medcli.2008.11.024

**Tabla 1**
Evidencia de acuerdo con el diseño del estudio

| Grado | Definición |
|---|---|
| I | Ensayos clínicos controlados aleatorizados |
| II-1 | Ensayos clínicos controlados no aleatorizados |
| II-2 | Estudios analíticos de cohorte o de casos y controles |
| II-3 | Múltiples series temporales, experimentos no controlados |
| III | Opinión de expertos, estudios epidemiológicos descriptivos |

radiología intervencionista), cirugía, anatomía patológica y oncología médica. Esta necesidad abarca todos los estadios evolutivos y debe considerarse un requisito fundamental para poder avanzar en el diagnóstico y en el tratamiento del CHC. La aparición de esta neoplasia en el seno de un hígado enfermo implica una complejidad elevada y, al mismo tiempo, todo el proceso de diagnóstico, estadificación y seguimiento obliga a una relación estrecha entre los diversos especialistas y a la aplicación de tecnología de última generación. Además, hay numerosos aspectos que requieren investigación clínica de calidad y esto únicamente será posible si se dispone de este tipo de dispositivo asistencial y de investigación.

Este documento expone un conjunto de recomendaciones para el diagnóstico, la estadificación y el tratamiento del CHC basadas en pruebas científicas. Se ha tomado como documento de referencia las guías de práctica clínica que publicó en 2005 la American Association for the Study of Liver Diseases (AASLD)[1] incorporando los avances más importantes que se han obtenido en los últimos años. Las recomendaciones realizadas en este documento se categorizaron de acuerdo con el nivel de evidencia científica propuesto por la AASLD (tabla 1). La evidencia científica en el tratamiento del CHC se han evaluado de acuerdo con las recomendaciones del National Cancer Institute (www.cancer.gov).

## Epidemiología y prevención

El CHC es un problema médico relevante. Actualmente es la sexta neoplasia más frecuente y la tercera causa de muerte por cáncer[2]. Su distribución mundial es muy heterogénea y está estrechamente relacionada con la prevalencia variable de los diferentes factores de riesgo asociados al desarrollo de esta neoplasia. La incidencia es máxima en el Sudeste asiático y en África subsahariana. La mayor parte de los casos que se presentan en esas zonas se hallan en relación con el virus de la hepatitis B (VHB) y la incidencia excede los 15 casos cada 100.000 habitantes por año. El sur de Europa (incluida España) presenta una incidencia intermedia (de 5 a 10 casos cada 100.000 habitantes por año) y, finalmente, el norte de Europa y América tienen la menor incidencia (aproximadamente 5 casos cada 100.000 habitantes por año)[3]. En ambas zonas, la infección por virus de la hepatitis C (VHC) y el alcoholismo desempeñan un papel predominante. No obstante, en los últimos años se han evidenciado ciertos cambios epidemiológicos en diversas áreas. Así, en países donde la infección crónica por el VHB es la principal causa de CHC, como Taiwán, la incidencia ha descendido debido a la implementación universal de la vacunación contra el VHB[4]. Por el contrario, la incidencia de CHC ha aumentado en países como el Reino Unido[5], Canadá[6] y EE. UU.[7], lo que refleja probablemente la diseminación de la infección crónica por el VHC. Finalmente, en aquellos países en los que la epidemia por VHC apareció más tempranamente, como Japón, la incidencia ha alcanzado su meseta[8]. Mundialmente, el principal factor de riesgo de CHC es el VHB asociado o no a aflatoxina. Sin embargo, en países industrializados, los factores de riesgo más frecuentemente asociados al CHC son la infección crónica por VHC[9] y el consumo crónico de etanol[10]. En España, el VHC es, en el momento actual, el principal factor de riesgo asociado a la aparición de CHC y, aunque los datos son heterogéneos dado que en muchas ocasiones las metástasis hepáticas se registran como tumores hepáticos primarios, hay pruebas de que la incidencia de CHC ha aumentado en los últimos años[11,12]. En todas las áreas geográficas, el riesgo de CHC varía según el grado de afectación hepática: es menor al 1% anual en sujetos con hepatitis crónica sin fibrosis significativa y se incrementa del 3 al 7% anual en sujetos con cirrosis[9]. El riesgo relevante se adquiere al establecerse la cirrosis hepática y es obvio que la intensidad de la inflamación hepática (relacionada con la carga vírica o el genotipo) es la causante del proceso crónico de necrosis y de regeneración que evoluciona a cirrosis; por tanto, éste es el parámetro que debe utilizarse para establecer la adquisición de riesgo clínicamente significativo. En este sentido, una vez que se presenta la cirrosis hepática, el riesgo de que el CHC se desarrolle continúa a pesar de obtener una respuesta vírica persistente tras tratamiento[13]. Por tanto, cualquier enfermedad que pueda dar lugar a una cirrosis hepática (hemocromatosis hereditaria, cirrosis biliar primaria o hepatitis autoinmunitaria) debe considerase un factor de riesgo para CHC. En los últimos años se ha demostrado que la diabetes mellitus[14] y otros factores asociados al síndrome metabólico, como la obesidad o la dislipidemia[15–18], se asocian a un incremento de muerte relacionada con CHC (al igual que el tabaquismo)[19,20]. El consumo de café disminuye el riesgo[21–23], mientras que los suplementos vitamínicos, la soja o los elementos de la medicina alternativa (como la aleta de tiburón) no tienen ninguna eficacia preventiva del CHC.

La prevención eficaz de la muerte por CHC debe conseguirse al evitar la adquisición de factores de riesgo. La vacuna frente al VHB ha demostrado su eficacia[4], mientras que la infección por VHC, la ingesta de aflatoxina, el consumo de alcohol o el síndrome metabólico pueden prevenirse mediante campañas dirigidas a mejorar las condiciones sociosanitarias de los ciudadanos y la promoción de hábitos de vida saludables. Si el factor de riesgo ya se ha adquirido, la única opción preventiva es evitar la progresión a cirrosis mediante la administración de tratamiento antivírico[24,25] y el abandono de los hábitos que implican riesgo aumentado. En este sentido, varios estudios han demostrado que la replicación del VHB incrementa el riesgo de CHC[24,26,27], por lo que el tratamiento antivírico debería traducirse en la disminución de la progresión de la enfermedad hepática y, por tanto, reducir el desarrollo de CHC a largo plazo. Si el tratamiento antivírico no logra erradicar la infección vírica o inhibir de forma persistente su replicación, no hay ningún agente que evite de forma eficaz la evolución a cirrosis con riesgo de CHC. Por tanto, la prevención primaria del CHC es la medida más eficaz.

Recomendaciones:

1. La vacunación universal contra el VHB reduce la incidencia de CHC (nivel I).
2. Una vez que se produce la lesión hepática con desarrollo de cirrosis la eliminación del agente etiológico disminuye, pero no elimina, el riesgo de aparición de CHC (nivel II).

## Diagnóstico precoz

Es bien conocido que más del 80% de los sujetos afectados de CHC presentan una cirrosis hepática subyacente y que en la actualidad el hecho de que se desarrolle CHC supone la principal causa de muerte en sujetos con cirrosis[28]. Teniendo en cuenta que la única posibilidad de aplicar tratamientos con intención

curativa es diagnosticando la enfermedad en una fase inicial, asintomática[29], y dado que esta posibilidad es únicamente factible si se efectúa cribado de la población en riesgo, se recomienda explorar periódicamente a los sujetos con cirrosis mediante ecografía abdominal. Se dispone de un único estudio prospectivo y aleatorizado que se efectuó en China. Incluyó sujetos con infección crónica por VHB y demostró que el programa de cribado basado en ecografía abdominal y en determinación de alfafetoproteína (AFP) cada 6 meses aumentaba la supervivencia de los sujetos en la cohorte bajo vigilancia[30]. La eficacia del programa se relacionó con la capacidad de la ecografía, mientras que la determinación de AFP no fue eficaz[31]. Diversos estudios de cohortes[32–34] y análisis de coste y eficacia[35–37] refuerzan el beneficio de establecer un seguimiento mediante ecografía abdominal cada 6 meses. Por tanto, hay consenso generalizado en recomendar incluir en programas de cribado periódico a los sujetos cirróticos que vayan a tratarse en caso de ser diagnosticados de CHC. En general, deben considerarse para cribado los sujetos cirróticos en clase funcional Child-Pugh A y B. Los sujetos en clase funcional B avanzada y en clase funcional C deben evaluarse para trasplante hepático. En ellos, la detección de CHC no cambiará la indicación de trasplante, a menos que se excedan los criterios de inclusión en la lista de espera y el CHC sea una contraindicación al trasplante. Dado que en estos sujetos el trasplante se debe considerar en caso de insuficiencia hepática con mal pronóstico a corto plazo, la detección de CHC y su posible tratamiento no tendrá impacto clínicamente significativo en la supervivencia. Por tanto, no tiene sentido efectuar cribado para detección precoz si el trasplante no es factible.

### *Intervalo de exploración*

Los datos referentes a la velocidad del crecimiento tumoral y a la progresión hasta un tamaño detectable mediante técnicas de imagen son limitados. Series antiguas indican que el tiempo para doblar el volumen tumoral oscila entre 2 y 4 meses[38,39] y estos resultados aportan la base racional para efectuar cribado cada 6 meses. Asimismo, este intervalo fue el que se utilizó en el único ensayo clínico aleatorizado que ha demostrado el beneficio del cribado de CHC en sujetos cirróticos[30]. En Japón, se recomienda un intervalo de 3 a 4 meses y algunos autores mantienen que los sujetos de alto riesgo deberían examinarse más frecuentemente. No obstante, no hay datos que demuestren que el mayor riesgo se asocia a una mayor velocidad de crecimiento tumoral. Además, un ensayo clínico aleatorizado realizado recientemente en Francia en 1.200 sujetos cirróticos concluyó que el cribado mediante ecografía cada 3 meses no mejora el diagnóstico ni el tratamiento del CHC respecto a realizarlo cada 6 meses[40]. Por tanto, se considera que el intervalo recomendado debe ser cada 6 meses.

### *Instrumentos para el cribado*

Las técnicas de cribado de CHC pueden dividirse en radiológicas y serológicas. La prueba radiológica más usada es la ecografía abdominal. Se trata de una técnica no invasiva, aceptada por la población, con una sensibilidad del 60 al 80% y una especificidad superior al 90% para la detección precoz de CHC[41]. Además, se dispone de una estrategia diagnóstica bien definida tras la detección de un nódulo sospechoso de CHC. Por tanto, la ecografía abdominal realizada por personal experto es actualmente la técnica de cribado más adecuada para la detección precoz de CHC. Con el objeto de asegurar el conocimiento y la experiencia para efectuar cribado basado en ecografía, es fundamental establecer programas de formación para certificar la capacitación a fin de llevar a término esta actividad. La realización de tomografía computarizada (TC) como técnica de cribado debe desaconsejarse por el riesgo asociado a la irradiación[42] así como por motivos de coste y eficacia, y de menor disponibilidad. También este aspecto afecta a la resonancia magnética (RM).

Respecto a las pruebas serológicas, se disponen en la actualidad de una multitud de marcadores tumorales. El más evaluado ha sido la AFP que hasta hace poco tiempo era la única herramienta disponible. Sin embargo, la AFP ha mostrado un bajo rendimiento diagnóstico, dado que sus valores en muchos casos son normales en tumores iniciales y es bien sabido que los sujetos con cirrosis hepática pueden presentar elevaciones transitorias de AFP en ausencia de CHC. Los análisis retrospectivos que evalúan el rendimiento diagnóstico mediante curvas de eficacia diagnóstica han mostrado que el punto de corte óptimo para el cribado es de 20 ng/ml; éstas ofrecen una sensibilidad aproximada del 60%[43]. Sin embargo, cuando se consideran estudios prospectivos, en los que específicamente se evalúa el rendimiento diagnóstico de las pruebas de cribado, la AFP con el mismo punto de corte muestra una sensibilidad inferior al 25% y una especificidad del 79%[44]. Además, no se dispone de ningún estudio que establezca qué incremento de AFP debe llevar a sospechar un CHC si la ecografía es negativa. En este sentido, estudios en explantes demuestran que puede no haber CHC, aunque la AFP supere 500 ng/ml[45]. Por último, hay una correlación entre valores de AFP y estadio tumoral, donde la AFP simplemente es un marcador de enfermedad avanzada. Por tanto, la AFP no es una herramienta de cribado eficaz y debe desaconsejarse su uso[46]. Se han propuesto otros marcadores, como la fracción de AFP ligada a lectina[47], des-gamma-carboxi protrombina[48] o el glipican-3[49], pero presentan los mismos defectos que la AFP y, en general, no pueden competir con la fiabilidad de la ecografía.

### *Candidatos a cribado de carcinoma hepatocelular*

Dado que el principal factor de riesgo de CHC es la presencia de cirrosis, deben considerarse candidatos a cribado todos los sujetos con cirrosis, independientemente de la etiología. En sujetos afectados de hepatopatía crónica por VHC con cirrosis establecida, la obtención de respuesta vírica persistente tras tratamiento no elimina el riesgo de que se desarrolle CHC[13]. Por tanto, también en estos sujetos se debería recomendar cribado de CHC.

Recomendaciones:

3. Los sujetos afectados de cirrosis hepática deben participar en programas de cribado (nivel I).
4. La técnica de cribado más adecuada es la ecografía abdominal que realiza personal experto (nivel II).
5. Se debe abandonar el uso de AFP como técnica de cribado (nivel II).
6. Las técnicas de cribado se deben realizar cada 6 meses. El intervalo de cribado no necesita acortarse en sujetos con mayor riesgo de desarrollar CHC (nivel II).

## Diagnóstico de carcinoma hepatocelular

En un sujeto afectado de cirrosis hepática, la probabilidad de que un nódulo detectado mediante ecografía sea un CHC es muy elevada, especialmente si su diámetro excede los 10 mm. Por tanto, si el nódulo detectado supera este límite, es recomendable realizar estudios complementarios para llegar a un diagnóstico

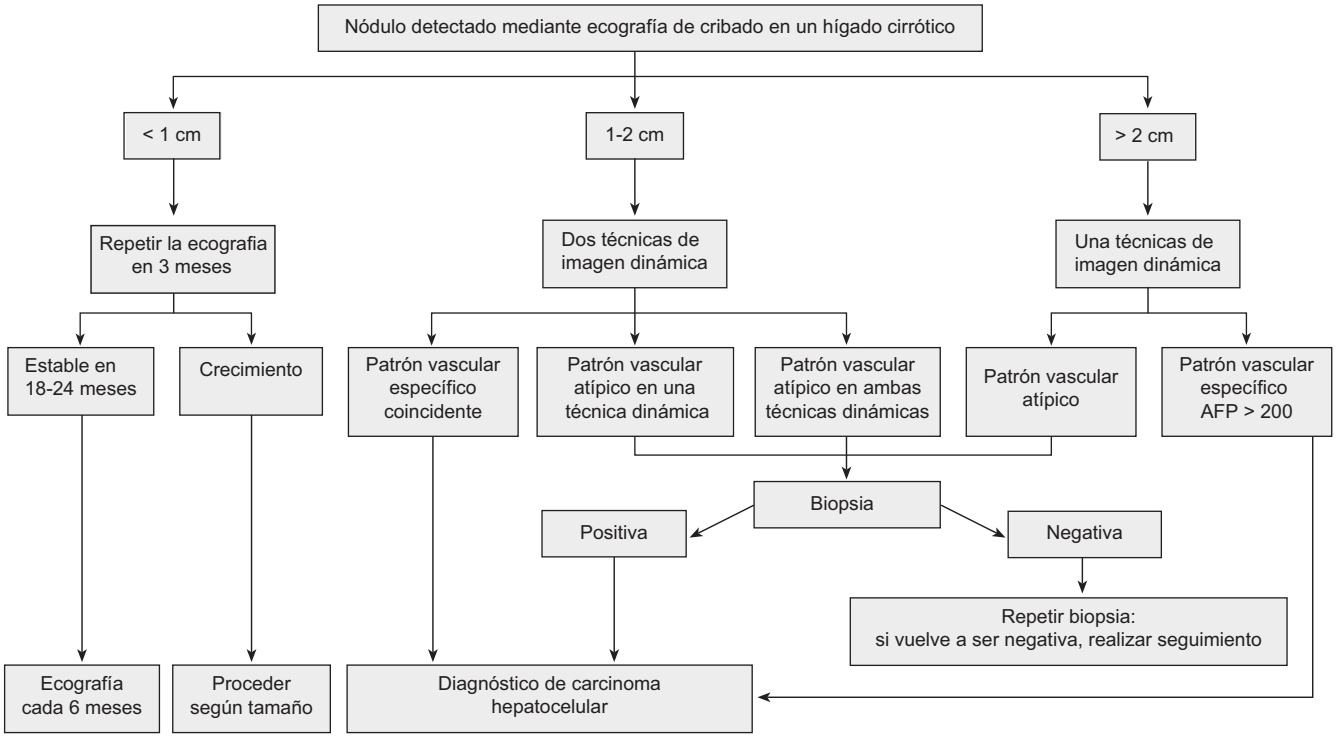



**Figura 1.** Algoritmo diagnóstico para el estudio de un nódulo hepático detectado mediante ecografía abdominal. Adaptado de Bruix et al[1]. AFP: alfafetoproteína.

concluyente. El CHC presenta una vascularización predominantemente arterial[50], a diferencia del parénquima hepático en donde la vascularización es mixta: arterial y portal. Esto determina un patrón vascular específico caracterizado por una intensa captación de contraste en fase arterial, seguido de un lavado rápido del contraste en fase venosa portal o en fase tardía (*washout* en la literatura médica inglesa). Este patrón ha mostrado ser específico para el diagnóstico de CHC cuando se ha correlacionado con el análisis anatomopatológico de explantes o de piezas de resección quirúrgica[51]. En la conferencia de consenso de la European Association for the Study of the Liver (EASL), celebrada en 2000 en Barcelona, se propusieron criterios diagnósticos no invasivos basados en este patrón radiológico. De este modo, si un nódulo hipervascular mayor de 2 cm sobre un hígado cirrótico presentaba hallazgos coincidentes mediante 2 técnicas de imagen[52], el diagnóstico de CHC se consideraba establecido. En nódulos menores de 2 cm se recomendaba basar el diagnóstico en la confirmación mediante biopsia. Estos criterios de imagen no invasivos se han aplicado clínicamente con éxito y han demostrado su utilidad[53], particularmente para el diagnóstico de tumores avanzados. No obstante, la descripción anecdótica de nódulos hipervasculares en hígados cirróticos sin diagnóstico final de CHC (p. ej. hemangioma atípico o colangiocarcinoma), ha llevado a refinar los criterios no invasivos[54,55] que se establecieron en las guías de práctica clínica que publicó la AASLD[1] y que aceptó un panel de expertos de la EASL. Así, para registrar el patrón dinámico como específico de CHC debe detectarse hipervascularización en fase arterial seguido de lavado precoz en la fase venosa y de equilibrio. De acuerdo con estos criterios nuevos, es posible establecer el diagnóstico no invasivo de CHC si un nódulo en un hígado cirrótico muestra intensa captación de contraste en fase arterial seguido de lavado precoz en fase venosa mediante una técnica de imagen dinámica (ecografía con contraste, RM o TC con contraste). En el caso de nódulos de entre 1 y 2 cm, se recomienda la demostración de este patrón vascular específico de forma coincidente en 2 pruebas de imagen a fin de evitar posibles falsos diagnósticos positivos basados en una lectura equivocada de una única prueba de imagen. Si el patrón vascular no es típico o si el nódulo no muestra captación de contraste, el diagnóstico concluyente de CHC debe basarse en la anatomía patológica. Finalmente, en el caso de nódulos menores de 1 cm, dada la baja probabilidad de que sean de naturaleza maligna[44] y dada la dificultad que supone su caracterización correcta, se recomienda realizar un seguimiento estrecho mediante una ecografía cada 3 a 6 meses con la finalidad de detectar su posible crecimiento, y emplear entonces los criterios anteriores (fig. 1). Los estudios futuros deberán establecer si la detección de grasa, de seudocápsula o de comportamiento tras la administración de contrastes intracelulares pueden ser criterios diagnósticos adicionales. En el caso de sujetos sin cirrosis establecida, la aplicación de estos criterios de imagen no es válida, y es necesaria la realización de una biopsia para obtener un diagnóstico concluyente. Estos criterios se han validado prospectivamente en sujetos cirróticos y han demostrado una especificidad y un valor predictivo positivo del 100%[44]. Sin embargo, la aplicación estricta de estos criterios no invasivos en nódulos menores de 2 cm tiene una sensibilidad del 33%, por lo que en la mayor parte de casos, el diagnóstico de CHC en estos nódulos depende de la obtención de una biopsia[44]. La realización de una biopsia de un nódulo hepático en un sujeto cirrótico no es siempre posible. En algunos casos, la presencia de ascitis o de alteraciones graves de la coagulación contraindica este procedimiento y, en otros casos, su localización en el hígado dificulta su acceso percutáneo. Además, el rendimiento diagnóstico de una biopsia de estos nódulos de tamaño pequeño no es óptimo y presenta una sensibilidad cercana al 70%[44,56]. Esto puede relacionarse con un error de muestreo y con la dificultad de realizar un diagnóstico diferencial entre nódulos displásicos y CHC muy iniciales mediante la escasa muestra obtenida a través de una biopsia percutánea[50]. Por tanto, ante una biopsia negativa no se puede descartar el diagnóstico de CHC y se debe valorar la necesidad de obtener una nueva biopsia. Respecto a la técnica para la obtención de material para el análisis anatomopatológico,

no hay ningún estudio que haya comparado adecuadamente el rendimiento de la punción aspirativa con aguja fina y la punción con aguja de corte, por lo que no se puede realizar una recomendación generalizada. La citología posee un elevado rendimiento diagnóstico, pero si se requiere el análisis de disposición arquitectural o de valoración de invasión vascular microscópica, el examen de bloque celular o de «minibiopsia» puede aportar información valiosa. Por último, algunos autores han alertado sobre el riesgo de diseminación local (*seeding*) tras la punción de estos nódulos. Sin embargo, la incidencia de esta complicación es muy baja (inferior al 0,1%)[57,58] y siempre se debe valorar este riesgo frente a la posibilidad de aplicar tratamientos invasivos ante lesiones falsamente diagnosticadas de CHC mediante pruebas de imagen no concluyentes[45].

Finalmente, el uso de AFP como herramienta diagnóstica presenta un rendimiento muy bajo[44,59]. Diferentes neoplasias, como el colangiocarcinoma o la metástasis de origen gastrointestinal, pueden presentar elevaciones de AFP[43,60,61]. Por tanto, a pesar de encontrar valores elevados de AFP (superiores a 200 ng/ml), si la masa hepática no presenta un patrón vascular específico por imagen, se debe realizar una biopsia confirmatoria.

En los últimos años se ha producido un gran avance en el conocimiento de las vías moleculares que determinan la aparición de CHC[62,63], lo que ha permitido evaluar técnicas de biología molecular que podrían actuar como nuevas herramientas diagnósticas. Se han propuesto diferentes firmas diagnósticas basadas en la expresión génica así como tinciones inmunohistoquímicas que reflejarían esta diferente expresión a nivel proteico[64–66]. Sin embargo, todos estos estudios se han realizado sobre tumores obtenidos tras resección quirúrgica o trasplante hepático. Dado que no se han evaluado en muestras adquiridas mediante biopsia percutánea, su utilidad en la práctica clínica real es desconocida.

Recomendaciones:

7. Los nódulos menores de 1 cm detectados mediante ecografía de cribado deben seguirse mediante una ecografía cada 3 a 6 meses. Si tras 2 años no se detecta crecimiento, se debe volver al cribado habitual cada 6 meses (nivel II).
8. Los nódulos mayores o iguales a 1 cm detectados mediante ecografía en sujetos cirróticos pueden diagnosticarse de CHC sin necesidad de obtener una biopsia si presentan en técnicas de imagen dinámicas (ecografía con contraste, TC y RM dinámicas) captación de contraste en fase arterial seguido de lavado en fases tardías. En nódulos de entre 1 y 2 cm, este patrón vascular debe detectarse de forma coincidente en 2 técnicas de imagen (nivel II).
9. Si el patrón vascular no es específico de CHC, se debe recomendar una biopsia (nivel II).
10. Si la biopsia es negativa, no se puede descartar el diagnóstico de CHC. Se debe valorar la realización de una biopsia nueva o un seguimiento estrecho de la lesión (nivel II).
11. En el caso de sujetos sin cirrosis establecida, la aplicación de estos criterios de imagen no es válida y es necesario la realización de una biopsia para obtener un diagnóstico concluyente (nivel II).

## Evaluación pronóstica

Una vez que se obtiene el diagnóstico, es necesario realizar el estudio de extensión de la enfermedad y una valoración pronóstica. Con esto, es posible informar al sujeto y a los familiares sobre la expectativa de vida, elegir el tratamiento más adecuado y evaluar su respuesta. El pronóstico de los tumores sólidos depende fundamentalmente del estadio tumoral. Sin embargo, dado que el CHC aparece en la mayoría de los casos asociado a una cirrosis hepática y que el grado de alteración de la función hepática determina las opciones terapéuticas y la supervivencia (independientemente de la presencia del CHC), es imprescindible considerar conjuntamente el grado de disfunción hepática y la extensión tumoral. Finalmente, la presencia de síntomas ha mostrado un gran valor pronóstico y, al igual que el grado de reserva funcional hepática, determina la aplicabilidad de los diferentes tratamientos disponibles. Por tanto, aquellos sistemas pronósticos que tienen en cuenta únicamente la extensión tumoral (como el sistema de estadificación por tumor, ganglios y metástasis)[67], la función hepática (como el sistema Child-Pugh[68] o el sistema MELD [Model for end stage liver disease])[69] o la presencia de síntomas (como la clasificación ECOG performance status[70] o el índice Karnofsky)[71] son inexactos y únicamente son útiles para detectar una enfermedad terminal. En la última década, han aparecido múltiples sistemas de estadificación que tienen en cuenta factores asociados a la extensión tumoral y a la función hepática[72–85]. El único que vincula estadificación con tratamiento y que además se ha validado en Europa[86,87], EE. UU.[88] y Asia es el sistema Barcelona Clinic Liver Cancer (BCLC)[74]. Por su reconocida capacidad predictiva y por su utilidad en el proceso de decisión de tratamiento, es el sistema que recomienda la AASLD[1] y un panel internacional de expertos que recientemente ha establecido las recomendaciones para diagnosticar y estratificar a los sujetos con el objeto de permitir estudios de investigación terapéutica con máxima calidad[89].

El sistema BCLC incluye variables asociadas al estadio tumoral, la función hepática y la presencia de síntomas; además, establece el pronóstico de acuerdo con 4 estadios que se vinculan a la posible indicación de tratamiento (fig. 2). El estadio inicial (estadio A) incluye a sujetos asintomáticos con función hepática conservada (Child-Pugh A y B) con un CHC solitario o con un máximo de 3 nódulos de hasta 3 cm de diámetro. Estos sujetos pueden tratarse con intención curativa mediante resección quirúrgica, ablación percutánea y trasplante hepático, con una supervivencia esperada a los 5 años en el 50 al 75% de los casos. Un subgrupo con especial buen pronóstico son aquellos sujetos con cirrosis hepática compensada (Child-Pugh A) con CHC muy inicial (estadio 0), totalmente asintomáticos y que presentan tumores únicos menores de 2 cm, sin invasión vascular ni diseminación. Este estadio muy inicial correspondería al concepto de carcinoma in situ[50]. En estos casos, la cirugía o la ablación por radiofrecuencia (RFA, radiofrequency ablation) ofrecen una alta probabilidad de curación[29], con supervivencia a los 5 años superior al 80%. El estadio intermedio (estadio B) consiste en sujetos con tumores multinodulares que exceden los criterios anteriormente descritos, sin invasión vascular ni extrahepática, con función hepática y estado general conservado. Si la función hepática corresponde al estadio A de Child-Pugh, los sujetos pueden beneficiarse de tratamiento mediante quimioembolización y su supervivencia mediana esperada es de 20 meses. Los sujetos con función hepática conservada, pero que presentan un CHC con invasión vascular, invasión extrahepática o con afectación leve del estado general se catalogan como sujetos en estadio avanzado (estadio C). En este grupo de sujetos, el único tratamiento que hasta la fecha ha mostrado beneficios en términos de supervivencia es el tratamiento con sorafenib, con una supervivencia mediana de aproximadamente 11 meses. Por último, los sujetos que presentan afectación grave del estado general o función hepática muy afectada (Child-Pugh C) y que no son candidatos a trasplante hepático corresponden al estadio D o terminal. En ellos, la mediana de supervivencia es menor a 3 meses y únicamente se debe indicar tratamiento sintomático.

Los avances recientes en el conocimiento de las vías moleculares que determinan la aparición y la progresión del CHC han

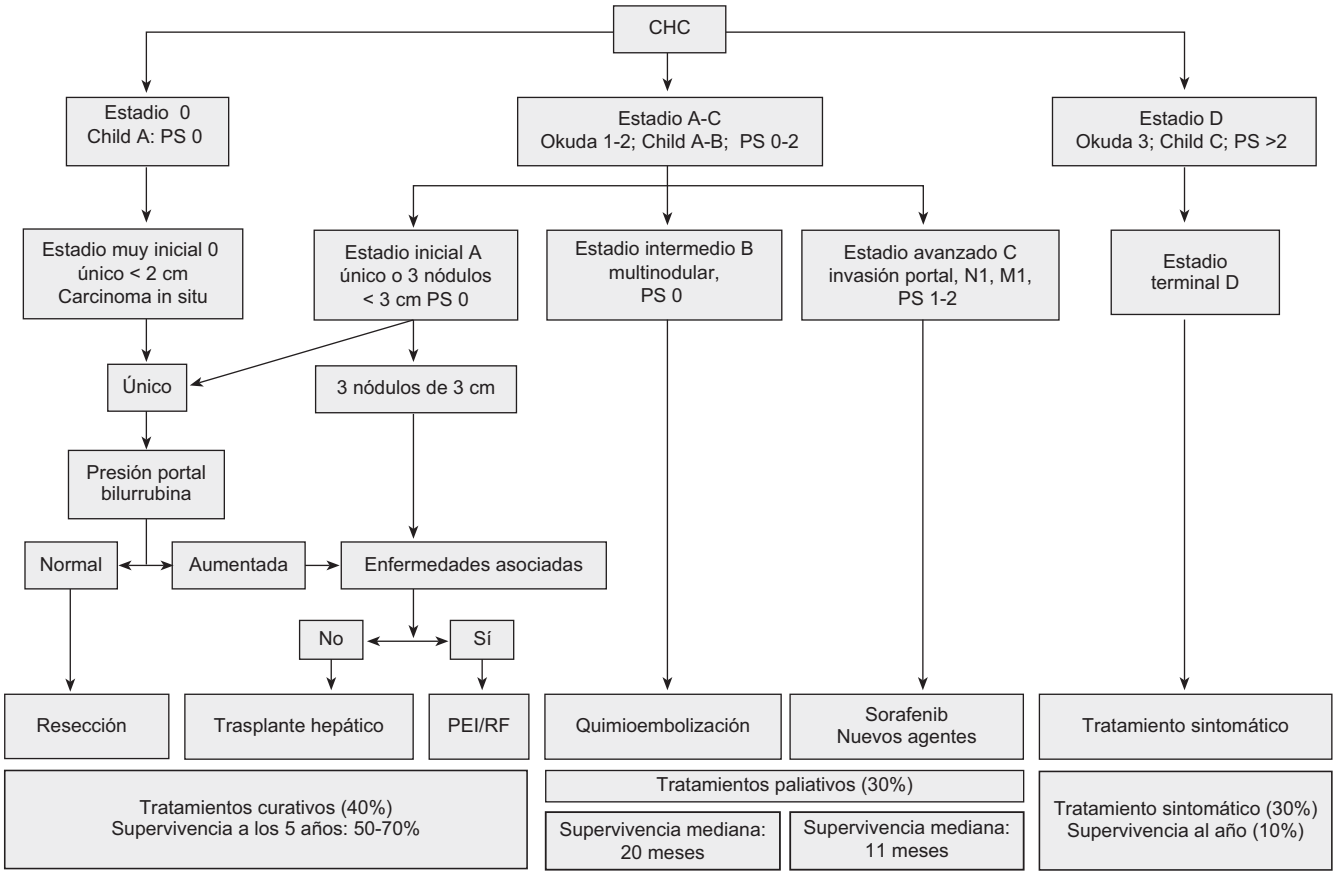



**Figura 2.** Sistema de estadificación del Barcelona Clinic Liver Cancer. Adaptado de Llovet et al[29]. CHC: carcinoma hepatocelular, PEI; *percutaneus ethanol injection* 'inyección percutánea de etanol', PS: *performance status* 'capacidad functional del sujeto', RF: *radiofrequencia*.

permitido definir diferentes patrones de expresión genética con posible significación pronóstica[90–92]. Aunque la información disponible en la actualidad es preliminar, en un futuro se podrán incorporar datos de expresión génica a los sistemas actuales de evaluación y se podrá basar la predicción de supervivencia así como la indicación de tratamiento en el perfil molecular del sujeto[93,94].

Recomendación:

12. Para evaluar el pronóstico de CHC, se debe considerar no sólo el estadio tumoral, sino también la función hepática y la presencia de síntomas. El sistema BCLC tiene en cuenta estos parámetros y es el único que relaciona la predicción pronóstica con la opción terapéutica recomendada (nivel II-2).

## Tratamiento del carcinoma hepatocelular

Hace décadas, el CHC se diagnosticaba habitualmente en una fase avanzada, cuando el sujeto presentaba síntomas o cuando experimentaba un empeoramiento de la función hepática. En este estadio no era posible realizar ningún tratamiento y, en la mayoría de los casos, el diagnóstico de CHC se consideraba un episodio terminal en el contexto de la cirrosis hepática. En los últimos años, a causa de la aplicación de programas de detección precoz, cada vez se diagnostica el CHC en fases más tempranas, cuando aún es posible aplicar tratamientos eficaces. Para obtener los mejores resultados, es imprescindible una evaluación correcta de la extensión tumoral y de la función hepática, para posteriormente poder realizar tratamiento en centros con experiencia adecuada. Por tanto, ante el diagnóstico o la sospecha de CHC se recomienda enviar al paciente a centros de referencia con equipos multidisciplinares de hepatólogos, radiólogos, cirujanos, patólogos y oncólogos con experiencia en el tratamiento de esta enfermedad.

La valoración de la eficacia de un tratamiento debería basarse en ensayos clínicos aleatorizados y metaanálisis de datos individuales. Otras fuentes de evidencia, como ensayos clínicos no aleatorizados o estudios observacionales, son menos consistentes. En el CHC, a diferencia de otras neoplasias prevalentes (como el cáncer de pulmón, mama, estómago, colon y recto), únicamente una minoría de las opciones terapéuticas se ha evaluado correctamente (tabla 2)[93].

En estadios iniciales es posible aplicar tratamientos con intención curativa. Éstos son la resección quirúrgica, el trasplante hepático y la ablación. En estadios intermedios, el único tratamiento que ha demostrado un aumento de supervivencia es la quimioembolización transarterial (TACE, *transarterial chemoembolization*). Hasta hace poco tiempo, en el CHC avanzado no había ninguna opción terapéutica eficaz y estos sujetos eran candidatos para participar en ensayos clínicos que evaluaran agentes nuevos. Actualmente, el beneficio obtenido en términos de supervivencia en el estudio SHARP ha convertido al sorafenib en el tratamiento de elección del CHC avanzado. Finalmente, en el estadio terminal se deben recomendar medidas paliativas. Obviamente, si un sujeto en un estadio determinado no puede ser candidato a la opción terapéutica recomendada, debe plantearse la indicación del tratamiento de menor prioridad que corresponda a un estadio más avanzado.

**Tabla 2**
Evidencia científica de los tratamientos de carcinoma hepatocelular de acuerdo con la calidad del diseño del estudio

| | Beneficio | Nivel de evidencia |
|---|---|---|
| *Tratamientos quirúrgicos* | | |
| Resección quirúrgica | Incrementa supervivencia | 3iiA |
| Tratamientos adyuvantes | Controvertido | 1A-D |
| Trasplante hepático | Incrementa supervivencia | 3iiA |
| Tratamientos neoadyuvantes | Respuesta terapéutica | 3Diii |
| *Tratamientos locorregionales* | | |
| Tratamiento percutáneo | Incrementa supervivencia | 3iiA |
| Ablación por radiofrecuencia | Mejor control local | 1iiD |
| Quimioembolización | Incrementa supervivencia | 1iiA |
| Lipiodolización | Respuesta terapéutica | 3iiDiii |
| Radiación interna ($I^{131}$, $Y^{90}$) | Respuesta terapéutica | 3iiDiii |
| *Tratamientos sistémicos* | | |
| Sorafenib | Incrementa supervivencia | 1iA |
| Compuestos hormonales | No incrementa supervivencia | 1iA |
| Tamoxifeno | | |
| Antiandrógenos | | |
| Seocalcitriol | | |
| Quimioterapia sistémica | No incrementa supervivencia | 1iiA |
| Inmunoterapia | No incrementa supervivencia | 1iiA |

Adaptado de Llovet et al[93]
Clasificación de la evidencia científica adaptadas del National Cancer Institute (www.cancer.gov)
- Diseño del estudio: ensayo clínico controlado y aleatorizado, metaanálisis = 1 (estudio doble ciego: 1i; no ciego: 1ii). Ensayo clínico controlado no aleatorizado = 2. Serie de casos = 3 (estudios poblacionales: 3i; no poblacionales, consecutivos: 3ii; no poblacionales, no consecutivos: 3iii)
- Objetivo: supervivencia (A), mortalidad específica de la causa (B), calidad de vida (C). Datos subrogados (D); supervivencia libre de enfermedad (Di); supervivencia libre de progresión (Dii); respuesta tumoral (Diii).

## Resección quirúrgica

La resección quirúrgica es la primera opción en aquellos tumores únicos que aparecen sobre hígados no cirróticos, en los que se pueden realizar resecciones amplias con un riesgo bajo de complicaciones[95,96]. Sin embargo, en España, la mayoría de los CHC (más del 90%) aparecen sobre una enfermedad hepática crónica, habitualmente en fase cirrótica. En este contexto, no es posible realizar resecciones amplias debido al riesgo de insuficiencia hepática postoperatoria, lo que limita la aplicabilidad de esta opción terapéutica. En sujetos con cirrosis hepática descompensada, la resección quirúrgica está formalmente contraindicada y es necesario evaluar la posibilidad de un trasplante hepático. En aquellos sujetos con cirrosis compensada es fundamental una correcta selección de los potenciales candidatos a resección quirúrgica, con análisis del grado de reserva funcional[97]. Los mejores candidatos son aquellos sujetos con tumores únicos, que presentan una bilirrubina normal y ausencia de hipertensión portal clínicamente relevante (recuento de plaquetas superior a $100 \times 10^9$/l, gradiente de presión venosa hepática inferior a 10 mmHg y ausencia de várices esofagogástricas o de esplenomegalia)[98,99]. Si no se cumplen estas condiciones, el riesgo de la cirugía aumenta y el pronóstico a medio plazo se deteriora. Así, en tumores multifocales o en presencia de hipertensión portal, se puede efectuar la resección y la morbimortalidad puede ser aceptable. No obstante, la supervivencia a los 5 años será del 50% o menor[99] y, por tanto, los sujetos deben considerarse para trasplante hepático si cumplen los criterios de selección. Debe remarcarse que estos criterios desarrollados en Europa para recomendar tratamiento quirúrgico se han validado recientemente en Asia[99]. Si la cirugía no es posible, debe considerarse que la ablación percutánea posee una gran eficacia terapéutica y que numerosos estudios han demostrado que la supervivencia puede ser muy similar a la obtenida mediante resección si se consigue una respuesta completa al tratamiento[100]. Respecto al tamaño de la lesión, no hay un punto de corte que contraindique la resección, pero se tiene que valorar cada caso de forma personalizada y siempre tiene que tenerse en cuenta que cuanto mayor es el tamaño del tumor, mayor es el riesgo de invasión microvascular y satelitosis, con lo que el riesgo de recidiva se incrementa[101,102] y potencialmente se puede obtener igual o mejor supervivencia con otras alternativas.

A pesar de los avances en la capacidad diagnóstica, sigue habiendo una infravaloración de la extensión tumoral[51]. Por esto, es imprescindible disponer de ecografía intraoperatoria con el objeto de detectar nódulos entre 0,5 y 1 cm, y optimizar la eficacia de la resección quirúrgica. No se ha demostrado que efectuar resecciones anatómicas (segmentectomía o subsegmentectomía) con un margen libre de enfermedad ofrezca una supervivencia superior a la resección atípica sin margen libre de tumor (siempre y cuando se garantice la resección completa). No obstante, dado que la vecindad inmediata al tumor es el lugar donde se localizan los focos de diseminación por vía venosa, desde un punto de vista oncológico es coherente intentar efectuar resecciones anatómicas con un margen de 1 cm. En estos sujetos rigurosamente seleccionados, la mortalidad perioperatoria debe ser inferior al 3% y la supervivencia a los 5 años debe ser superior al 50%[97].

### *Tratamiento adyuvante para prevenir la recidiva de carcinoma hepatocelular*

A pesar de una selección estricta de los candidatos y de los excelentes resultados obtenidos en términos de supervivencia, la tasa de recidiva de la enfermedad es muy alta y puede llegar al 70% a los 5 años[97]. A partir de diferentes estudios genéticos, se ha podido determinar que entre el 60 y el 70% de las recidivas corresponden a metástasis intrahepáticas no detectadas en el momento de la resección, y que entre el 30 y el 40% son CHC de novo[103,104]. El primer tipo aparece durante los 2 primeros años de seguimiento, suele cursar en forma de enfermedad multifocal, se considera como recidivas verdaderas y sus principales factores de riesgo son la presencia de invasión microvascular o satelitosis y un bajo grado de diferenciación histológica[101,103,105]. En este sentido, ante la presencia de invasión microvascular y satelitosis en el análisis histológico de la pieza quirúrgica, es recomendable valorar la inclusión del sujeto en la lista de trasplante hepático antes de la aparición de la recidiva[106]. Se han evaluado múltiples tratamientos adyuvantes para prevenir la recurrencia verdadera, como la quimioembolización y lipiodolización[107,108], la radiación intrahepática[109], la quimioterapia[110] o la inmunoterapia[111]. En cambio, las recidivas de novo suelen aparecer tardíamente: a partir del tercer año de seguimiento[112–115]. En estos sujetos se han evaluado diferentes tratamientos quimiopreventivos, como los derivados de los retinoides[116] y el interferón[117,118]. A pesar de los resultados iniciales esperanzadores, la eficacia de todas estas estrategias no se ha reproducido en estudios más consistentes y, en el momento actual, éstas no se pueden considerar parte de la práctica clínica habitual.

Recomendaciones:

13. La resección quirúrgica está recomendada en sujetos con CHC únicos sobre hígados no cirróticos o en sujetos cirróticos con función hepática preservada, bilirrubina normal y gradiente de presión portal inferior a 10 mmHg (nivel II).
14. En el momento actual, no hay ningún tratamiento adyuvante que haya demostrado eficacia (nivel II).

## Trasplante hepático

Hace 2 décadas, los resultados obtenidos tras el trasplante hepático, con tasas de recidiva del 50% y con supervivencia a los 5 años inferior al 40% cuestionaron la aceptación del trasplante hepático como opción terapéutica válida para el CHC. Estos datos fueron la consecuencia de la selección de candidatos con neoplasias de gran tamaño y también con presencia de invasión vascular o de diseminación extrahepática. Sin embargo, aquellos sujetos en los que se hallaba un CHC de forma incidental en el explante presentaban una mínima probabilidad de recidiva y una supervivencia comparable a la de los sujetos trasplantados sin CHC. Ésta fue la base racional para demostrar que cuando se limitaba el trasplante hepático a sujetos con tumores únicos menores o iguales a 5 cm o con un máximo de 3 nódulos menores de 3 cm, sin invasión vascular ni diseminación extrahepática, se obtenía una supervivencia a los 4 años del 75% y una tasa de recurrencia del 8%[119]. Diferentes grupos[120–122] han validado estos resultados. Asimismo son los criterios de trasplante hepático que aceptan la EASL[52], la AASLD[1], la United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) (www.optn.org) y la SETH[123]. Por tanto, el trasplante hepático es el tratamiento de elección en aquellos sujetos con CHC que no son candidatos óptimos para resección quirúrgica y que no tienen ninguna enfermedad extrahepática que contraindique el procedimiento y que presenten un CHC dentro de los criterios de Milán[1,52,123].

La aplicabilidad del trasplante es limitada. El número de candidatos excede el número de órganos disponibles y, por tanto, hay un tiempo de espera entre la indicación y el trasplante. Durante este tiempo, la neoplasia puede progresar y llegar a contraindicar la intervención. Esta circunstancia puede alcanzar al 25% de los sujetos si la espera es de 12 meses y, por tanto, la supervivencia de acuerdo con la intención del tratamiento se ve significativamente deteriorada[105]. Se han propuesto las siguientes estrategias para disminuir el riesgo de progresión durante el tiempo de espera:

- Aumentar el número de donantes: ésta sería la estrategia más eficaz, pero su impacto es limitado. A pesar de usar donantes de alto riesgo (sujetos con hígados esteatóticos y con edad avanzada) o de desarrollarse el trasplante dominó, el número de candidatos sigue excediendo a los donantes disponibles. Esto lleva a considerar que una opción potencialmente más eficaz es el desarrollo de programas de trasplante a partir de donante vivo[124]. Esta última alternativa ha mostrado resultados similares al trasplante cadavérico[125] y análisis de coste y eficacia han evidenciado su utilidad cuando la lista de espera supera los 7 meses[126]. Sin embargo, su aplicabilidad en la práctica clínica habitual es baja[127]. Además, se debe considerar la posibilidad de morbimortalidad en el donante y la mayor tasa de complicaciones postoperatorias de origen biliar en el receptor[128,129], particularmente en aquellos centros con experiencia limitada[128]. Al mismo tiempo, hay controversias respecto a la posible mayor intensidad de la recidiva de la infección por VHC[130,131].
- Sistemas de priorización: el objetivo es trasplantar antes a aquellos sujetos con alta probabilidad de progresión durante el tiempo en lista de espera y demorar a aquellos con enfermedad menos agresiva. En los últimos años se ha implantado el sistema MELD para sujetos con hepatopatía avanzada y para los sujetos con CHC. Asimismo se ha propuesto otorgar unos puntos del sistema MELD que equilibren el riesgo de exclusión y de muerte en la lista de espera, entre todas las categorías de los sujetos en lista. Dado que la proporción de sujetos con hepatopatía avanzada y que la intensidad de ésta no es estable ni homogénea entre diferentes áreas, la utilización de un mismo valor de puntos para los sujetos con CHC implica que la probabilidad de exclusión de la lista sea difícilmente equiparable entre las distintas zonas geográficas. Esta heterogeneidad se ha constatado en EE. UU., donde hace años que se implantó este sistema[132]. Por tanto, por el momento no se dispone de una estrategia de priorización óptima[123].
- Aplicación de tratamientos durante el tiempo de espera: no hay ningún ensayo clínico aleatorizado que haya demostrado que la aplicación de tratamientos locorregionales durante el tiempo de espera aumente la supervivencia. Sin embargo, diferentes estudios observacionales han demostrado que el tratamiento en lista mediante RFA[133,134] o mediante TACE[135,136] disminuye la tasa de exclusión. Asimismo, el análisis de coste y eficacia ha demostrado su utilidad cuando la lista de espera supera los 6 meses[137]. Por tanto, en aquellos centros donde el tiempo de espera excede este período está indicado considerar la realización de tratamiento locorregional.

Recientemente se ha propuesto que se podrían expandir los criterios de inclusión en la lista de espera sin que se incremente la tasa de recidiva ni que se deteriore la supervivencia a largo plazo. Esta sugerencia se basa en que algunos sujetos en los que en el análisis del explante mostraba un CHC que excedía discretamente los criterios de Milán presentaban una supervivencia y una tasa de recidiva aceptable[138–142]. Sin embargo, todas estas series incluyeron un número bajo de sujetos con criterio expandido que en muchos casos se basaba en análisis retrospectivos y en los hallazgos del explante (y no en la valoración por técnicas de imagen en el momento de la inclusión), y no consideraban ni registraban la tasa de caída en la lista. Por otra parte, hay estudios en los que el análisis de los sujetos que exceden discretamente los límites de los criterios de Milán demuestran una peor supervivencia[143,144]. Por último, el tiempo de seguimiento es escaso y, por tanto, la supervivencia a los 5 años de acuerdo con el principio de intención de tratamiento no es bien conocida. Además de estos datos, debe tenerse en cuenta que la expansión de criterios aumentará el número de sujetos en lista de espera, con lo que la escasez de donantes se incrementará y, por tanto, al mismo tiempo que se usen órganos en sujetos con una expectativa vital inferior, se dejará de trasplantar a sujetos con supervivencia postrasplante excelente. Los análisis de coste y eficacia hechos teniendo en cuenta el impacto que la expansión de criterios tendría en los programas de trasplante con escasez de órganos desaconsejan esta estrategia[145].

Otros grupos han demostrado que aquellos sujetos con CHC que exceden los criterios de Milán con respuesta objetiva tras la aplicación de un tratamiento locorregional (*downstaging*) presentan una excelente evolución tras la realización de un trasplante hepático[135,146,147]. Esta recomendación está fundamentada en que la respuesta al tratamiento con disminución del estadio tumoral podría ser un marcador de menos agresividad neoplásica, por lo que permitiría seleccionar a aquellos sujetos con tumores que tendrían una evolución satisfactoria tras el trasplante hepático. Sin embargo, todas estas series incluyen un número bajo de sujetos, la expansión aceptada no es uniforme, los tratamientos aplicados son heterogéneos y la definición de *downstaging* no es común. Además, el seguimiento es escaso y no es factible establecer una recomendación.

Finalmente, teniendo en cuenta la disponibilidad no restringida de órganos y el tiempo mínimo de espera cuando se considera el trasplante hepático de donante vivo, algunos autores han propuesto que los criterios de selección de sujetos con CHC para trasplante podrían expanderse[125,148–153]. Esta propuesta no debe considerarse como práctica clínica convencional hasta que se

establezca su eficacia en estudios de investigación. En este sentido, el comité ético de la Transplantation Society recomienda que mientras se esperan estos resultados, los criterios para indicar trasplante hepático por CHC sean los mismos en el donante vivo que en el donante cadavérico[154].

Recomendaciones:

15. El trasplante hepático es una opción eficaz para sujetos que presentan un CHC que cumple los criterios de Milán: tumor único menor o igual a 5 cm o hasta 3 nódulos menores de 3 cm (nivel II).
16. El trasplante hepático de donante vivo es una opción válida, si el tiempo de espera es lo suficientemente largo para considerar que puede haber riesgo de exclusión por progresión tumoral (nivel II).
17. No se puede realizar ninguna recomendación respecto a la expansión de los criterios de inclusión más allá de los criterios convencionales de Milán (nivel III).
18. El tratamiento locorregional preoperatorio puede considerarse cuando el tiempo de espera esperado es mayor de 6 meses (nivel II).

## Técnicas de ablación

La ablación percutánea es el tratamiento de elección de aquellos sujetos afectados de CHC en estadio inicial, en los que la resección quirúrgica no es posible y el trasplante hepático está contraindicado por comorbilidad asociada. Al mismo tiempo, es una opción terapéutica para intentar evitar la progresión tumoral durante el tiempo de espera de trasplante hepático. La ablación percutánea presenta los mejores resultados en sujetos con tumores únicos menores de 2 cm[100] y con función hepática conservada, especialmente cuando se consigue la ablación completa tras el procedimiento[155].

La ablación del tumor puede realizarse a través de la instilación de sustancias químicas (principalmente etanol y ácido acético) o mediante modificación de la temperatura intratumoral (como en el caso de la RFA o la crioablación). La inyección percutánea de alcohol (PEI, *percutaneous ethanol injection*) es la técnica más evaluada[156]. La PEI obtiene la necrosis tumoral completa en aproximadamente el 80% de los tumores menores de 3 cm y alcanza una supervivencia a los 5 años superior al 50% en sujetos con función hepática compensada[155,157]. En tumores de mayor tamaño, la PEI pierde su eficacia debido a la presencia de septos fibrosos intratumorales que impiden la correcta difusión del etanol[155,157,158]. La RFA posee mayor capacidad ablativa y obtiene mayor tasa de respuestas que la PEI en tumores mayores de 3 cm con menor número de sesiones[156,159]. Sin embargo, presenta como inconvenientes una mayor frecuencia y gravedad de efectos adversos[160,161], un mayor coste y una menor aplicabilidad ya que no se recomienda su uso en tumores subcapsulares ni adyacentes a la vesícula biliar, al hilio hepático, al corazón o a los vasos sanguíneos. En los últimos años se ha comparado directamente la ablación mediante PEI respecto a la RFA[162–166]. La RFA únicamente ha demostrado beneficio en términos de supervivencia en un estudio en Japón[166] (resultado que no se reprodujo en los estudios europeos). Sin embargo, en todos estos ensayos, la RFA ha mostrado una mayor capacidad de ablación, ya que obtiene una mayor tasa de respuesta completa y una menor probabilidad de recurrencia local. Por tanto, si se tienen en cuenta los datos disponibles en la actualidad, la RFA es más eficaz que la PEI en el control local de la enfermedad, especialmente en tumores mayores de 2 cm. Posiblemente es en este grupo donde la RFA ofrezca ventajas en términos de supervivencia.

Al igual que la resección quirúrgica, el principal inconveniente de la ablación percutánea es la alta recurrencia (el 80% a los 5 años) a pesar de obtener una respuesta completa inicial[100].

Dada la gran eficacia terapéutica de la ablación en tumores menores de 2 cm y la baja probabilidad de efectos secundarios, varios grupos han comparado directamente la ablación percutánea con la resección quirúrgica[167,168] sin encontrar diferencias significativas en supervivencia ni en tasa de recidiva entre ambos tratamientos. Lamentablemente, estos trabajos presentan problemas metodológicos (particularmente en la asignación de tratamiento) que invalidan sus resultados, por lo que no hay suficientes pruebas científicas para establecer la superioridad de una sobre otra en tumores menores de 2 cm.

Recomendaciones:

19. La ablación tumoral es un tratamiento eficaz en aquellos sujetos con CHC iniciales que no son candidatos a resección quirúrgica o como tratamiento eficaz durante el tiempo de espera del trasplante hepático (nivel II).
20. La PEI y la RFA poseen una eficacia similar en tumores menores de 2 cm. Sin embargo, la RFA tiene más capacidad ablativa y su eficacia es claramente mayor a la PEI en tumores mayores de 2 cm (nivel I).
21. En tumores menores de 2 cm, la ablación percutánea presenta una eficacia terapéutica similar a la resección quirúrgica (nivel II).

## Quimioembolización y otros tratamientos locorregionales

El único tratamiento que ha mostrado beneficio en términos de supervivencia en sujetos con CHC intermedio (estadio B de acuerdo con la clasificación BCLC) es la TACE. Este tratamiento está basado en la vascularización predominantemente arterial del CHC. Consiste en la cateterización selectiva de la arteria hepática, la inyección de un agente quimioterápico incrustado en un medio transportador (habitualmente lipiodol) y la posterior oclusión del flujo arterial con diversas sustancias embolizantes[169]. La TACE está contraindicada en sujetos con alteración del flujo portal (trombosis o flujo hepatofugal), con alteraciones significativas de la coagulación, con insuficiencia renal o con pobre reserva funcional hepática. En estos casos hay un alto riesgo de descompensación de la hepatopatía y el beneficio en la supervivencia es marginal[169]. Además, a pesar de la selección estricta de los sujetos y de una técnica cuidadosa, la TACE no es un procedimiento exento de efectos secundarios, que pueden variar desde un simple síndrome postembolización (el más frecuente, que consiste en fiebre, íleo y dolor abdominal) hasta un fallo hepático, abscesos, colecistitis isquémica o incluso la muerte. Su beneficio inequívoco en términos de supervivencia se basa en 2 ensayos clínicos aleatorizados y controlados[170,171] y un metaanálisis posterior de los datos acumulados[172] que demostraron que la TACE es superior respecto a placebo en sujetos con CHC intermedio, obteniendo una superviviencia mediana con tratamiento de aproximadamente 20 meses. Sin embargo, a pesar de que se consiguen respuestas radiológicas en más de la mitad de los casos, su principal inconveniente es que la mayoría de los sujetos experimentan progresión de su enfermedad a pesar de una respuesta inicial.

Aún hay muchos aspectos que investigar respecto a la TACE. En primer lugar, se desconoce cuál es el mejor agente quimioterápico o embolizante, ya que hasta la fecha ningún estudio ha comparado correctamente las diferentes opciones técnicas. Se ha evaluado el uso de esferas de alcohol polivinilo cargadas de adriamicina. Estas esferas liberan lentamente la quimioterapia una vez en contacto con la sangre, con lo que el paso de ésta a la circulación sistémica se reduce y minimiza los efectos secundarios. Además, permiten

elegir el calibre en función del vaso que se emboliza e incrementan la homogeneidad de la embolización resultante. Asimismo, han obtenido una respuesta radiológica cercana al 80%, aparentemente superior a la respuesta radiológica publicada con la TACE convencional[173–175]. Por tanto, hay suficiente base racional para comparar esta técnica respecto a la TACE estándar en un ensayo clínico aleatorizado. Por otra parte, es necesario evaluar cuál es el mejor esquema terapéutico (pauta fija o retratar únicamente cuando se detecta revascularización de las lesiones) y se debe investigar cómo se puede evitar o enlentecer la progresión de la enfermedad después del tratamiento. En este sentido, los resultados positivos del sorafenib en el CHC avanzado y su acción (fundamentalmente antiangiogénica) han sentado las bases racionales para evaluarlo como tratamiento adyuvante tras la realización de TACE en CHC intermedio. Por último, se está investigando activamente la realización de tratamientos locorregionales combinados con la finalidad de aumentar la necrosis tumoral y, de forma indirecta, la supervivencia del sujeto. En el momento actual, los resultados disponibles son positivos, pero están basados en estudios piloto muy preliminares[176].

En los últimos años han aparecido otros tratamientos locorregionales potencialmente útiles. Entre ellos cabe destacar la radioembolización mediante esferas de Yttrium-90[177,178]. Ensayos clínicos fase II en sujetos afectados de CHC inoperable con trombosis portal han mostrado una alta tasa de respuesta radiológica con buena tolerancia clínica[179]. A pesar de estos resultados prometedores, en el momento actual no hay datos concluyentes sobre su beneficio en términos de supervivencia y su uso debe ser reservado al ámbito experimental hasta que se disponga de pruebas científicas que demuestren su validez en la práctica clínica convencional.

Recomendaciones:

22. La TACE es el tratamiento de elección en sujetos asintomáticos, con función hepática conservada, que presentan un CHC multinodular, sin invasión vascular ni extrahepática (nivel I).
23. Otros tratamientos locorregionales, como la radioterapia intratumoral con Yttrium-90, han mostrado eficacia en estudios preliminares. Se recomienda su evaluación en el contexto de ensayos clínicos (nivel II).

## Tratamiento sistémico: sorafenib

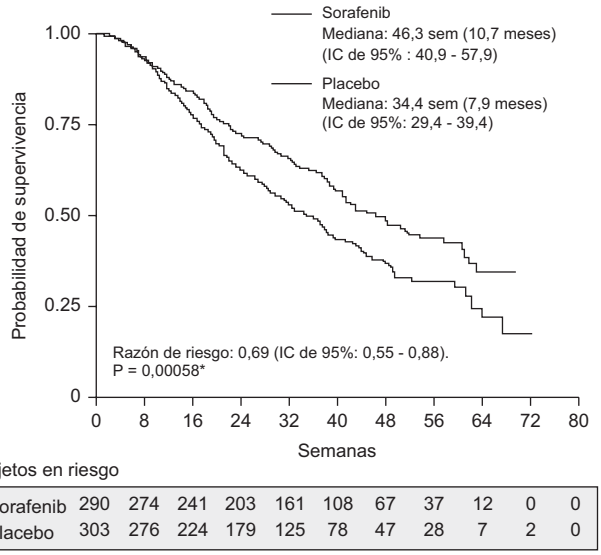
En los últimos años se han evaluado múltiples agentes y pautas de quimioterapia, la mayoría de éstas basadas en doxorrubicina[180,181]. Sin embargo, ninguna pauta se ha demostrado eficaz en prolongar la supervivencia de los sujetos con CHC y su uso no es recomendado[172,182]. Asimismo, se había indicado que sustancias antiestrogénicas (como el tamoxifeno) podrían ser eficaces en el tratamiento del CHC avanzado, pero múltiples ensayos aleatorizados y metaanálisis han demostrado de forma concluyente la ausencia de beneficio de estas sustancias[172,183–186]. Algunos tratamientos, como megestrol[187], octreotride[188,189], derivados antiandrogénicos[190,191] y seocalcitol[192], tampoco han demostrado eficacia en el CHC.

En los últimos años se han producido grandes progresos en el conocimiento de las alteraciones moleculares que condicionan la progresión tumoral[63]. Esto ha permitido desarrollar múltiples agentes que actúan de forma específica en las vías moleculares alteradas. Se han evaluado múltiples tratamientos moleculares y habitualmente los resultados siempre se presentan como prometedores[193]. La tabla 3 resume los principales fármacos evaluados. Hasta la fecha, el único agente que ha mostrado eficacia en términos de supervivencia en un estudio fase 3 controlado con placebo es el sorafenib. Esta molécula es un inhibidor multicinasa de bajo peso molecular y de gran biodisponibilidad que se administra por vía oral y que actúa bloqueando diferentes vías de señalización asociadas a la hepatocarcinogénesis, en especial la vía Raf/MEK/ERK a través de la inhibición de Raf cinasa y diferentes tirosincinasas (receptor 2 del factor de crecimiento endotelial vascular, receptor del factor de crecimiento derivado de plaquetas, receptores c-Kit)[194]. Sus acciones fundamentales son reducir la angiogénesis y enlentecer la proliferación celular. Tras los resultados positivos de estudios preclínicos[195] y de un ensayo fase II[196], se efectuó un estudio clínico internacional, multicéntrico, aleatorizado, controlado y doble ciego en el que se evaluó el sorafenib en dosis de 400 mg/12 h respecto a placebo en sujetos con CHC avanzado y función hepática compensada (estudio SHARP). Se seleccionó un total de 602 sujetos. Se asignó un total de 299 sujetos al grupo sorafenib y 303 sujetos al grupo placebo y se administró el tratamiento hasta evidenciar progresión radiológica y sintomática o aparición de efectos adversos graves. En el segundo análisis interino se decidió finalizar el estudio dado el aumento significativo de supervivencia en el grupo de sorafenib. La supervivencia mediana fue de 10,7 meses con sorafenib y de 7,9 meses con placebo (razón de riesgo [*Hazard ratio*, HR] [HR] de 0,69; intervalo de confianza [IC] del 95%: 0,55 a 0,87; $p<0,001$) (fig. 3). La mediana de tiempo respecto a la progresión fue de 5,5 meses con sorafenib frente a 2,8 meses con placebo (HR de 0,58; IC del 95%: 0,45 a 0,74; $p<0,001$). Los efectos secundarios más frecuentes fueron diarrea, pérdida de peso y reacción manopié (alteración exclusiva de palmas o plantas que puede variar desde eritema hasta aparición de flictenas y áreas de necrosis). En la mayoría de los casos, los efectos secundarios fueron leves y de fácil control, de modo que el tratamiento se mantuvo en el 90% de los casos[197]. Estos resultados se reprodujeron en un ensayo clínico con un diseño similar realizado en Asia, en el que los sujetos presentaban un CHC más avanzado y la mayoría de éstos eran secundarios a cirrosis por VHB[198]. El sorafenib se ha evaluado en sujetos con función hepática compensada (Child-Pugh A) y hay pocos datos respecto a su utilidad en sujetos Child-Pugh B en cuanto al impacto en la supervivencia. El perfil farmacocinético no se ve significativamente modificado y no se ha reportado un aumento significativo de los efectos secundarios. No obstante, debe señalarse que el estadio Child-Pugh B comprende un espectro clínico muy amplio y que el posible impacto sobre la

**Tabla 3**
Tratamientos moleculares evaluados en carcinoma hepatocelular

| Tratamiento | Tipo de molécula (diana) | Fase clínica |
|---|---|---|
| Sorafenib | Molécula de tamaño pequeño (TKI) Inhibidor Raf, VEGFR y PDGFR | III-positivo[197] |
| Erlotinib | Molécula de tamaño pequeño (TKI) Inhibidor *EGFR* | II-cerrado[204] |
| Cetuximab | AcMo Inhibidor *EGFR* | II-activo |
| Lapatinib | Molécula de tamaño pequeño (TKI) *EGFR*, *Her2/neu* | II-activo |
| Sunitinib | Molécula de tamaño pequeño (TKI) Inhibidor PDGFR, VEGFR y Kit(KI) | II-cerrado[205,206] |
| Erlotinib+ bevacizumab | Molécula de tamaño pequeño + AcMo *EGFR* (TKI), VEGFR (AcMo) | II-cerrado[207] |
| Bevacizumab | AcMo Anticuerpo contra inhibidor VEGFR | II-cerrado[208] |
| Bortezomib | Inhibidor de proteasoma | II-negativo |
| Nolatrexed | *Thymidylate synthase* | III-negativo[181] |
| T138067 | Inhibidor de la tubulina | III-negativo |
| RAD001 | Inhibidor mTOR | I/II-activo |
| Brivanib | Molécula de tamaño pequeño Inhibidor del VEGFR-2 | II-activo |

AcMo: anticuerpo monoclonal; EGFR: receptor del factor de crecimiento epidérmico; PDGFR: receptor del factor de crecimiento derivado de plaquetas; TKI: inhibidor tirosincinasa (*Tyrosine-kinase inhibitor*) VEGFR: receptor del factor de crecimiento endotelial vascular.




Sujetos en riesgo

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sorafenib | 290 | 274 | 241 | 203 | 161 | 108 | 67 | 37 | 12 | 0 | 0 |
| Placebo | 303 | 276 | 224 | 179 | 125 | 78 | 47 | 28 | 7 | 2 | 0 |

**Figura 3.** Curva de supervivencia de los sujetos aleatorizados a sorafenib o a placebo (estudio SHARP). La supervivencia mediana del grupo sorafenib (299 sujetos) fue de 10,7 meses comparados con los 7,9 meses del grupo placebo (303 sujetos). Cociente de riesgos instantáneos de muerte de 0,69 (intervalo de confianza del 95%: 0,55 a 0,88). Adaptado con permiso de Llovet et al, N Engl J Med 2008[197]. IC: intervalo de confianza.

progresión tumoral puede no modificar la supervivencia del sujeto en relación con el deterioro de la función hepática[199]. Por tanto, el uso de sorafenib en sujetos Child-Pugh B debería evaluarse de forma individualizada. No hay información respecto a la seguridad y a la eficacia en sujetos con disfunción hepática avanzada (Child-Pugh C), pero si se extrapolan los resultados en sujetos con Child-Pugh B y en la experiencia acumulada, su uso en estos sujetos debe desaconsejarse. Por último, no hay hasta la fecha marcadores biológicos que permitan predecir la respuesta al sorafenib. Asimismo, se desconoce si la presencia de progresión radiológica se traduce en una pérdida de eficacia, dado que en el estudio SHARP el tratamiento se mantuvo hasta progresión sintomática. Por tanto, no se puede realizar ninguna recomendación respecto a suspender el tratamiento ante progresión radiológica y se debe evaluar cada caso de forma individualizada.

Sobre la base de estos resultados, la Food and Drug Administration (FDA) y la European Agency for the Evaluation of Medical Products (EMEA) aprobaron el sorafenib, que se ha convertido en el tratamiento de elección en el CHC avanzado. El subanálisis de los sujetos del estudio SHARP demuestra que la eficacia del sorafenib se mantiene en todos los grupos relevantes (sexo, etiología, invasión vascular o extrahepática y tratamiento previo).

El sorafenib ha demostrado que los tratamientos moleculares pueden ser útiles en el tratamiento del CHC y abre el camino para evaluar el bloqueo de múltiples vías de señalización de la misma forma que ya se está haciendo desde hace años en otras neoplasias[93,193]. En este sentido, debe señalarse que el beneficio en términos de probabilidad de supervivencia y en valor absoluto es superponible al que se obtiene mediante otro tipo de tratamientos moleculares en sujetos con cáncer de mama[200], pulmón[201], colon[202] o cabeza y cuello[203] en fase clínica. Por tanto, el beneficio obtenido mediante sorafenib no puede negligirse ni considerarse marginal.

Recomendaciones:

24. La quimioterapia se ha mostrado ineficaz en el CHC y su uso no está recomendado (nivel I).
25. El sorafenib es el tratamiento de elección en sujetos afectados de CHC avanzado (nivel I).

## Perspectivas de futuro. Objetivos en la investigación del carcinoma hepatocelular

Aún son necesarios grandes avances en el campo del CHC. Además de aplicar las estrategias preventivas antes mencionadas, es necesario progresar en el área de la detección precoz y en el aumento de la eficacia terapéutica. Es imprescindible que en los diferentes ámbitos asistenciales deje de verse el CHC como una neoplasia imposible de detectar en fase inicial para la que no hay tratamiento. Con esto se incrementará el número de sujetos susceptibles de recibir tratamiento radical y, además, se les permitirá acceder a tratamiento a sujetos que actualmente se detectan únicamente cuando se hallan en fase terminal. Dado que la población en riesgo se encuentra plenamente identificada, es crítico que las recomendaciones de cribado se apliquen de manera correcta y por parte de personal formado adecuadamente. La investigación en cuanto a técnicas de imagen y marcadores tumorales será de importancia capital para aumentar la eficacia de los planes de seguimiento. Por tanto, debe desarrollarse una actividad intensa de investigación en el área de detección, de diagnóstico y de estadificación. La investigación translacional debe permitir incorporar los hallazgos de laboratorio en criterios para la caracterización y la evaluación pronóstica de los sujetos. Además, el mejor conocimiento de las alteraciones biológicas implicadas en la oncogénesis hepática conducirá a identificar nuevas dianas de tratamiento. Éstas deberán evaluarse siguiendo un análisis específico para sujetos con CHC, dado que la coexistencia del tumor con enfermedad hepática de base obliga a un desarrollo diferente al que convencionalmente se sigue en otras neoplasias. En este sentido, un panel internacional de expertos de diferentes especialidades promovido por la AASLD ha elaborado un documento de consenso con recomendaciones para seguir en el campo del tratamiento del CHC[89] (tabla 4). En el caso de ensayos fase I, es necesario incluir a sujetos con cirrosis hepática compensada Child-Pugh A para evaluar la dosis exacta, la toxicidad y los episodios específicos asociados a la hepatopatía que no serían capturados en estudios fase I tradicionales, que incluyen sujetos con diferentes neoplasias. Respecto a los ensayos fase II, el panel de expertos recomendó el uso de ensayos fase II aleatorizados diseñados para evaluar un episodio subrogado dependiente del tiempo, como por ejemplo el tiempo de progresión. La supervivencia global debe reportarse como un objetivo secundario junto con datos de seguridad. Asimismo, se debe evitar el uso de medidas compuestas (como la supervivencia libre de enfermedad y la supervivencia libre de progresión) como objetivos primarios en estos estudios. En ensayos clínicos de tratamientos nuevos, es recomendable incluir un análisis de biomarcadores que permita determinar los predictores de respuesta. De acuerdo con los resultados del estudio SHARP, el sorafenib debe ser el tratamiento estándar en todos aquellos ensayos que evalúen tratamientos de primera línea en CHC avanzado. Los agentes nuevos que se evalúen como segunda línea de tratamiento en CHC avanzado deben compararse con placebo y/o tratamiento de soporte, y únicamente aquellos fármacos que hayan mostrado eficacia como segunda línea de tratamiento en ensayos fase III pueden considerarse para su comparación directa con el sorafenib en estudios fase II. Para la evaluación del tratamiento de primera línea en el CHC avanzado, el diseño ideal sería el agente nuevo asociado a sorafenib comparado con sorafenib. Para tratamientos de segunda línea, se deben incluir sujetos con contraindicaciones o fracaso tras tratamiento con sorafenib y para el grupo control deberían incluirse sujetos con placebo y/o tratamiento de soporte. Asimismo, aquellos agentes evaluados como tratamiento adyuvante o neoadyuvante deberán compararse con placebo y/o tratamiento de soporte en estudios fase II. En el caso de ensayos fase III, el objetivo primario debe ser la

**Tabla 4**
Propuesta para el estudio de ensayos clínicos de fase III en carcinoma hepatocelular siguiendo las recomendaciones de la American Association for the Study of Liver Diseases y el Journal National Cancer Institute[89]

| | Evaluación de agentes nuevos | |
|---|---|---|
| Estadio de CHC (estándar de tratamiento) | Tratamiento de primera línea | Tratamiento de segunda línea[a] |
| BCLC estadio 0 o A Estadio inicial (resección, trasplante o ablación) | Adyuvante: fármaco frente a placebo | - |
| BCLC estadio B Estadio intermedio (TACE) | TACE frente a TACE+fármaco | - |
| | TACE frente a fármaco o dispositivo[b]<br>Sorafenib frente a sorafenib + fármaco | |
| BCLC estadio C Estadio avanzado (sorafenib) | Sorafenib frente a fármaco[b] | Fármaco frente a placebo |

BCLC: Barcelona Clinic Liver Cancer; CHC: carcinoma hepatocelular; TACE: *transarterial chemoembolization* 'quimioembolización trasarterial'.
[a] En caso de fracaso del tratamiento estándar.
[b] Las comparaciones directas con el tratamiento estándar están sólo justificadas si los resultados del ensayo en fase II son prometedores.

supervivencia global. Los episodios dependientes del tiempo, como por ejemplo el tiempo hasta la progresión, deben considerarse como objetivos secundarios y, de nuevo, debe evitarse el uso de medidas compuestas, como la supervivencia libre de enfermedad y la supervivencia libre de progresión. Los estudios fase III de tratamientos adyuvantes deben usar supervivencia o tiempo de recurrencia como objetivos primarios. Únicamente puede plantearse un objetivo compuesto (supervivencia libre de recidiva) si la población del estudio es muy selectiva y si se evita casi en su totalidad la mortalidad no relacionada con cáncer.

## Agradecimientos

Esta actuación se ha realizado en el marco de colaboración previsto en la Acción Transversal del Cáncer aprobada por el Consejo de Ministros de 11 de octubre de 2007, al amparo del convenio suscrito por el ISCIII, organismo autónomo dependiente actualmente del Ministerio de Ciencia e Innovación, y el CIBER para el área temática de enfermedades digestivas (CIBERehd).

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