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**Análise da sobrevida de pacientes com
carcinoma hepatocelular atendidos no
Instituto do Câncer do Estado de São Paulo**

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Medicina da Universidade de São
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Programa de Ciências em
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Orientador: Prof. Dr. Flair José Carrilho

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trabalhar com vocês no ICESP, exemplos de
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LISTA DE ABREVIATURAS

AASLD	<i>American Association for the Study of Liver Diseases</i>
AFB1	aflatoxina B1
AFP	alfa-fetoproteína
AgHBs	antígeno de superfície S do vírus da hepatite B
BCLC	<i>Barcelona Clinic Liver Cancer group</i>
CHC	carcinoma hepatocelular
cm	centímetro
DEB	<i>Drug Eluting Beads</i>
DHGNA	Doença Hepática Gordurosa Não Alcoólica
EASL	<i>European Association for the Study of the Liver</i>
ECOG-PS	<i>Eastern Cooperative Oncology Group Performance Status</i>
g/dia	gramas por dia
HCFMUSP	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
HFE	gene da hemocromatose
HIV	vírus da imunodeficiência humana
HR	<i>Hazard Ratio</i>
IC	Intervalo de Confiança
ICESP	Instituto do Câncer do Estado de São Paulo
MELD	<i>Model for End stage Liver Disease</i>
mm	milímetro
mRECIST	RECIST modificado
ng/ml	nanogramas por mililitro
PCR	reação de polimerização em cadeia
PEI	<i>Percutaneous Ethanol Injection</i>
PIAF	cisplatina, interferon, doxorrubicina e fluoracil
pmp	por milhão por pessoa
RECIST	<i>Response Evaluation Criteria In Solid Tumors</i>
RM	ressonância magnética

RNI	relação normatizada internacional
SBRT	<i>Stereotatic Body Radiation Therapy</i>
TACE	<i>TransArterial ChemoEmbolisation</i>
TC	tomografia computadorizada
TNM	<i>Tumor-Node-Metastasis</i>
TP	tempo de protrombina
US	ultrassonografia
VHB	vírus da hepatite B
VHC	vírus da hepatite C
γ^{90}	ítrio-90

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RESUMO

Kikuchi LOO. *Análise da sobrevida de pacientes com carcinoma hepatocelular atendidos no Instituto do Câncer do Estado de São Paulo* [Tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2015.

INTRODUÇÃO: Na maioria dos casos, o carcinoma hepatocelular (CHC) acomete pacientes com cirrose hepática. O algoritmo do *Barcelona Clinic Liver Cancer group* (BCLC) considera função hepática, características tumorais e, estado geral do paciente para definir o tratamento. Entretanto, a aplicabilidade de um algoritmo terapêutico nem sempre é possível na prática clínica. Este estudo buscou avaliar a aderência às recomendações do BCLC para tratamento dos pacientes com CHC e analisar o impacto sobre a sobrevida nos diferentes estádios. **MÉTODOS:** Este estudo incluiu todos os pacientes encaminhados para o Instituto do Câncer do Estado de São Paulo para tratamento do CHC entre 2010 e 2012. Os pacientes ($n = 364$) foram classificados de acordo com as recomendações do BCLC. Se a terapia proposta não foi aplicada, o caso foi considerado como não aderente e as causas foram investigadas. A curva de sobrevida global foi estimada pelo método de sobrevida de Kaplan-Meier e comparada pela regressão de Cox. **RESULTADOS:** A porcentagem de aderência às recomendações do BCLC foi de 52% e variou entre os estádios: BCLC 0/A, 44%; BCLC B, 78%; BCLC C, 35%; e BCLC D, 67%. A taxa de sobrevida global, em um, dois e três anos, foi de 63, 45 e 33%, respectivamente. Nos pacientes aderentes do estágio BCLC 0/A, a sobrevida global foi significativamente melhor se comparada aos pacientes não aderentes (razão de risco [RR] = 0,19, intervalo de confiança [IC] 95%: 0,09–0,42; $p < 0,001$). Nos pacientes do estágio BCLC D, a taxa de sobrevida global foi pior em pacientes aderentes comparada aos pacientes não aderentes (RR = 4,0; IC 95%: 1,67–9,88; $p < 0,001$). Nenhuma diferença foi observada em pacientes do estágio BCLC B ou C classificados como aderentes ou não aderentes. **CONCLUSÕES:** A porcentagem de aderência às recomendações do BCLC na prática clínica é baixa e varia entre os estádios. A não aderência está associada a pior prognóstico, particularmente em pacientes com estágio precoce.

Descritores: Carcinoma hepatocelular; Prognóstico; Análise de sobrevida; Estadiamento de neoplasias; Mortalidade; Cirrose hepática; Neoplasias hepáticas.

SUMMARY

Kikuchi LOO. *Survival analysis of patients with hepatocellular carcinoma treated at Instituto do Cancer do Estado de São Paulo* [Thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2015.

INTRODUCTION: In most cases, hepatocellular carcinoma (HCC) affects patients with liver cirrhosis. *Barcelona Clinic Liver Cancer group* (BCLC) algorithm takes into consideration liver function, tumor variables and patients general status to guide therapy. However, the application of a therapeutic algorithm is not always feasible in clinical practice. The aim of this study was to assess the adherence of newly diagnosed hepatocellular carcinoma patients to the BCLC treatment guidelines, as well as examine the impact on survival in different stages. **METHODS:** This study included all patients referred to Instituto do Câncer do Estado de São Paulo for HCC therapy between 2010 and 2012. Patients ($n = 364$) were classified according to BCLC stage. If the proposed HCC therapy could not be applied, the case was considered to represent deviations from the recommended BCLC guideline. Causes of treatment deviations were investigated. The overall survival (OS) curves were estimated by the Kaplan–Meier survival method and compared by Cox regression. **RESULTS:** The overall percentage of adherence to BCLC guidelines was 52 % and varied among the disease stages: BCLC 0/A, 44 %; BCLC B, 78 %; BCLC C, 35 %; and BCLC D, 67 %. One-, two-, and three-year OS rates were 63, 45, and 33 %, respectively. In BCLC 0/A, adherent patients presented a significantly better OS compared to non-adherent patients (hazard ratio [HR] = 0.19, 95% confidence interval [CI]: 0.09–0.42; $p < 0.001$). In BCLC D, the OS rate was worse in adherent patients compared to non-adherent patients (HR = 4.0, 95% CI: 1.67–9.88; $p < 0.001$), whereas no differences were observed in BCLC stage B or C. **CONCLUSIONS:** The percentage of adherence to BCLC recommendations in clinical practice is low and varies among the clinical stages. Non-adherence is associated with a worse prognosis, particularly in early stage disease.

Descriptors: Hepatocellular carcinoma; Prognosis; Survival analysis; Neoplasm staging; Mortality; Liver cirrhosis; Liver neoplasms.

1 INTRODUÇÃO

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1 INTRODUÇÃO

Os tumores malignos primários do fígado correspondem à 6ª causa de câncer e 3ª causa de morte por câncer no mundo. A incidência global estimada é de 500.000-1.000.000 casos novos/ano de carcinoma hepatocelular (CHC), levando a 600.000 mortes por ano, em todo o mundo¹. O CHC é a complicação mais frequente e a principal causa de óbito em pacientes com cirrose hepática compensada^{2,3}.

O CHC corresponde a 85 a 90% das neoplasias malignas primárias do fígado. Outras formas incluem: hepatoblastoma, colangiocarcinoma, angiossarcoma e a variante fibrolamelar. Eles acometem população diversa e a evolução, assim como as propostas de tratamento são diferentes em relação ao CHC⁴⁻⁷.

1.1 Epidemiologia e fatores de risco do CHC

Na grande maioria dos casos, o CHC se desenvolve dentro do contexto de doença hepática crônica (70-90% de todos os pacientes)^{8,9}. A heterogeneidade na incidência mundial reflete variações da distribuição dos principais fatores de risco^{1,8,10}. Estima-se que a infecção crônica pelo vírus da hepatite B (VHB) e vírus da hepatite C (VHC) esteja associada a mais de 80% dos casos de CHC no mundo¹¹.

Estudos recentes em países ocidentais demonstram aumento da mortalidade por CHC, enquanto a mortalidade por cirrose hepática diminuiu ou permaneceu estável^{10,12}. Nos Estados Unidos da América, o CHC é a causa de morte por câncer que apresenta crescimento mais rápido, com aumento de 80% da incidência anual nas últimas duas décadas¹². O Brasil é considerado um país de baixa incidência de CHC. Entretanto, mudanças no perfil dos pacientes com CHC foram observadas nos últimos anos. A

infecção crônica pelo VHC se tornou o principal fator de risco para CHC na maioria das regiões brasileiras^{13,14}.

Há cerca de 130 milhões a 170 milhões de pessoas no mundo infectadas pelo VHC ou, aproximadamente, 3% da população global. Estima-se que 25% desses pacientes evoluem para cirrose¹⁵. A incidência de CHC em pessoas com cirrose hepática pelo VHC é de 3-5% ao ano¹⁶. Não há vacina que evite a transmissão do VHC. O tratamento da hepatite C crônica, com interrupção da infecção crônica e, por consequência, evolução para cirrose, diminui o risco de desenvolver CHC. Entretanto, se a cirrose estiver estabelecida, o risco de CHC persiste independente do tratamento antiviral¹⁷. No Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a infecção crônica pelo VHC é a principal etiologia dos pacientes com CHC¹⁸.

A infecção crônica pelo VHB é a causa mais frequente de CHC no mundo. Existem, hoje, 350 milhões de pessoas infectadas pelo VHB, o que corresponde a 5% da população mundial. Nos portadores crônicos, o risco de desenvolver CHC é 5-15 vezes maior que na população geral. Nos pacientes com VHB, 70 a 90% dos tumores acontecem em pacientes cirróticos. Entretanto, o CHC pode surgir também em pacientes com hepatite B não cirróticos^{19,20}. O VHB é considerado um vírus carcinogênico, pois o ácido desoxirribonucleico do vírus se integra no genoma do hospedeiro. Além disso, a proteína viral HBx também parece exercer papel importante na hepatocarcinogênese²¹. O CHC relacionado ao VHB pode ser prevenido pela vacinação. Após a implantação do programa de vacinação em crianças, houve uma redução na incidência de CHC nesta população em Taiwan de maneira significativa²². Se houver infecção crônica, o uso de antivirais pode prevenir a progressão da doença hepática e, possivelmente, o surgimento do CHC em longo prazo²³. No Brasil, os casos de CHC relacionados ao VHB variam de acordo com a região geográfica. Na região Norte, em que a proporção é maior, cerca de 25% dos casos de CHC estão relacionados ao VHB¹⁴.

O álcool é um importante fator de risco para o desenvolvimento do CHC e exerce um efeito sinérgico em indivíduos infectados cronicamente pelo VHB, VHC ou ambos¹⁶. O efeito do álcool no risco para o CHC parece ser dose-dependente, níveis de ingestão > 50 a 70 g/dia estão associados a risco aumentado de desenvolver o tumor na presença de cirrose hepática¹².

A doença hepática gordurosa não alcoólica (DHGNA) passou a ser uma causa bem estabelecida de cirrose hepática, podendo evoluir para o CHC. O tumor em geral se desenvolve nas fases avançadas da doença, em que os marcadores histológicos de esteato-hepatite estão ausentes. Foi observado que a maioria dos pacientes com CHC associada à cirrose criptogênica apresentava fatores de risco para síndrome metabólica, como hipertensão arterial, diabetes melito, obesidade, entre outros¹². A cirrose hepática criptogênica corresponde a 13% dos casos de CHC. A obesidade é um fator de risco independente para o desenvolvimento de CHC, aumentando o risco em 1,5 a 4 vezes²⁴. O diabetes melito está presente em 20 a 30% dos pacientes com cirrose hepática. Também representa fator de risco independente para o desenvolvimento do CHC e aumenta o risco para este tumor em pacientes portadores de outras hepatopatias crônicas, como VHC, VHB e álcool²⁵. No HCFMUSP, entre 394 pacientes com CHC diagnosticados durante um período de 8 anos, sete foram identificados com CHC na presença de DHGNA confirmada por biópsia. A cirrose estava presente em 6 de 7 pacientes, mas foi identificado 1 paciente com CHC bem diferenciado no contexto de DHGNA sem cirrose (fibrose estágio 1)²⁶. Algumas evidências sugerem que patogênese molecular, quadro clínico e prognóstico dos pacientes com CHC relacionados à DHGNA podem ser diferentes dos pacientes com CHC induzidos por vírus²⁷. Estudo recente observou que, na maioria dos casos de CHC associados à DHGNA, o tratamento é aplicável de acordo com as recomendações internacionais²⁸.

A aflatoxina B1 (AFB1) é um carcinógeno químico relacionado à hepatocarcinogênese. Estima-se que a exposição à aflatoxina aumente o risco de CHC em 4 vezes. Quando associada ao VHB, estes dois fatores aumentam o risco de CHC em 60 vezes¹¹. Os eventos moleculares

associados ao CHC estão relacionados a alterações genéticas e mutações (como a mutação no gene p53) desencadeadas pela exposição à toxina. Uma elevada prevalência da mutação 249^{Ser} TP53 foi encontrada em 28% das amostras de CHC no Brasil²⁹.

Os pacientes portadores de hemocromatose hereditária apresentam um risco 20 vezes maior do que a população geral para desenvolvimento do CHC. A hemocromatose hereditária relacionada à mutação do gene HFE está mais associada ao CHC³⁰. Outras doenças que evoluem para cirrose, como a cirrose biliar primária, deficiência de alfa-1 antitripsina, hepatite autoimune e síndrome de Budd-Chiari também devem ser consideradas como fatores de risco para CHC após a instalação da cirrose hepática³¹.

1.2 Rastreamento e diagnóstico do CHC

Em pacientes com cirrose hepática estabelecida, é recomendado o rastreamento do CHC. O objetivo é detectar precocemente o tumor, para que tratamentos potencialmente curativos possam ser empregados com objetivo de reduzir mortalidade. A decisão sobre realizar rastreamento depende do risco do paciente em desenvolver CHC e a chance de receber tratamento se o tumor for diagnosticado. Não há dúvida sobre a indicação do rastreamento em pacientes com cirrose estabelecida e pacientes com infecção crônica pelo VHB sem cirrose.

O rastreamento deve ser feito com ultrassonografia de abdome a cada 6 meses³². Esse intervalo foi baseado no tempo de duplicação tumoral. O marcador sorológico mais utilizado é a alfa-fetoproteína (AFP) sérica. Infelizmente, a sensibilidade desse exame é baixa, em torno de 60%³³. Estudos recentes sugerem benefício na prática clínica se a AFP for avaliada de forma dinâmica e sempre associada à ultrassonografia (US) de abdome³⁴.

O programa de rastreamento dos pacientes com cirrose hepática está bem estabelecido no HCFMUSP. Em 2014, os resultados de 10 anos desse programa foram publicados e a incidência anual de CHC em pacientes cirróticos foi de 3,5%. Nos últimos anos, entretanto, foi observado um aumento progressivo desses índices. Cerca de 79% dos pacientes foram detectados com tumor em estágio precoce, dentro dos critérios de Milão, e puderam receber tratamento potencialmente curativo¹⁸.

Caso o paciente seja cirrótico e um nódulo hepático for detectado, o diagnóstico de CHC precisa ser descartado. Em nódulos menores que 1 cm, o diagnóstico de CHC é infrequente e é quase impossível fazer um diagnóstico preciso com as técnicas disponíveis (a biopsia pode errar o alvo e o padrão vascular, geralmente, não está presente nesta fase). Quando o nódulo excede 1 cm, o diagnóstico pode ser estabelecido por biopsia ou por exame de imagem no contexto de cirrose hepática. O diagnóstico radiológico de CHC se baseia na demonstração da hipervascularização do nódulo na fase arterial, e no clareamento nas fases portal e de equilíbrio³². Esses achados estão relacionados à alteração no suprimento sanguíneo que se torna predominantemente arterial durante os passos da hepatocarcinogênese³⁵. O valor dos critérios não invasivos para diagnóstico de CHC foi confirmado prospectivamente^{36,37}. A biopsia hepática para diagnóstico do CHC é recomendada nos casos em que os métodos de imagem não conseguem estabelecer o diagnóstico (por ex.: nódulos hipovascularizados ou nódulos hipervascularizados sem *washout*). Para os pacientes sem cirrose hepática ou evidência de hepatopatia crônica, a biopsia hepática é recomendada para diagnóstico do CHC³² (Figura 1).

Figura 1 - Fluxograma para diagnóstico do carcinoma hepatocelular³².

1.3 Estadiamento e prognóstico do CHC

A avaliação prognóstica é uma etapa muito importante no tratamento do paciente com qualquer tipo de câncer. No paciente com CHC, ela se torna ainda mais desafiadora. Vários fatores influenciam no prognóstico do paciente com CHC e qualquer tentativa de estratificar o risco de óbito deve considerar a função hepática, o grau de comprometimento tumoral e o estado geral do paciente. Atualmente, há vários sistemas de estadiamento propostos para os pacientes com CHC. A seguir, comentaremos sobre alguns deles.

1.3.1 TNM

A classificação TNM (*Tumor-Node-Metastasis*) utilizada para definir prognóstico e o tratamento em outras neoplasias malignas apresenta limitações nos pacientes com CHC³⁸. Uma das principais limitações deve-se

ao fato de ela necessitar uma avaliação cirúrgica para ser completa. Nos pacientes com CHC, apenas a minoria consegue ser submetida à ressecção ou ao transplante. Vários estudos também já demonstraram não haver correlação entre o TNM do explante e prognóstico do paciente³⁹.

1.3.2 Okuda

Na década de 80, o grupo do Prof. Kunio Okuda, da Universidade de Chiba, observou que, além do tamanho do tumor (+ ou - 50% do volume total hepático), a presença de ascite, e os níveis de bilirrubina e albumina eram importantes em predizer o prognóstico dos pacientes com CHC. Desta forma, foi criada a classificação de Okuda⁴⁰. Com a melhora nos programas de rastreamento e detecção mais precoce do CHC, a classificação de Okuda tornou-se obsoleta e, atualmente, serve somente para identificar os casos avançados.

1.3.3 CLIP (*The Cancer of the Liver Italian Program Investigators*)

No final da década de 90, um grupo italiano formulou o sistema de CLIP, que inclui variáveis tumorais e de função hepática⁴¹. De acordo com esta classificação, o paciente pode ser classificado em seis categorias. Diversos trabalhos demonstraram a superioridade da classificação de CLIP em predizer o prognóstico em relação a Okuda^{42,43}. Entretanto, uma das desvantagens encontradas é a falta de correlação entre esta classificação e a terapêutica a ser empregada.

1.3.4 BCLC (*Barcelona Clinic Liver Cancer group*)

Em 1999, o grupo de Barcelona, baseado em trabalhos do grupo e metanálises, formulou o sistema de estadiamento BCLC^{32,44}. Um trabalho realizado num grupo de pacientes americanos mostrou que o BCLC foi o melhor sistema de estadiamento entre sete testados. Entre os diferentes estágios, a sobrevida dos pacientes era diferente e os pacientes de um mesmo grupo apresentavam sobrevida semelhante⁴⁵. Uma das vantagens do BCLC é que ele orienta terapêutica de acordo com estadiamento.

Atualmente, o sistema de estadiamento BCLC estratifica os pacientes com CHC em 5 estádios (BCLC 0: muito precoce, BCLC A: precoce, BCLC B: intermediário, BCLC C: avançado e BCLC D: terminal) (Figura 2).

Pacientes no estágio BCLC 0 são aqueles com tumor único ≤ 2 cm, Child-Pugh A e assintomáticos (ECOG-PS 0). Esses pacientes apresentam uma baixa probabilidade de disseminação microscópica, portanto, as terapias radicais podem erradicar completamente o tumor.

Pacientes no estágio BCLC A são aqueles com tumor único ou até 3 nódulos ≤ 3 cm com função hepática relativamente preservada (Child-Pugh A-B) e assintomáticos (ECOG-PS 0). Esses pacientes devem ser avaliados para ressecção cirúrgica, transplante hepático ou ablação.

Pacientes no estágio BCLC B são aqueles com função hepática relativamente preservada (Child Pugh A-B) e assintomáticos (ECOG-PS 0), mas com tumor grande ou multifocal sem invasão vascular macroscópica ou metástase extra-hepática. A quimioembolização transarterial é o tratamento de escolha.

Pacientes com estágio BCLC C são aqueles com metástase extra-hepática, invasão vascular macroscópica e/ou sintomas constitucionais (ECOG-PS 1-2). O único tratamento que demonstrou impacto positivo sobre a sobrevida desses pacientes foi o sorafenibe.

Pacientes no estágio BCLC D são aqueles com função hepática ruim (Child-Pugh C) e/ou estado geral muito comprometido (ECOG-PS 3-4). Eles

devem receber somente tratamento sintomático, pois apresentam uma expectativa de vida menor que 3 meses.

No Instituto do Câncer do Estado de São Paulo (ICESP), a classificação BCLC é adotada, pois, além de estadiar o paciente, também nos orienta quanto à melhor terapêutica.

Figura 2 – Algoritmo para estadiamento e tratamento do CHC segundo as recomendações do BCLC³².

1.4 Tratamento do CHC

Não há estratégia terapêutica única para os pacientes com CHC. Desta forma, várias propostas têm sido publicadas. Ao contrário de outros tumores, poucas intervenções médicas foram extensivamente avaliadas no CHC. A quantidade de informações advindas de estudos controlados é escassa⁴⁶. Nenhum estudo randomizado controlado com mais de 1.000 pacientes, considerado a melhor fonte de evidência, foi realizado em pacientes com CHC. Há cerca de 80 estudos randomizados controlados menores avaliando

as diversas opções terapêuticas realizadas em centros de referência para o tratamento deste tumor. Portanto, o grau de evidência para qualquer intervenção no CHC deve ser analisado com ressalva⁴⁷.

1.4.1 Tratamentos cirúrgicos

Nos últimos anos, com a disseminação do programa de rastreamento para detecção precoce do CHC entre os pacientes cirróticos, houve aumento nos casos de CHC diagnosticados em estágio precoce. Atualmente, cerca de 30-40% dos pacientes com CHC se beneficiam de terapias potencialmente curativas no momento do diagnóstico nos países ocidentais. Dentre essas opções terapêuticas, há a ressecção, o transplante e as terapias ablativas percutâneas. Com essas opções, a sobrevida em 5 anos varia de 50 a 70%³².

Os tratamentos cirúrgicos são a base do tratamento do CHC. A ressecção e o transplante hepático alcançam os melhores resultados em candidatos bem selecionados (sobrevida de 60-70% em 5 anos), e são considerados a primeira opção de tratamento em pacientes com tumores precoces³².

1.4.1.1 Ressecção hepática

A ressecção hepática é o tratamento de escolha para os pacientes com CHC com função hepática preservada. Graças aos avanços no diagnóstico, nas técnicas cirúrgicas e nos cuidados perioperatórios, a ressecção hepática atualmente apresenta taxa de sobrevida que excede 50% em 5 anos com mortalidade cirúrgica variando de 0 a 6,4%, em centros especializados de cirurgia hepatobiliar^{48,49}.

O grau de comprometimento da função hepática é fator prognóstico significativo após a ressecção para CHC. Pacientes com CHC e hipertensão

portal submetidos à ressecção apresenta elevada incidência de descompensação hepática pós-operatória, com taxa de sobrevida de 5 anos de menos de 50%. Os resultados pioram em pacientes com elevação dos níveis de bilirrubina⁵⁰. No Sudeste asiático, especialmente no Japão, a reserva funcional hepática antes da cirurgia é avaliada pelo teste da indocianina verde⁴⁸. E, desta forma, as indicações cirúrgicas por CHC associadas com hipertensão portal ainda são controversas.

A principal desvantagem da ressecção hepática é a alta taxa de recidiva tumoral. A sobrevida livre de doença é em torno de 58% em 3 anos e a recidiva pode chegar a 70-100% em 5 anos^{49,51}. Essa recorrência pode ser precoce ou tardia, se antes ou depois de 2 anos da ressecção, respectivamente. Na recorrência precoce, as variáveis tumorais, como presença de nódulos satélites, invasão microvascular e número de tumores, são os principais preditores de recidiva. Já na recorrência tardia, as variáveis relacionadas à atividade necroinflamatória viral parecem ser mais importantes⁵¹.

Embora a ressecção cirúrgica seja considerada terapia curativa para os pacientes com CHC, menos de 20% dos pacientes são candidatos a este tratamento. Ela é reservada para pacientes com tumor único sem hipertensão portal e com níveis normais de bilirrubina. Se essas condições não forem preenchidas, pacientes devem ser considerados para o transplante hepático ou terapias ablativas locais³².

1.4.1.2 Transplante hepático

Com relação ao controle da doença de base (cirrose hepática), a ressecção e as terapias ablativas locais não têm efeito ou apresentam efeito negativo na função hepática remanescente. O transplante hepático pode controlar o tumor em estágio precoce e o fígado subjacente que pode conter lesões pré-cancerosas, metástáticas ou novas lesões. Portanto, a sobrevida

livre de recorrência é melhor nos pacientes submetidos ao transplante que à ressecção³².

O amplo critério de seleção aplicado duas décadas atrás levou a resultados muito ruins em termos de recorrência (32-54%) e sobrevida (sobrevida < 40% em 5 anos), mas permitiu a identificação dos melhores candidatos ao transplante. Alguns trabalhos publicados na década de 90 estabeleceram o transplante hepático como uma opção viável para tratar o CHC. Eles mostraram que, quando o transplante era restrito a pacientes com CHC precoce (definido como 1 tumor $\leq$ 5 cm ou 2-3 tumores todos < 3 cm), a sobrevida em 4 anos era de 75%, similar a de pacientes com cirrose sem CHC^{52,53}. Assim surgiu o critério de Milão, que tem sido amplamente aplicado ao redor do mundo para seleção de pacientes para o transplante com CHC⁵³. Esses resultados foram confirmados por outros grupos^{39,54}.

Estudos sobre a história natural do CHC e o risco de progressão da doença mostraram que, em pacientes com tumor único < 3 cm, há baixa probabilidade de evoluir para além do critério de Milão dentro de 1 ano, enquanto pacientes com mais de um nódulo ou tumor entre 3-5 cm apresentam taxa de progressão de 50% em 1 ano⁵⁵. Esses resultados relacionando o longo tempo de espera em lista e a taxa de progressão tumoral levaram à mudança nos critérios de alocação de órgãos no Brasil em julho de 2006, levando à implantação pelos critérios de gravidade⁵⁶. A pontuação MELD (*Model for End Stage Liver Disease*), que mostrou ser ferramenta útil em estimar mortalidade em pacientes com doença hepática crônica e cirrose, apareceu como instrumento eficaz para alocação de fígados. O MELD é baseado em três variáveis bioquímicas: bilirrubina sérica, níveis de creatinina e RNI (relação normatizada internacional). O MELD demonstrou prospectivamente pontuar de forma razoável o risco de morte de acordo com o tempo nos pacientes em lista de transplante hepático⁵⁷.

Uma das limitações com o MELD é que a maioria dos pacientes com CHC tem MELD baixo no momento do diagnóstico. Para tentar resolver este problema, os pacientes com CHC receberam arbitrariamente uma pontuação MELD, na tentativa de lhes proporcionar uma espera adequada para o

transplante. Desta forma, os pacientes com CHC em estágio T2 (1 nódulo ≥ 2 cm ou 3 lesões todas ≤ 3 cm), ao serem incluídos na lista, recebem pontuação de 20. Após 3 meses, se ainda não forem transplantados, esta pontuação sobe para 24 e, em 6 meses, para 29⁵⁶.

1.4.2 Tratamentos não cirúrgicos

Há muitos pacientes que, devido às características tumorais, reserva hepática ruim e/ou presença de comorbidades, não são candidatos aos tratamentos cirúrgicos. As modalidades não cirúrgicas do tratamento do CHC incluem terapias ablativas percutâneas, terapia transcateter guiada por imagem, radioterapia e terapia sistêmica. Essas modalidades apresentam efeito antitumoral reconhecido e aumentam a sobrevida⁵⁸.

1.4.2.1 Terapias ablativas percutâneas

As terapias ablativas percutâneas são, atualmente, opção de tratamento para pacientes com CHC precoce e muito precoce. A ablação induz à necrose tumoral por meio de injeção de substâncias químicas (por ex.: etanol, ácido acético) ou pela modificação da temperatura (radiofrequência, *laser*, micro-ondas, crioablação). Embora a ablação possa ser realizada por via laparoscópica ou cirúrgica, a maioria dos procedimentos é realizada por via percutânea⁵⁹.

A primeira técnica utilizada para ablação química do tumor foi a injeção percutânea de etanol (PEI – *percutaneous ethanol injection*). O álcool induz necrose coagulativa da lesão por desidratação celular, desnaturação proteica e oclusão química de pequenos vasos tumorais. Uma alternativa ao álcool é a injeção de ácido acético, que é utilizada por um número pequeno de centro ao redor do mundo⁵⁹.

No HCFMUSP, a sobrevida do paciente tratado com PEI foi influenciada pela função hepática e resposta inicial ao tratamento. Nos pacientes Child-Pugh A e com resposta completa, a sobrevida em 5 anos foi de 55%. Enquanto nos pacientes Child-Pugh B e ausência de resposta completa, essa taxa caiu para 9%⁶⁰.

A principal limitação da PEI é a alta taxa de recorrência local, que é em torno de 18% em lesões menores que 3 cm e pode chegar a 43% em lesões maiores que 3 cm⁶¹. Isto se deve à limitação da difusão do álcool pela presença de septos intratumorais. A PEI pode ser realizada em qualquer segmento hepático e a localização da lesão, geralmente, não é empecilho para realização do procedimento. A mortalidade relacionada ao procedimento é menor que 1% e a alteração na função hepática após a PEI é mínima⁶².

Nos últimos anos, em alguns centros, a RFA (*radiofrequency ablation*) tem substituído a PEI. Ela também é realizada na maioria dos casos por via percutânea, guiada por US ou TC. Um eletrodo é inserido no centro do tumor e o calor gerado ao redor da ponta induz área de necrose tumoral. Os eletrodos de RFA são acoplados a um gerador de RFA capaz de produzir 200 W de energia. Cada aplicação dura 8-12 minutos⁵⁹.

Tanto a PEI quanto a RFA atingem necrose completa em tumores < 2 cm. Na última atualização do BCLC, publicada após o início deste estudo, nos pacientes com CHC único < 2 cm e não candidatos ao transplante hepático, a ablação é indicada como primeira opção de tratamento⁶³. Nesse cenário, a eficácia da ablação é próxima a 100% e a sobrevida é quase idêntica à ressecção. A eficácia da PEI em comparação à RFA diminuiu em lesões maiores, e ambas não são indicadas para tumores > 5 cm. O melhor controle da doença da RFA em comparação à PEI se reflete em melhor sobrevida^{64,65}.

No ICESP, a experiência inicial com RFA em pacientes com CHC precoce mostrou que a sobrevida é fortemente influenciada pelo grau de disfunção hepática, avaliada pela classificação de Child-Pugh ou MELD. A taxa inicial de necrose tumoral completa foi de 90%. A probabilidade de

atingir resposta completa foi significativamente maior em pacientes com nódulo único ($p=0,04$)⁶⁶. Os eventos adversos são mais frequentes após RFA se comparada à PEI. A localização tumoral (subcapsular, próximo a grandes vasos ou árvore biliar, próximo ao intestino ou coração) também limita o emprego da RFA em alguns casos⁶⁷. Novas técnicas ablativas, como micro-ondas e eletroporação, surgiram como opção de tratamento para o CHC, mas seu uso é limitado a alguns centros⁶⁸.

1.4.2.2 Terapia transcateter guiada por imagem

A terapia transcateter guiada por imagem baseia-se na entrega intravascular de agentes terapêuticos por meio da cateterização seletiva do vaso nutridor da lesão guiada por imagem. Vários agentes, como quimioterápicos, partículas embolizantes ou material radioativo, podem ser injetados com objetivo de citorredução tumoral⁵⁹. A progressão do CHC está intimamente relacionada à atividade neoangiogênica. Em estágios mais precoces, o tumor não é altamente vascularizado e recebe seu fluxo sanguíneo tanto da veia porta quanto da artéria hepática. Entretanto, quando a neoplasia cresce em estágio mais avançado, o suprimento sanguíneo fica mais dependente da artéria hepática³⁵. Este perfil arterial específico permite a base do desenvolvimento da obstrução arterial como terapia efetiva. A obstrução arterial aguda resulta em necrose tumoral isquêmica com alta taxa de resposta objetiva.

A embolização arterial leva à oclusão do fluxo arterial pelo uso de agentes embolizantes dentro da luz do vaso. A obstrução da artéria hepática pode ser obtida pela injeção intra-arterial de vários agentes. A maioria dos trabalhos publicados utiliza partícula embolizante ou Gelfoam⁶⁹.

A quimioembolização transarterial (TACE – *transarterial chemoembolization*) é a técnica mais utilizada para tratamento do CHC no Brasil e mostrou melhorar a sobrevida em candidatos bem selecionados^{14,69}. A quimioembolização leva à oclusão do fluxo arterial pelo uso de agentes

embolizantes associados à administração de um agente quimioterápico. As técnicas e os agentes utilizados para tratar o CHC de maneira intra-arterial são muito heterogêneos⁷⁰. Os melhores candidatos à TACE são pacientes Child-Pugh A, assintomáticos e tumor multifocal ou grande (não candidatos à ressecção). A presença de trombose portal, mesmo segmentar, é um preditor de pior sobrevida⁷¹.

Na tentativa de aumentar a exposição das células tumorais ao quimioterápico, e promover a liberação controlada e mais lenta da medicação, novos agentes embolizantes estão sendo utilizados. Microesferas com capacidade de carregar o quimioterápico promovem menor nível sistêmico da medicação e maiores taxas de necrose tumoral⁷². Os estudos iniciais com DEB (*drug eluting beads*)-TACE mostraram redução na toxicidade hepática e melhor controle local do tumor^{73,74}. A resposta inicial ao tratamento, observada por meio da devascularização do tumor, é importante fator prognóstico⁷⁵.

Radioembolização é definida com a infusão de substâncias radioativas usando microesferas que contenham ítrio-90 (Y^{90}) ou agentes similares na artéria hepática. Atualmente, a técnica de radioembolização mais popular utiliza microesferas cobertas com Y^{90} , um isótopo que emite radiação beta. Devido à hipervascularização do CHC, as microesferas injetadas via intra-arterial atingem a área do tumor, e emitem alta energia com baixa penetração ao tumor. Os resultados apresentados até o momento parecem ser promissores para os pacientes com CHC^{76,77}. Os estudos iniciais mostram segurança e eficácia com este tipo de radioterapia, inclusive em pacientes com trombose de veia porta⁷⁸. Entretanto, a ausência de estudos randomizados controlados que comparem esse tratamento com outras modalidades de tratamento já estabelecidas dificulta a definição do seu papel na prática clínica.

1.4.2.3 Radioterapia

Recentemente, o avanço tecnológico relacionado à radioterapia têm possibilitado o tratamento de lesões focais irressecáveis com doses ablativas de radiação. Essa modalidade de radioterapia é conhecida como radioterapia estereotática corpórea (SBRT – *stereotatic body radiation therapy*)^{79,80}. Diversos grupos têm estudado o papel da SBRT no tratamento do CHC. Uma revisão sistemática de ensaios clínicos prospectivos de SBRT para o tratamento de lesões primárias ou secundárias do fígado avaliou 15 estudos com 158 pacientes com lesões primárias e 341 pacientes com metástases. O controle local em 1 ano variou de 50-100%, com sobrevida de 33-100%⁸¹. Um estudo-piloto sobre segurança e eficácia da radioterapia em pacientes que apresentam tumor viável após TACE está sendo conduzido no ICESP⁸².

1.4.2.4 Tratamentos sistêmicos

A quimioterapia sistêmica convencional e o tratamento hormonal não mostraram benefícios em termos de sobrevida nos pacientes com CHC. Um estudo randomizado controlado que comparou tamoxifeno *versus* tratamento conservador não demonstrou efeito antitumoral ou melhora na sobrevida⁸³. A quimioterapia sistêmica foi testada em vários estudos randomizados controlados. A doxorrubicina e a cisplatina foram as drogas que apresentaram melhores resultados *in vitro*. A doxorrubicina sistêmica foi avaliada em mais de 1.000 pacientes dentro de ensaios clínicos e resposta parcial foi atingida em cerca de 10% dos casos, sem nenhuma evidência de benefício em termos de sobrevida⁸⁴. O esquema PIAF (cisplatina/interferon/doxorrubicina/fluoracil) foi comparado à doxorrubicina e a sobrevida foi menor que 8 meses, sem diferença entre os grupos. O grupo que recebeu PIAF teve elevada taxa de mielotoxicidade, com mortalidade relacionada ao tratamento de 9%, casos de reativação do VHB e

insuficiência hepática⁸⁵. Portanto, a quimioterapia sistêmica é desaconselhada para o tratamento de pacientes com CHC⁴⁶.

O aumento do conhecimento sobre a patogênese molecular do CHC, assim como a introdução de terapias-alvo moleculares na oncologia trouxeram novas perspectivas para o tratamento deste tumor. A maioria dos tratamentos tem como objetivo interferir nas vias moleculares relacionadas à proliferação e sobrevivência celular, e no bloqueio de fatores de crescimento e sinalização relacionados à disseminação da doença (angiogênese, ativação de telomerase, etc.)⁸⁶.

Até o momento, a única terapia molecular que se mostrou eficaz em aumentar a sobrevivência dos pacientes com CHC avançado foi o tansilato de sorafenibe⁸⁷. Esta molécula é um inibidor de multiquinase, que se administra por via oral e atua bloqueando diferentes vias de sinalização associadas à hepatocarcinogênese, em especial, a via Raf/MEK/ERK, por meio da inibição da Raf quinase e diferentes tirosinas quinases. As principais ações são inibir a angiogênese e a proliferação celular⁸⁸.

A partir dos resultados positivos de ensaios pré-clínicos e estudos clínicos fase II, um estudo multicêntrico randomizado controlado duplo-cego avaliou sorafenibe na dose de 400 mg duas vezes ao dia *versus* placebo em pacientes com CHC avançado e função hepática preservada⁸⁷. Foram selecionados 602 pacientes, incluindo pacientes do HCFMUSP. No grupo sorafenibe, foram incluídos 299 pacientes e 303 no grupo placebo, e a medicação foi administrada até progressão radiológica e sintomática ou surgimento de eventos adversos graves. Na segunda análise interina, o estudo foi interrompido devido ao aumento significativo da sobrevivência no grupo sorafenibe. A sobrevivência mediana foi de 10,7 meses no grupo sorafenibe e de 7,9 meses no grupo placebo (RR 0,69 - IC 95% 0,55-0,87, $p < 0,001$). Os efeitos adversos mais frequentes foram diarreia, perda de peso, e síndrome mão e pé. Na maioria dos casos, os sintomas foram leves e de fácil manejo, de modo que o tratamento pode ser continuado em 90% dos casos. Esses resultados se reproduziram em ensaio clínico com desenho semelhante realizado na Ásia, onde os pacientes apresentavam, na maioria,

cirrose hepática pelo VHB e CHC em fase mais avançada⁸⁹. O sorafenibe foi avaliado em pacientes com função hepática compensada (Child-Pugh A) e há poucos dados sobre benefício em termos de sobrevida em pacientes Child-Pugh B. Entretanto, o perfil farmacocinético não foi significativamente modificado e não foi relatado um aumento significativo dos eventos adversos⁹⁰.

O sorafenibe demonstrou que as terapias moleculares podem ser úteis no tratamento do CHC e abre caminho para avaliar o bloqueio de múltiplas vias de sinalização da mesma forma que se vem fazendo com outras neoplasias⁸⁶.

1.5 Justificativa

Os algoritmos têm importante papel em guiar e padronizar o manejo de determinada doença. O sistema de estadiamento do BCLC, introduzido em 1998 e atualizado em 2012, é endossado pelas principais sociedades médicas ocidentais^{32,91}. Ele é considerado um sistema de estadiamento completo e acurado, pois avalia características do tumor, função hepática e estado geral do paciente, além de orientar o tratamento. Entretanto, a aplicação clínica deste sistema de estadiamento é desafiadora devido à variabilidade no perfil dos pacientes, e acessibilidade a certos tratamentos, como o transplante hepático.

O manejo dos pacientes com CHC é complexo e a decisão sobre o tratamento envolve a participação de vários especialistas, como hepatologistas, cirurgiões, radiologistas, oncologistas e patologistas. Os pacientes com CHC atendidos no ICESP têm à disposição todos as terapias recomendadas pelo BCLC. A análise da sobrevida desses pacientes é fundamental para verificar se as escolhas estão sendo feitas de forma correta, se a sobrevida está de acordo com a esperada e onde o manejo dos pacientes pode ser melhorado para obter melhor uso das ferramentas disponíveis.

2 OBJETIVOS

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2 OBJETIVOS

Este estudo teve como **objetivo principal** analisar a sobrevida dos pacientes com CHC e avaliar a porcentagem de aderência às recomendações do BCLC no geral e em cada estágio.

O **objetivo secundário** deste trabalho foi analisar o impacto sobre a sobrevida de acordo com a aderência às recomendações do BCLC no geral e em cada estágio.

3 CASUÍSTICA E MÉTODOS

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3 CASUÍSTICA E MÉTODOS

3.1 Aspectos éticos

Este estudo foi regido pelos princípios básicos do código de Ética Médica, sendo, portanto, a confidencialidade dos exames um dos aspectos que foram rigorosamente respeitados. A documentação obtida foi utilizada exclusivamente para fins de obtenção das informações concernentes à pesquisa, e foi arquivada junto ao prontuário médico do paciente. Este estudo foi aprovado como Protocolo de Pesquisa nº 382/12 pelo Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo, em novembro de 2012.

3.2 Desenho do estudo

Este foi um estudo de coorte retrospectivo e prospectivo, que avaliou, por meio dos prontuários médicos, a sobrevida dos pacientes com CHC atendidos no ICESP.

3.3 Casuística

Os pacientes estudados eram acompanhados nos ambulatórios de Gastroenterologia e Hepatologia Clínica do ICESP, Divisão de Gastroenterologia e Hepatologia Clínica do Hospital das Clínicas, e do Departamento de Gastroenterologia da FMUSP. Foram incluídos no estudo, os pacientes com diagnóstico recente de CHC, entre o período de maio de 2010 a maio de 2012. Os dados foram coletados retrospectivamente do prontuário médico após inclusão do paciente no estudo.

O diagnóstico de CHC foi baseado nos critérios diagnósticos da Associação Europeia para Estudos do Fígado (*European Association for the Study of the Liver – EASL*) e da Associação Americana para Estudo do Fígado (*American Association for the Study of Liver Diseases – AASLD*)^{32,91}. Em todos os pacientes, foram realizadas tomografia computadorizada (TC) ou ressonância magnética (RM) de abdômen no momento do diagnóstico. Exames de imagem adicionais e/ou biopsia do nódulo hepático foram realizadas em pacientes que não apresentavam o padrão de vascularização típico para CHC (Figura 1).

3.3.1 Critérios de inclusão

- 1) Pacientes com diagnóstico recente de CHC e que não havia tratado o tumor previamente.

3.3.2 Critérios de exclusão

- 1) Pacientes com dados incompletos, como dados clínicos, laboratoriais, tumorais ou relacionados ao tratamento;
- 2) Pacientes com diagnóstico de CHC não confirmado;
- 3) Pacientes com carcinoma hepatocelular da variante fibrolamelar.

3.4 Obtenção de dados

3.4.1 Obtenção de dados clínicos

Os dados clínicos foram obtidos retrospectivamente por revisão de prontuários, realizada por um único pesquisador. Os dados obtidos referem-se ao momento do diagnóstico do tumor. Os seguintes dados foram obtidos:

idade, sexo, presença de cirrose hepática e ECOG-PS (*Eastern Cooperative Oncology Group – Performance Status*)⁹². A função hepática foi avaliada de acordo com o escore de Child-Pugh⁹³ e MELD. A presença de hipertensão porta foi considerada na presença de varizes de esôfago à endoscopia digestiva alta ou associação de esplenomegalia com nível de plaquetas < 100.000/mm³. O tratamento inicial do CHC assim como a inclusão do paciente em lista de transplante, e se este procedimento foi ou não realizado, foram extraídos do prontuário.

3.4.2 Obtenção de dados laboratoriais

Foram obtidas as seguintes variáveis laboratoriais: sorologia para hepatite C, sorologia para hepatite B, nível sérico de bilirrubinas total e frações, albumina sérica, creatinina, contagem de plaquetas, RNI e dosagem sérica de alfa fetoproteína (AFP) sérica.

De acordo com os dados obtidos no prontuário médico dos pacientes e dos exames laboratoriais, os pacientes foram classificados da seguinte forma de acordo com a etiologia da cirrose hepática: (1) hepatite C, confirmada na presença de anti-VHC positivo e RNA do VHC positivo por PCR; (2) hepatite B, confirmada presença de AgHBs positivo; (3) álcool, história de ingestão de mais de 60 g/dia de etanol para mulheres e 80 g/dia para os homens, por mais de 10 anos; (4) doença hepática gordurosa não alcoólica, confirmada por histologia hepática ou suspeita radiológica de doença gordurosa, na presença de síndrome metabólica, como obesidade e diabetes melito tipo 2; e (5) outras causas: os pacientes com nenhum dos fatores acima.

3.4.3 Obtenção de dados de imagem

Os exames radiológicos, realizados para diagnóstico do CHC, foram obtidos do arquivo de imagens do Departamento de Radiologia do ICESP. Após confirmação do diagnóstico de CHC, as seguintes variáveis foram obtidas: diâmetro do maior nódulo (em milímetros), número de nódulos, presença de invasão vascular macroscópica e presença de metástase extra-hepática. Para análise, foram consideradas as características da maior lesão. O tamanho do tumor foi definido como o maior diâmetro do nódulo medido à TC ou RM. A presença de invasão vascular foi definida como presença de trombose venosa em continuidade com o tumor. A pesquisa de disseminação extra-hepática do tumor foi realizada por meio de tomografia de tórax e cintilografia óssea.

3.5 Aderência à classificação de BCLC

Para determinar o estadiamento do paciente de acordo com as recomendações da BCLC, as seguintes variáveis foram avaliadas: número e tamanho do tumor, presença de invasão vascular ou metástase extra-hepática, função hepática e ECOG-PS. Após essa avaliação inicial, os pacientes foram estratificados em 5 estádios (0, A, B, C e D)³². O tratamento proposto de acordo com as recomendações do BCLC era, inicialmente, considerado pela equipe da Hepatologia. Os casos que envolviam o desvio das recomendações eram discutidos em reunião multidisciplinar composta por hepatologistas, cirurgiões, radiologistas, oncologistas e patologistas. A razão da escolha de determinado tratamento era anotada em prontuário e a decisão final era discutida com cada paciente. O tratamento do CHC era realizado somente após consentimento do paciente e/ou responsáveis.

De acordo com o tratamento realizado, os pacientes foram classificados em aderentes ou não às recomendações do BCLC. Foram classificados como aderentes os pacientes que efetivamente realizaram o

tratamento proposto pelo BCLC, independente do tempo entre a indicação e o tratamento. Para os pacientes em lista de transplante hepático, os pacientes que realizaram tratamento-ponte e, posteriormente, realizaram o transplante hepático foram considerados como aderentes. Para os pacientes em lista de transplante hepático que realizaram o tratamento-ponte, mas que ainda não haviam sido transplantados até o final do seguimento, esses foram considerados como não aderentes. Também foram considerados como não aderentes os pacientes que estavam em lista de transplante hepático e foram excluídos por progressão tumoral ou evoluíram a óbito por descompensação da cirrose hepática.

3.6 Análise da sobrevida

O objetivo do estudo foi a análise da sobrevida do paciente com CHC atendidos no ICESP. Para o cálculo da sobrevida, considerou-se como tempo zero o momento do diagnóstico do CHC; e, como evento, o óbito de causa hepática (progressão do CHC e/ou descompensação da cirrose hepática). Ao final do estudo, foram censurados os pacientes que continuavam vivos, os pacientes que abandonaram o seguimento e os óbitos de causa não hepática. O seguimento dos pacientes encerrou em 31 de maio de 2014.

A confirmação do óbito foi obtida por meio dos registros em prontuário dos pacientes ou por contato telefônico com familiares. Os pacientes que continuavam vivos até o final do seguimento mantinham seguimento ambulatorial no serviço. Foi considerado abandono de seguimento os pacientes com que não se conseguiu contato após o diagnóstico ou tratamento do CHC.

3.7 Análise estatística

As variáveis contínuas foram expressas em média $\pm$ desvio padrão, enquanto as variáveis qualitativas como frequência (porcentagem). Os pacientes classificados como BCLC 0 e A foram agrupados para fins de análise estatística.

Para as variáveis contínuas, foi aplicada a maximização da estatística Log-Rank proposta por Lausen *et al.* para identificar o ponto de corte que melhor diferenciava a sobrevida entre os grupos⁹⁴. No caso da AFP, o ponto de corte identificado foi de 107 ng/ml. Entretanto, o valor de 100 ng/ml também apresentava capacidade de diferenciar os grupos em termos de sobrevida e foi utilizado. O ponto de corte identificado para o valor de MELD foi de 11 pontos. E, para o tamanho da maior lesão, foi de 50 mm.

As curvas de sobrevida dos pacientes incluídos foram expressas em gráficos por meio do método de Kaplan-Meier e comparadas pela regressão de Cox. Para cada variável pré-tratamento, a sobrevida mediana com seu respectivo intervalo de confiança de 95% foi reportada. A regressão de Cox simples por estratos foi utilizada para avaliar o impacto na sobrevida da aplicação do BCLC.

Em uma segunda etapa, a análise de regressão múltipla foi realizada considerando as variáveis com valores de p menor do que 0,10 na análise simples e as variáveis mais informativas acerca da sobrevida foram identificadas pelo método *backward* de seleção de variáveis.

O nível de significância estabelecido para a análise foi de 0,05. O programa utilizado para todos os cálculos foi o pacote estatístico R, versão 3.1.1⁹⁵.

4 RESULTADOS

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4 RESULTADOS

4.1 Casuística

No período do estudo, foram avaliados 509 pacientes com suspeita de CHC. Após aplicação dos critérios de inclusão e exclusão, foram elegíveis para análise final do estudo 364 pacientes. Foram excluídos deste estudo 126 pacientes que tinham diagnóstico confirmado de CHC, mas cujo diagnóstico foi anterior a maio de 2010. Três pacientes foram excluídos por apresentar CHC do tipo fibrolamelar. Dois pacientes foram excluídos por falta de dados relacionados ao tumor no momento do diagnóstico. Quatorze pacientes foram excluídos pois o diagnóstico de CHC não pode ser confirmado (Figura 3).

Figura 3 – Fluxograma de pacientes incluídos no estudo.

4.2 Características demográficas

As características clínicas e laboratoriais estão resumidas na Tabela 1. Quase todos os pacientes (344/364; 95%) eram cirróticos, sendo que a infecção crônica pelo VHC era a causa mais frequente (202/344; 59%). A maioria (244/364; 67%) dos pacientes era assintomática (ECOG 0). Duzentos e sessenta e seis (62%) pacientes eram Child-Pugh A e o escore MELD mediano era de 11. A maioria dos pacientes (207/364; 57%) tinha nódulo único e o diâmetro médio do maior nódulo era de 40 mm. Invasão vascular e metástase extra-hepática foram encontradas em 41/364 (11%) e 30/364 (8%) dos pacientes, respectivamente. De acordo com a classificação de BCLC, 130 (36%), 85 (23%), 115 (32%) e 34 (9%) pacientes foram classificados em estágio 0/A, B, C e D, respectivamente.

Tabela 1 – Características clínicas e demográficas de acordo com classificação de BCLC, *n* (%)

Característica	Estádio 0-A (<i>n</i> = 130)	Estádio B (<i>n</i> = 85)	Estádio C (<i>n</i> = 115)	Estádio D (<i>n</i> = 34)
Idade, anos	60 ± 11	61 ± 12	62 ± 12	67 ± 12
Sexo, masculino	95 (73)	61 (72)	87 (76)	25 (74)
Etiologia da cirrose				
VHC	82 (63)	42 (49)	62 (54)	16 (47)
VHB	19 (15)	10 (12)	15 (13)	3 (8)
Álcool	20 (16)	10 (12)	22 (19)	5 (15)
DHGNA	8 (6)	10 (12)	9 (8)	5 (15)
Outra	1 (0)	13 (15)	7 (6)	5 (15)
Hipertensão portal	102 (78)	63 (74)	89 (77)	28 (82)
Child-Pugh				
A	103 (79)	64 (75)	56 (49)	3 (9)
B	27 (21)	21 (25)	59 (51)	13 (38)
C	0	0	0	18 (53)
MELD	10 ± 3	9 ± 3	11 ± 4	13 ± 4

continua

Característica	conclusão			
	Estádio 0-A (n = 130)	Estádio B (n = 85)	Estádio C (n = 115)	Estádio D (n = 34)
ECOG-PS				
0	130 (100)	85 (100)	27 (23)	2 (6)
1	0	0	71 (62)	5 (15)
2	0	0	17 (15)	10 (29)
> 2	0	0	0	17 (50)
Número de nódulos				
1	99 (76)	29 (34)	59 (51)	20 (59)
2	17 (13)	27 (32)	21 (18)	6 (18)
> 2	14 (11)	29 (34)	35 (41)	8 (23)
Diâmetro do maior nódulo, mm	27 ± 8	58 ± 24	76 ± 50	75 ± 40
Invasão vascular	0	0	37 (32)	4 (12)
Metástase extra-hepática	0	0	26 (23)	4 (12)

ECOG-PS: *Eastern Cooperative Oncology Group Performance Status*; VHB: Vírus da hepatite B; CHC: Carcinoma hepatocelular; VHC: Vírus da hepatite C; MELD: *Model for End-stage Liver Disease*; DHGNA: Doença hepática gordurosa não alcoólica.

4.3 Classificação e aderência ao BCLC

Um total de 189/364 (52%) pacientes foram elegíveis e receberam o tratamento recomendado pelo BCLC. Entretanto, a porcentagem de aderência variou entre os estádios (Figura 1). As maiores porcentagens de aderência ocorreram em pacientes do estágio B e D, enquanto as menores taxas ocorreram nos pacientes dos estádios 0/A e C.

Figura 4 – Aderência às recomendações do BCLC (*Barcelona Clinic Liver Cancer*) em cada estágio.

4.4 Tratamento do CHC e razões de não aderência

4.4.1 BCLC 0/A

Vinte e três pacientes foram elegíveis para ressecção. Neste grupo, somente um paciente foi classificado como BCLC 0. Foram tratados com ressecção 35% (8/23) dos pacientes. A localização do tumor e presença de comorbidade contraindicou o procedimento em 12 e 3 pacientes, respectivamente. Estes foram tratados com RFA ou PEI ($n = 7$) e TACE ($n = 8$).

Oitenta e três pacientes neste grupo foram considerados para transplante hepático com doador cadáver. Entretanto, somente 36 pacientes (43%) foram transplantados até o final do seguimento. Desses pacientes, 33/36 receberam tratamento-ponte com TACE ($n = 16$) ou RFA/PEI ($n = 17$)

durante os 15 meses de tempo de espera em lista. O transplante não foi realizado nos outros pacientes devido à recusa do paciente ($n = 5$), comorbidades, como outras neoplasias, abuso de drogas, HIV ou doença cardíaca ou pulmonar ($n = 11$), óbito em lista ($n = 14$), preferência pela ressecção ($n = 4$) ou outros motivos ($n = 4$). No final do estudo, 9 pacientes ainda estavam em lista de transplante hepático.

Terapias ablativas percutâneas, como PEI e RFA, foram recomendadas como tratamento de primeira linha para 24 pacientes classificados como BCLC 0 e A. Desses, 13 (54%) pacientes receberam RFA ou PEI. Em 9 (37%) pacientes, a localização do tumor foi motivo da contraindicação, e foram tratados com TACE, e, em 2 pacientes, o tratamento não foi realizado pela presença de comorbidades.

4.4.2 BCLC B

A TACE foi o tratamento recomendado para 85 pacientes classificados como BCLC B e 66/85 pacientes (78%) seguiram as recomendações. Cinco pacientes com nódulo único, mas maior que 5 cm, função hepática preservada e sem sinais clínicos de hipertensão portal foram tratados com ressecção. Um paciente recebeu transplante hepático intervivos, dois pacientes foram tratados com RFA e dez receberam tratamento de suporte devido a comorbidades e/ou à progressão de doença.

4.4.3 BCLC C

Somente 41/115 (36%) dos pacientes do estágio BCLC C receberam o tratamento recomendado pelo BCLC, que é o sorafenibe. Em 44 pacientes sem invasão vascular ou metástase extra-hepática, que foram classificados como BCLC C em decorrência do estado geral comprometido (ECOG 1-2), receberam tratamento de acordo com tamanho e número de lesões:

transplante hepático (n = 2), ressecção (n = 5), RFA/PEI (n = 9) e TACE (n = 28). Trinta pacientes não foram candidatos a nenhum tratamento convencional ou experimental devido às características do tumor e da falência hepática, e receberam tratamento de suporte exclusivo.

4.4.4 BCLC D

Entre os pacientes BCLC D (n = 34), vinte e três (68%) aderiram ao BCLC e receberam tratamento de suporte. A não aderência foi reservada para paciente que preenchiam os critérios de Milão (n = 11) e estavam em lista de transplante hepático. Durante o tempo em lista, TACE superseletiva e RFA foram realizadas em 7 e 2 pacientes, respectivamente. Entretanto, no final do seguimento, somente 2 pacientes receberam o transplante hepático.

4.5 Seguimento

O tempo médio de seguimento dos pacientes após o diagnóstico do CHC foi de 19 meses (IC 95%, 0,5-52 meses) para todo o grupo. Durante o seguimento, ocorreram 217 óbitos. Entre os óbitos, 6/217 (3%) faleceram de causa não relacionada à insuficiência hepática ou à progressão do CHC. A maioria dos pacientes faleceu em decorrência da progressão tumoral (n = 150/217, 69%), seguido por insuficiência hepática (sem evidências de progressão tumoral) (n = 42/217, 19%) e por complicações relacionadas ao tratamento oncológico (n=19/217, 9%).

4.6 Sobrevida

A sobrevida foi de 63%, 45% e 33% em 12, 24 e 36 meses, respectivamente (Figura 5). A classificação de BCLC conseguiu diferenciar

os pacientes de acordo com o estágio (Figura 6). A análise univariada identificou como fatores prognósticos idade, classificação de Child-Pugh, escore MELD, nível sérico de AFP, ECOG-PS, tamanho do tumor, número de nódulos, presença de invasão vascular, metástase extra-hepática e classificação de BCLC (todos com $p < 0,05$) (Tabela 2). Na análise multivariada, idade > 66 anos, Child-Pugh B/C, MELD > 11 , ECOG-PS > 0 , nível AFP > 100 ng/ml, tamanho do tumor > 50 mm, invasão vascular e metástase extra-hepática permaneceram como fatores independentes de mau prognóstico.

Tabela 2 - Análise univariada e multivariada de fatores prognósticos de sobrevida

Variável	Univariada		Multivariada	
	HR (IC 95%)	<i>p</i> valor	HR (IC 95%)	<i>p</i> valor
Sexo	1.04 (0.77–1.40)	0.80	-	-
Idade (≤ 66 vs > 66 anos)	1.36 (1.03–1.79)	0.02	1.71 (1.28–2.28)	0.01
Cirrose (sim vs não)	1.48 (0.76–2.88)	0.25	-	-
Child-Pugh (B/C vs A)	2.91 (2.20–3.86)	< 0.01	2.19 (1.52–3.17)	< 0.01
MELD (≤ 11 vs > 11)	1.84 (1.39–2.42)	< 0.01	1.07 (1.03–1.12)	< 0.01
Hipert. portal (sim vs não)	1.26 (0.90–1.77)	0.17	-	-
ECOG-PS (0 vs ≥ 1)	3.03 (2.30–3.88)	< 0.01	1.54 (1.10–2.15)	0.01
AFP (≤ 100 vs > 100 ng/mL)	2.74 (2.09–3.60)	< 0.01	2.84 (2.13–3.8)	< 0.01
Tamanho tumor (≤ 50 vs > 50 mm)	2.85 (2.18–3.74)	< 0.01	2.07 (1.52–2.82)	< 0.01
Núm. de nódulos (1 vs ≥ 2)	1.61 (1.23–2.11)	< 0.01	-	-
Invasão vascular (sim vs não)	2.85 (1.98–4.11)	< 0.01	1.67 (1.09–2.47)	0.01
Metástase extra-hepática (sim vs não)	4.47 (2.95–6.76)	< 0.01	2.52 (1.54–4.12)	< 0.01
BCLC (B vs 0/A)	2.58 (1.71–3.88)	< 0.01	-	-
BCLC (C vs 0/A)	5.14 (3.53–7.49)	< 0.01	-	-
BCLC (D vs 0/A)	7.51 (4.64–12.16)	< 0.01	-	-

AFP: Alfa-fetoproteína; BCLC: *Barcelona Clinic Liver Cancer*; IC: Intervalo de confiança; ECOG-PS: *Eastern Cooperative Oncology Group Performance Status*; HR: *Hazard ratio*; MELD: *Model for End-stage Liver Disease*.

4.6.1 Sobrevida e aderência às recomendações do BCLC

De uma maneira geral, não houve diferença na sobrevida global de acordo com a aderência às recomendações do BCLC. As taxas de sobrevida em 1, 2 e 3 anos foram de 63, 52 e 30%, respectivamente, para o grupo aderente, e de 62, 38 e 30%, respectivamente, para o grupo não aderente (Figura 4). Entretanto, diferenças significantes foram encontradas entre os vários estádios do BCLC (Figura 7). No estágio BCLC 0 e A, pacientes que aderiram às recomendações do BCLC apresentaram melhor sobrevida comparado ao grupo não aderente (RR = 0,19, IC 95%: 0,09-0,42; $p < 0,001$). Por outro lado, as taxas de sobrevida foram menores entre os pacientes aderentes do estágio BCLC D (RR = 4,0, IC 95%: 1,67-9,8; $p < 0,001$). A aderência às recomendações do BCLC não influenciou a sobrevida global dos pacientes com CHC dos estádios B e C (Figuras 8 a 11).

Figura 5 – Curva de sobrevida global dos pacientes com CHC.

Figura 6 – Curva de sobrevida dos pacientes com CHC de acordo com a classificação BCLC.

Figura 7 – Curva de sobrevida dos pacientes com CHC de acordo com a aderência ou não ao BCLC em todos os estádios.

Figura 8 – Curva de sobrevida dos pacientes com CHC de acordo com a aderência ou não ao BCLC no estágio 0/A.

Figura 9 – Curva de sobrevida dos pacientes com CHC de acordo com a aderência ou não ao BCLC no estágio B.

Figura 10 – Curva de sobrevida dos pacientes com CHC de acordo com a aderência ou não ao BCLC no estágio C.

Figura 11 – Curva de sobrevida dos pacientes com CHC de acordo com a aderência ou não ao BCLC no estágio D.

5 DISCUSSÃO

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5 DISCUSSÃO

Este é o primeiro estudo que avalia a aderência às recomendações do BCLC para o tratamento do CHC e o impacto sobre a sobrevida num centro de referência para o tratamento do CHC no Brasil. Os achados demonstraram que a aderência às recomendações do BCLC varia entre os diversos estádios do BCLC e afeta de maneira diferenciada a sobrevida do paciente.

A porcentagem de aderência ao tratamento recomendado pelo BCLC para o paciente com CHC encontrada neste estudo foi baixa (52%), considerando que o centro estudado dispunha de todas as modalidades de tratamento propostas. Um estudo coreano prévio encontrou que, de 160 pacientes com CHC, somente 40% foram tratados de acordo com as recomendações do BCLC⁹⁶. De forma semelhante, um estudo multicêntrico italiano com 536 pacientes diagnosticados entre 2008 e 2011 observou que a aderência também não era uniforme, e 40% dos pacientes do estágio A não receberam tratamento potencialmente curativo⁹⁷.

Neste estudo, pacientes do estágio 0/A, candidatos a terapias curativas, a aderência às recomendações do BCLC esteve associada com melhor sobrevida. Entretanto, somente 45% dos pacientes receberam o tratamento prescrito. Nos pacientes com indicação de transplante hepático com doador cadáver, o longo tempo de espera limitou o acesso a esse tratamento. Em São Paulo, esse tempo é em torno de um ano para pacientes com CHC, mesmo após a adoção da política de prioridade pelo MELD em 2006, em que pacientes com CHC recebem 29 pontos após 6 meses em lista. Apesar de o Brasil ser o segundo país do mundo em número de transplantes, a falta de órgãos continua sendo um importante problema. Embora a taxa de doação tenha dobrado na última década e o número de doadores cadáver estar em torno de 8,4 por milhão por pessoa (pmp) no Brasil, essa taxa é ainda menor que na Europa (15 pmp) e nos Estados

Unidos (26 pmp)⁹⁸. Como sempre haverá uma procura maior que a oferta por órgãos, novas estratégias para aumentar a chance de transplante devem ser discutidas e estudadas, particularmente para os pacientes com CHC precoce e cirrose hepática descompensada.

O aumento no número de doadores, uso de terapias locais para controle do tumor e políticas de prioridade para os pacientes com CHC são algumas das tentativas para melhorar a taxa de sobrevida dos pacientes com CHC e indicação de transplante hepático. O longo tempo em lista e a consequente retirada de lista por progressão tumoral força a maioria dos centros a realizar o tratamento do CHC com outras opções durante a espera pelo transplante hepático. Na análise por intenção de tratamento, se o tempo de espera é de 2 meses, a sobrevida em 2 anos é de 84% no grupo transplantado, mas, se for mais de 5 meses, cai para 54%, mesmo nos pacientes dentro dos critérios de Milão⁵⁵. As modalidades de tratamento-ponte utilizadas são a injeção percutânea de etanol, quimioembolização e ablação por radiofrequência. Não há dados robustos de estudos randomizados controlados comparando essas terapias. Potenciais benefícios alegados a uma das determinadas terapias derivam de estudos observacionais e análises de custo-benefício⁹⁹.

A escassez de doadores para o transplante hepático pode ser melhorada pelo desenvolvimento dos programas de transplante intervivos e campanhas de saúde pública sobre doação de órgãos. O transplante intervivos é prática comum em alguns centros e atinge resultados semelhantes àqueles do transplante com doador cadáver. As dificuldades técnicas têm sido superadas na última década com a maior experiência dos centros. O doador vivo permite uma fonte sem limites de enxertos de boa qualidade para cirurgias planejadas assim que o diagnóstico do CHC é realizado. A incerteza do tempo de espera pode ser reduzida e a possibilidade da progressão tumoral eliminada¹⁰⁰. Entretanto, há problemas não resolvidos no transplante intervivos em pacientes com CHC. Questiona-se, por exemplo, se a ausência do tempo de espera é realmente um ponto positivo, pois, durante o período de espera, os pacientes com progressão

tumoral são retirados e selecionados de acordo com a biologia do tumor. Portanto, esse processo é negado aos pacientes no transplante intervivos. Desta forma, um vício de seleção para tumores com comportamento agressivo por causa do curto tempo de espera pode ocorrer. Apesar da crescente implantação deste procedimento, uma análise dos resultados ainda está incompleta, especialmente nos adultos¹⁰¹.

Uma outra situação que limita a aderência às recomendações do BCLC é no caso de pacientes com CHC < 2 cm e indicação de transplante hepático. Mesmo nos casos com diagnóstico confirmado por histologia, mais de um tumor e/ou cirrose descompensada, o paciente com CHC < 2 cm não ganha situação especial, de acordo com as regras do órgão que regulamenta o transplante hepático no Brasil. A sobrevida dos pacientes com CHC < 2 cm está associado a melhor sobrevida, pois a chance de tratamento curativo nesses casos é maior¹⁰².

A ressecção do CHC poderia ser utilizada como ferramenta para selecionar os pacientes que mais se beneficiariam com o transplante por meio do estudo da biologia tumoral. Entretanto, os pacientes com CHC submetidos à ressecção não ganham situação especial em lista de transplante hepático, mesmo que sejam identificados marcadores associados à alta taxa de recidiva, como invasão microvascular, nódulos satélites e grau de indiferenciação celular¹⁰³. O estudo do CHC ressecado permitiria que o transplante fosse postergado num paciente com CHC com bom comportamento biológico ou poderia ser realizado como terapia de resgate num paciente com CHC com comportamento biológico agressivo e alta chance de recidiva.

No cenário de longo tempo de espera em lista de transplante hepático (> 9 meses), a ressecção é indicada para pacientes com CHC único e função hepática preservada. Neste mesmo cenário, os resultados em longo prazo podem ser comparáveis ao transplante hepático na análise por intenção de tratamento. Os melhores resultados são obtidos em pacientes Child-Pugh A, sem sinais de hipertensão portal e bilirrubina normal. Nesses pacientes, a sobrevida em 5 anos é em torno de 70%¹⁰⁴. Neste estudo,

somente 6% (n = 23) dos pacientes com CHC eram candidatos à ressecção como primeira linha de tratamento. A localização do tumor foi a principal contraindicação ao procedimento.

A ressecção hepática tornou-se um procedimento seguro nos últimos anos com taxas de mortalidade menores que 5%, em centros especializados^{105,106}. Entre os avanços relacionados à ressecção hepática no paciente hepatopata crônica nos últimos anos, pode-se citar a ressecção laparoscópica do CHC. Essa abordagem permite menor tempo de hospitalização, menor necessidade de hemotransfusão e menor morbidade pós-operatória. Num estudo recente realizado no HCFMUSP, em 35% (n = 30/85) dos pacientes submetidos à ressecção do CHC, a abordagem foi por via laparoscópica. Ressecção anatômica foi possível em 2/3 dos casos e a conversão para cirurgia aberta foi necessária em 4 pacientes. A taxa de sobrevida e a sobrevida livre de doença em 3 anos foi de 76 e 58%, respectivamente⁴⁹.

Um dos principais problemas relacionados à ressecção é a alta taxa de recidiva pós-operatória. A recorrência após ressecção ocorre em até 80% dos pacientes em cinco anos⁵¹. Várias estratégias foram avaliadas na tentativa de evitar a recidiva, como quimioembolização, quimioterapia, radiação interna, imunoterapia, retinoides, interferon e sorafenibe¹⁰⁷. Uma recente revisão sistemática mostrou que não há evidência robusta que justifique nenhuma terapia adjuvante ou neoadjuvante neste cenário¹⁰⁸. Desta forma, nenhuma destas estratégias é recomendada na prática clínica.

Apenas 10-15% dos pacientes com CHC são candidatos à ressecção cirúrgica ou ao transplante hepático no momento do diagnóstico³². Para tentar preencher esta lacuna, terapias locorregionais surgiram como opção de tratamento para o paciente com CHC. Essas terapias apresentam efeito antitumoral reconhecido e aumentam a sobrevida⁵⁸. Neste estudo, dos 130 pacientes classificados como BCLC 0/A, as terapias ablativas percutâneas (PEI e RFA) foram indicadas em 24 pacientes (18%). A localização do tumor contraindicou o procedimento em 9 pacientes. Essa porcentagem é maior à relatada por outros autores⁵⁹. Algumas técnicas para aumentar a

aplicabilidade da radiofrequência em pacientes com CHC localizados próximo a vísceras, domo hepático e vesícula biliar são descritas e utilizadas pelo grupo¹⁰⁹. Mesmo assim, o risco de lesão em tumores localizados próximo à via biliar impediu a aplicação deste tratamento na maioria dos casos.

No ICESP, a RFA é primeira opção de tratamento para os pacientes com CHC não candidatos à cirurgia, especialmente naqueles com até 3 tumores ≤ 3 cm de diâmetro cada. A PEI é primeira indicação de tratamento para os pacientes com CHC único menor que 2 cm, sem indicação de ressecção. Uma metanálise de estudos randomizados controlados mostrou superioridade da RFA em relação à PEI no controle da doença e na sobrevida global; entretanto, esse benefício não foi observado para pacientes com tumor único menor que 2 cm¹¹⁰. Considerando os custos elevados da RFA em relação à PEI e a falta de evidência de que a RFA seja superior à PEI como tratamento-ponte para os pacientes em lista de transplante hepático, a PEI não deve ser abandonada como opção de tratamento, principalmente em países como o Brasil.

A experiência com RFA no ICESP iniciou em 2010 e em paciente Child-Pugh A e B, a sobrevida em 1 ano é de 96% e 37%, respectivamente⁶⁶. Esses dados mostram que, apesar da segurança e eficácia relacionadas às terapias minimamente invasivas, ele não deve ser considerado um tratamento curativo nos pacientes com função hepática comprometida (Child-Pugh B), pois a sobrevida é comprometida mesmo nos casos em que se obtém resposta completa. Nesses casos, a indicação do transplante hepático deve ser prioridade e a RFA deve ser opção de tratamento-ponte.

A maior porcentagem de aderência foi observada no estágio BCLC B. Os pacientes do estágio intermediário são definidos como aqueles que apresentam doença multifocal extensa restrita ao fígado, sem invasão vascular com função hepática preservada e sem sintomas relacionados ao câncer. Para esses pacientes, a TACE é considerada o tratamento de referência³². Há várias explicações possíveis para maior taxa de aderência

neste grupo. A definição atual de estágio intermediário é muito ampla, e inclui pacientes com tamanho e número de nódulos variados e diversos graus de comprometimento da função hepática, o que diminui as contraindicações ao tratamento. Devido a esta heterogeneidade, uma subclassificação deste estágio foi proposta, que sugere tratamento de suporte exclusivo para pacientes BCLC B e Child-Pugh B8 ou B9, e sorafenibe para pacientes com CHC multifocal grande em ambos os lobos¹¹¹. Na prática, TACE é, geralmente, prescrita para todos os pacientes deste grupo devido à possibilidade de diminuição do número e tamanho dos nódulos (*downstaging*), e subsequente inclusão do paciente em lista de transplante. Entretanto, nossos resultados indicam que a aderência ao BCLC não influencia a sobrevida, o que vai contra o resultado de dois estudos prévios que observaram melhor sobrevida em pacientes deste estágio que foram tratados com ressecção. Em um desses estudos, uma baixa taxa de aderência (10%) em pacientes BCLC B estava associada a acesso limitado à TACE.

Uma importante lacuna que precisa ser preenchida no manejo do paciente com CHC refere-se ao seguimento após tratamento inicial. O método RECIST (*Response Evaluation Criteria In Solid Tumors*) baseado na diminuição do tumor e muito utilizado em oncologia para avaliar resposta tumoral à quimioterapia convencional é questionado para avaliação de tratamento locorregional, particularmente a quimioembolização, que causa devascularização do tumor e necrose sem correlacionar com a redução do tamanho do tumor¹¹². Uma versão modificada do critério de RECIST, denominada mRECIST (RECIST modificada), que leva em consideração alterações no grau da vascularização tumoral, apresenta maior aplicabilidade prática, principalmente no controle dos tratamentos locorregionais¹¹³.

A presença de resposta completa na avaliação inicial após os tratamentos locorregionais está associada com melhores taxas de sobrevida e deve ser considerada alvo terapêutico^{75,114}. Na avaliação inicial dos pacientes submetidos à quimioembolização com partículas carregadas com

quimioterápico, a presença de resposta completa esteve associada com sobrevida de 100% no primeiro ano⁷⁵.

O sorafenibe é o tratamento de escolha para pacientes Child-Pugh A ou B com invasão vascular, metástase extra-hepática e/ou estado geral comprometido (ECOG-PS 1-2)³². Este é o tratamento recomendado para estágio C, o grupo em que foi observada menor porcentagem de aderência às recomendações do BCLC. Neste estudo, pacientes sem invasão vascular ou metástase extra-hepática, mas com estado geral comprometido (ECOG-PS 1-2), receberam tratamento de acordo com tamanho e número de lesões. Por exemplo, 27 pacientes dentro dos critérios de Milão e ECOG 1 foram incluídos em lista de transplante hepático e receberam tratamento-ponte. Isso justifica a grande porcentagem de não aderência neste grupo e também a alta taxa de pacientes classificados como CHC em estágio avançado nesta casuística. Não foi observada diferença na sobrevida quando comparados pacientes aderentes a não aderentes. Entretanto, quando os pacientes não aderentes foram subdivididos em 2 grupos, sem tratamento oncológico e com tratamento oncológico (TACE, RFA, ressecção e transplante), a sobrevida é melhor no último grupo, mas sem significância estatística (dados não apresentados).

A indicação de tratamento com melhores chances de sobrevida, mesmo num paciente com estado geral comprometido, é prática comum entre outros grupos e na prática clínica. O sistema de estadiamento do grupo de Hong Kong sugere um tratamento mais agressivo para os pacientes com tumor mais avançado, como quimioembolização hepática para pacientes com invasão de ramo portal esquerdo ou direito, mas boa reserva hepática. No restante dos pacientes que não aderiram ao BCLC, o motivo de não aderência foi a presença de comorbidades. No ICESP, o sorafenibe é administrado somente para pacientes Child-Pugh A. Houve alguns pacientes que não receberam sorafenibe, pois eram classificados com Child-Pugh B.

Deve-se ressaltar que a não aderência às recomendações do BCLC esteve associado com melhor sobrevida em pacientes do estágio terminal (BCLC D). Embora a presença de cirrose avançada (Child-Pugh C) dificulte

a aplicação de terapias potencialmente curativas, pacientes em lista de transplante hepático devem ser rastreados para CHC com objetivo de detectar tumores que excedem as indicações de transplante, e auxiliar na definição de prioridades para o transplante. Nos pacientes BCLC D, a não aderência estava limitada àqueles pacientes que poderiam se beneficiar do transplante hepático. Esses pacientes receberam TACE devido ao longo tempo de espera em lista e o risco de progressão tumoral. Neste estudo, nove pacientes foram tratados, mas somente dois realizaram o transplante hepático. Na atualização de 2014 do BCLC, há uma recomendação de inclusão em lista de transplante hepático para os pacientes Child-Pugh C e dentro dos critérios de Milão⁶³.

Uma limitação deste estudo é a inclusão de pacientes encaminhados somente para um hospital terciário, e, portanto, os achados não podem ser generalizados para outros centros. O estudo tinha um desenho retrospectivo e pode estar sujeito a vícios de seleção dos pacientes. Por exemplo, pacientes com um perfil pior não aderiram às recomendações do BCLC, portanto, possivelmente, apresentando um pior prognóstico. O desenho retrospectivo do estudo também não permite comparação entre os tratamentos, mesmo para pacientes do mesmo estágio.

O sistema de estadiamento BCLC é reconhecido como ferramenta prognóstica e um método para alocação de tratamento. Entretanto, na prática clínica, a disponibilidade deve ser considerada para seleção individual do tratamento, que deve ser realizado por uma equipe multidisciplinar. As estratégias de tratamento devem focar em melhorar o manejo dos pacientes com CHC, particularmente naqueles com estágio precoce em que a aderência ao BCLC está associada com melhor sobrevida. Além disso, esforços futuros devem ser feitos para definir terapias de segunda e terceira linha para pacientes com CHC de acordo com a resposta ao tratamento de primeira linha dentro de cada estágio.

6 CONCLUSÕES

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1. A porcentagem de aderência às recomendações do BCLC é baixa, mesmo num centro terciário de referência para tratamento do CHC com todas as modalidades de tratamento disponíveis;
2. A porcentagem de não aderência às recomendações do BCLC varia de acordo com estágio da doença;
3. Entre os pacientes classificados como BCLC 0/A, a aderência ao BCLC apresentou impacto positivo sobre a sobrevida dos pacientes com CHC;
4. Os pacientes classificados como BCLC B apresentaram maior porcentagem de aderência e a não aderência neste grupo não esteve associada com melhor sobrevida;
5. Os pacientes classificados como BCLC C apresentaram maior taxa de não aderência, e a não aderência não esteve associada com melhor sobrevida;
6. A possibilidade de não aderência no grupo BCLC D apresentou impacto positivo sobre a sobrevida dos pacientes.

7 REFERÊNCIAS

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APÊNDICES

APÊNDICES

Apêndice A – Variáveis analisadas dos 364 pacientes incluídos no estudo

N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
1	M	59	S	OH	1	26	0	S	B	18	4,3	N	N	A	Tx	S	RFA	S	vivo	715
2	M	67	S	VHC	4	19	0	S	A	7	34,3	N	N	B	TACE	N	RFA	N	óbito	473
3	M	41	N	VHB	1	19	0	N	A	7	66,6	N	N	0	Rx	N	TACE	N	vivo	403
4	M	58	S	VHC	3	20	0	S	B	13	4,3	N	N	A	Tx	N	TACE	N	vivo	259
5	M	59	S	OH	1	50	1	S	B	9	6,6	N	N	C	SOR	N	RFA	S	vivo	660
6	M	67	S	VHC	10	115	1	S	A	7	239,9	N	S	C	SOR	N	Nen	N	óbito	126
7	M	60	S	VHC	1	26	0	S	A	8	76,3	N	N	A	Tx	N	RFA	N	vivo	427
8	M	64	S	VHC	3	17	0	S	A	12	178,8	N	N	A	Tx	N	RFA	N	óbito	144
9	M	54	S	VHC	3	25	1	S	B	15	58,2	N	N	C	SOR	N	Tx	S	óbito	623
10	M	77	S	OH	1	22	0	S	B	15	5,8	N	N	A	RFA	S	RFA	N	vivo	233
11	M	63	S	VHC	1	21	1	N	A	6	16	N	N	C	SOR	N	Rx	N	vivo	880
12	M	82	S	OH	1	40	0	N	A	6	5,3	N	N	A	Rx	N	RFA	N	vivo	1044
13	M	68	S	OH	3	15	0	S	A	11	4,9	N	N	A	Tx	N	TACE	N	vivo	452
14	M	70	S	VHC	1	25	0	S	A	7	5,3	N	N	A	Tx	N	RFA	N	vivo	528
15	F	74	S	VHC	1	30	0	S	B	14	179	N	N	A	RFA	N	TACE	N	vivo	230
16	F	74	S	VHC	1	21	0	S	A	7	92,6	N	N	A	RFA	S	PEI	N	vivo	599
17	M	84	S	Outra	2	40	1	S	A	8	12	N	N	C	SOR	N	TACE	N	óbito	505
18	M	56	S	VHC	2	80	1	N	A	8	129	N	S	C	SOR	S	SOR	N	vivo	277
19	F	76	S	VHC	1	30	3	S	B	12	120	N	N	D	Nen	S	Nen	N	óbito	342
20	M	69	S	Outra	4	65	0	S	B	13	3,6	N	N	B	TACE	S	TACE	N	óbito	416
21	M	73	S	VHC	1	110	1	S	B	12	6718	S	N	C	SOR	N	Qt	N	óbito	104
22	M	56	S	VHC	2	20	1	S	B	14	4,5	N	N	C	SOR	N	RFA	S	vivo	569
23	M	50	S	VHC	1	29	0	S	A	10	50,4	N	N	A	Tx	N	RFA	N	vivo	1054
24	M	71	S	VHC	2	20	0	S	A	8	307	N	N	A	Tx	N	RFA	N	vivo	659
25	M	59	S	VHC	2	28	0	S	B	15	3,1	N	N	A	Tx	N	RFA	N	óbito	373
26	M	71	N	NASH	1	62	0	N	A	7	3,8	N	N	B	TACE	N	Rx	N	vivo	921
27	M	62	S	VHC	3	36	0	S	B	13	1132	N	N	B	TACE	S	TACE	N	óbito	271
28	M	66	S	OH	4	27	1	S	A	11	7	N	N	C	SOR	N	TACE	N	óbito	453
29	M	63	S	VHC	1	44	0	S	B	11	124,6	N	N	A	Tx	N	RFA	N	óbito	76
30	M	87	S	VHC	10	110	0	S	A	15	60500	S	N	C	SOR	N	Nen	N	óbito	219
31	M	57	S	VHB	4	32	0	S	A	8	8,6	N	N	B	TACE	S	TACE	N	vivo	439
32	M	66	S	VHC	3	43	0	S	B	11	267,1	N	N	C	SOR	S	SOR	N	óbito	352

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N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
33	M	67	S	VHC	2	37	0	S	A	7	288	N	N	B	TACE	S	TACE	N	vivo	260
34	M	72	S	OH	2	34	0	S	A	11	4,9	N	N	B	TACE	N	PEI	N	óbito	453
35	M	60	S	VHC	1	27	0	S	A	12	44,9	N	N	A	Tx	N	TACE	N	vivo	313
36	M	66	S	VHC	2	44	0	S	A	11	12701	N	N	B	TACE	N	RFA	N	vivo	654
37	M	73	S	OH	6	45	1	S	B	12	7,9	N	N	C	SOR	N	TACE	N	vivo	699
38	M	59	S	VHC	1	55	1	S	B	14	7,2	N	N	C	SOR	N	TACE	N	óbito	294
39	M	66	S	OH	1	20	0	S	A	13	11088	N	N	A	Tx	N	TACE	N	óbito	863
40	F	69	S	NASH	3	29	0	S	A	9	11,4	N	N	A	Tx	N	TACE	N	óbito	786
41	F	73	S	VHC	1	9	1	N	A	7	3	N	N	C	SOR	N	RFA	N	óbito	256
42	F	57	S	VHC	5	14	0	S	A	12	25,2	N	N	B	TACE	S	TACE	S	vivo	498
43	F	68	S	VHC	6	24	0	N	A	9	168,4	N	N	B	TACE	S	TACE	S	óbito	491
44	M	60	S	NASH	1	26	1	S	B	16	2,4	N	N	C	SOR	N	Tx	S	óbito	251
45	M	53	S	Outra	5	55	0	S	B	19	228,5	N	N	B	TACE	N	Nen	N	óbito	270
46	M	51	S	VHC	1	15	0	S	A	14	5,9	N	N	0	RFA	N	Nen	N	óbito	284
47	M	58	S	VHC	6	100	2	S	B	12	19788	N	N	C	SOR	S	SOR	N	óbito	103
48	M	51	S	VHC	2	28	0	S	C	16	2,3	N	N	D	Nen	N	TACE	S	vivo	1034
49	M	53	S	VHC	4	30	0	S	A	8	6916	N	N	B	TACE	S	TACE	N	vivo	500
50	M	68	S	OH	1	20	0	S	A	7	74	N	N	A	RFA	S	TACE	N	vivo	733
51	M	67	S	VHC	10	160	2	S	B	15	570,7	N	N	C	SOR	N	Nen	N	óbito	84
52	M	55	S	NASH	1	22	0	S	A	11	25,2	N	N	A	Tx	S	TACE	S	vivo	603
53	M	55	S	VHC	1	25	1	S	B	10	14084	S	N	C	SOR	Sim	SOR	N	vivo	637
54	M	56	S	VHC	1	33	2	S	C	13	49,8	N	N	D	Nen	S	Transplante	S	vivo	528
55	F	59	S	VHC	2	25	0	S	A	6	288,5	N	N	A	Tx	N	TACE	N	óbito	696
56	F	61	S	VHC	2	22	0	S	A	7	2717	N	N	A	Tx	S	RFA	S	vivo	981
57	M	56	S	VHC	1	55	1	S	A	10	16,5	S	N	C	SOR	N	Rx	N	óbito	1077
58	F	69	N	NASH	1	90	0	N	A	7	826,9	N	N	B	TACE	N	Rx	N	vivo	1372
59	M	60	S	VHC	1	20	0	S	A	7	3,6	N	N	A	Tx	S	PEI	S	vivo	1043
60	M	55	S	VHC	3	110	1	S	A	11	10,3	N	S	C	SOR	S	SOR	N	óbito	203
61	F	65	S	VHC	1	55	0	S	A	6	14,1	N	N	B	TACE	S	TACE	N	óbito	706
62	M	53	S	VHB	1	110	0	S	A	9	60500	S	N	C	SOR	Sim	SOR	N	óbito	146
63	F	81	S	VHC	1	33	3	S	C	22	2732	N	N	D	Nen	S	Nen	N	óbito	185
64	M	72	S	OH	5	78	1	S	B	10	8,5	N	N	C	SOR	N	TACE	N	óbito	546
65	M	46	S	VHC	3	21	1	S	B	11	674,6	N	N	C	SOR	N	TACE	N	óbito	608
66	M	71	S	NASH	1	150	3	S	B	8	189,9	N	N	D	Nen	S	Nen	N	óbito	85
67	M	29	N	VHB	1	100	1	N	B	14	60500	N	S	C	SOR	S	SOR	N	óbito	31
68	M	51	S	NASH	2	55	1	S	C	14	187,8	N	N	D	Nen	N	TACE	S	óbito	181
69	M	74	S	OH	3	30	0	S	B	13	165,5	S	N	C	SOR	N	Nen	N	vivo	196
70	M	65	S	NASH	2	52	0	S	A	7	4,8	N	N	B	TACE	S	TACE	N	vivo	1031

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N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
71	M	71	S	Outra	1	74	0	S	B	16	5,1	N	N	B	TACE	N	Sorafenibe	N	óbito	428
72	M	62	S	OH	1	35	1	S	A	10	119,7	N	N	C	SOR	N	TACE	N	óbito	232
73	M	56	S	VHC	1	23	0	S	A	8	22,6	N	N	A	Tx	N	Sorafenibe	N	vivo	720
74	M	59	S	VHB	1	95	1	S	B	8	60500	N	N	C	SOR	N	TACE	N	óbito	96
75	M	76	S	NASH	1	50	0	S	A	10	8	N	N	A	RFA	N	TACE	N	óbito	618
76	M	63	S	VHC	10	80	2	S	C	16	109,8	N	S	D	Nen	S	Nen	N	óbito	55
77	M	38	S	VHB	1	110	1	N	A	13	60500	S	N	C	SOR	N	Nen	N	óbito	40
78	M	50	S	VHC	3	42	0	S	B	14	37,3	N	N	B	TACE	S	TACE	N	óbito	403
79	M	69	S	OH	1	48	0	S	A	10	908,9	N	S	C	SOR	N	Qt	NA	óbito	408
80	M	51	S	VHC	1	33	0	S	B	13	57,3	N	N	A	Tx	S	RFA	S	óbito	956
81	F	53	S	VHC	2	52	0	S	A	7	100,5	N	N	B	TACE	S	TACE	N	óbito	657
82	M	60	S	VHC	1	31	0	S	B	11	3	N	N	A	Tx	N	RFA	N	óbito	440
83	M	52	S	Outra	1	72	0	S	A	10	2563	N	N	B	TACE	S	TACE	N	óbito	1101
84	M	54	S	VHC	1	28	0	S	B	19	4,7	N	N	A	Tx	N	PEI	N	óbito	771
85	F	65	S	VHC	1	37	0	S	B	13	38,8	N	N	A	RFA	N	TACE	N	vivo	1232
86	F	67	S	VHC	1	40	0	S	A	9	2,7	S	N	C	SOR	Sim	SOR	N	óbito	756
87	M	55	S	VHC	1	218	0	N	B	13	1,3	N	N	C	SOR	N	Qt	NA	óbito	304
88	F	21	S	Outra	1	56	0	S	A	9	1,8	N	N	B	TACE	N	Transplante	S	vivo	1329
89	F	72	S	Outra	10	110	2	N	B	22	3,9	N	S	C	SOR	N	Nen	NA	óbito	52
90	F	63	S	VHC	1	27	1	S	B	16	16,5	N	N	C	SOR	N	TACE	N	óbito	604
91	M	62	S	VHC	1	26	0	N	A	8	4,5	N	N	A	Rx	N	RFA	NA	vivo	1139
92	M	46	S	VHB	1	65	0	S	A	9	1,2	N	N	B	TACE	S	TACE	NA	vivo	1294
93	M	55	S	VHC	3	40	0	S	A	7	72	N	N	B	TACE	S	TACE	N	óbito	313
94	F	53	N	Outra	1	170	3	N	B	6	125,2	N	N	D	Nen	S	Nen	NA	óbito	69
95	M	64	S	VHC	1	35	0	S	A	12	11,6	N	N	A	Tx	S	TACE	S	vivo	616
96	M	53	S	VHC	10	190	2	S	B	8	4206	N	N	C	SOR	N	Nen	NA	óbito	82
97	M	69	S	NASH	1	30	1	S	B	23	8091	S	N	C	SOR	N	Nen	NA	óbito	77
98	M	58	S	VHC	1	22	0	S	A	14	4,6	N	N	A	Tx	S	Transplante	S	vivo	883
99	M	33	N	Outra	2	90	0	N	A	6	1,3	N	N	B	TACE	N	Rx	NA	vivo	1228
100	M	53	S	VHB	1	23	0	N	A	7	447,2	N	N	A	Rx	N	TACE	N	vivo	658
101	M	64	S	OH	7	21	1	S	B	13	48,9	N	N	C	SOR	N	TACE	S	óbito	277
102	M	88	N	Outra	1	140	0	N	A	9	172,3	N	N	B	TACE	N	Nen	NA	vivo	1424
103	M	60	S	VHC	2	23	0	S	A	15	186,4	N	N	A	Tx	S	TACE	S	vivo	1078
104	M	64	S	OH	1	45	0	S	A	9	5,2	N	N	A	RFA	N	TACE	NA	vivo	588
105	M	56	S	VHC	1	23	0	S	A	11	2757	N	N	A	Tx	S	PEI	S	vivo	1262
106	F	72	S	VHC	1	30	0	N	A	13	42,8	N	N	A	RFA	S	RFA	NA	óbito	879
107	M	70	S	NASH	1	22	1	S	B	16	2,8	N	N	C	SOR	N	PEI	N	óbito	502

continua

continuação

N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
108	M	63	S	Outra	6	48	0	S	A	7	103	N	N	B	TACE	S	TACE	N	outra causa	473
109	F	73	S	NASH	2	19	0	S	A	10	12,6	N	N	A	RFA	S	RFA	N	vivo	602
110	F	73	S	VHC	2	18	0	S	A	9	439,6	N	N	A	RFA	S	RFA	N	óbito	343
111	M	42	S	VHB	1	48	0	N	A	6	2,6	N	N	A	Rx	S	Rx	N	vivo	1314
112	F	70	S	VHC	3	40	0	S	A	8	730,5	N	N	B	TACE	S	TACE	N	óbito	824
113	F	66	S	NASH	1	74	2	S	B	13	1170	N	N	C	SOR	N	Qt	N	óbito	112
114	M	66	S	VHC	3	200	3	S	B	9	1167	N	S	D	Nen	N	TACE	N	óbito	310
115	M	60	S	VHC	2	28	0	S	A	18	22,5	N	N	A	RFA	S	PEI	N	óbito	992
116	F	79	S	Outra	1	20	1	S	C	18	30	N	N	D	Nen	N	PEI	N	óbito	752
117	F	53	S	VHB	2	55	1	S	A	8	262,5	S	N	C	SOR	Sim	SOR	N	óbito	93
118	F	41	S	NASH	1	65	0	S	A	9	11001	N	N	B	TACE	N	Nen	N	óbito	64
119	F	78	S	VHC	2	22	0	S	A	7	340,8	N	N	A	RFA	N	TACE	N	vivo	1147
120	M	63	S	VHC	1	25	0	N	A	7	70,6	N	N	A	Rx	S	Rx	N	vivo	829
121	M	38	S	Outra	1	106	1	S	B	16	1962	S	N	C	SOR	N	TACE	N	óbito	391
122	M	59	S	VHC	1	25	0	N	A	7	37,1	N	N	A	Rx	S	Rx	N	vivo	1006
123	M	60	S	VHC	3	16	0	S	A	10	176,8	N	N	A	Tx	N	Rx	N	vivo	1290
124	M	79	S	Outra	2	40	0	S	A	8	138,2	N	N	B	TACE	S	TACE	N	óbito	774
125	F	72	S	VHC	1	47	0	S	A	10	1698	N	N	A	RFA	N	TACE	N	óbito	476
126	F	55	S	VHC	2	45	0	S	A	8	2208	N	N	B	TACE	S	TACE	N	óbito	1016
127	F	76	S	VHC	2	40	0	S	A	9	17,2	N	N	B	TACE	S	TACE	N	óbito	751
128	M	59	S	VHB	1	42	0	S	C	11	3188	N	N	D	Nen	N	TACE	N	óbito	316
129	F	48	S	VHC	2	35	1	S	C	16	2,9	N	N	D	Nen	N	TACE	S	vivo	844
130	M	65	S	VHC	3	26	0	S	B	13	6,4	N	N	A	Tx	S	TACE	S	vivo	1024
131	M	69	S	VHC	1	26	0	S	A	10	18	N	N	A	Tx	N	Rx	N	óbito	528
132	M	69	S	Outra	1	80	0	N	A	20	258,6	N	N	B	TACE	N	Nen	N	óbito	602
133	M	49	S	VHB	1	37	0	S	B	12	2189	N	N	A	Tx	N	TACE	N	óbito	148
134	M	71	S	VHC	1	28	0	N	A	8	621	N	N	A	Rx	N	RFA	NA	vivo	1121
135	M	72	S	NASH	1	16	2	S	C	19		N	N	D	Nen	S	Nen	NA	óbito	91
136	M	69	S	OH	1	42	1	S	B	9	2,7	N	N	C	SOR	N	TACE	N	óbito	466
137	M	65	S	VHB	3	41	1	S	B	16	7,9	N	N	C	SOR	N	TACE	N	óbito	381
138	M	54	N	VHC	1	100	0	N	B	10	3	N	S	C	SOR	S	SOR	NA	óbito	183
139	M	53	S	VHB	1	37	0	S	A	11	446	N	N	A	Tx	S	TACE	S	vivo	1456
140	M	71	S	OH	5	25	0	N	A	10	5671	N	N	B	TACE	S	TACE	NA	óbito	249
141	F	46	S	VHC	3	23	0	S	A	10	9,4	N	N	A	Tx	S	PEI	S	óbito	153
142	M	58	S	NASH	1	85	1	S	C	16	27988	N	N	D	Nen	N	TACE	NA	óbito	132
143	M	47	S	VHB	1	47	0	S	B	14	16,4	N	N	A	Tx	N	TACE	NA	óbito	316
144	M	66	S	OH	1	25	0	S	A	8	1,6	N	N	A	Tx	S	PEI	S	vivo	1069

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continuação

N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
145	M	62	S	VHB	4	50	0	S	B	9	920,2	N	N	B	TACE	S	TACE	NA	óbito	291
146	M	77	S	VHB	1	70	3	S	B	11	6277	N	N	D	Nen	S	Nen	NA	óbito	144
147	M	60	S	VHC	1	66	0	S	A	9	104,2	N	N	B	TACE	S	TACE	NA	vivo	1068
148	M	67	S	OH	1	100	0	S	B	12	22,8	S	N	C	SOR	Sim	SOR	NA	vivo	221
149	M	66	S	VHC	1	20	0	N	A	10		N	N	A	Rx	N	TACE	S	óbito	712
150	M	62	S	VHC	2	37	0	N	A	10	2407	N	N	B	TACE	S	TACE	N	óbito	308
151	M	65	S	OH	1	30	0	S	A	14	15,2	N	N	A	RFA	N	TACE	N	óbito	672
152	M	48	S	VHB	2	23	0	S	A	7	2,4	N	N	A	Tx	N	PEI	NA	vivo	1175
153	M	74	S	OH	2	60	0	S	B	7	2,9	N	N	B	TACE	S	TACE	NA	óbito	398
154	M	83	S	VHB	1	120	0	S	A	8	60500	N	N	B	TACE	S	TACE	NA	óbito	157
155	M	56	S	VHB	2	35	0	N	A	6	6,7	N	N	B	TACE	S	TACE	N	óbito	283
156	M	60	S	VHC	1	30	1	S	C	20	2,3	N	N	D	Nen	N	Transplante	S	óbito	439
157	M	56	S	VHC	3	37	0	N	B	13	185,8	N	N	B	TACE	S	TACE	NA	óbito	327
158	M	68	S	OH	2	16	0	S	A	9	59	N	N	A	Tx	N	RFA	NA	óbito	725
159	M	55	S	VHB	2	120	0	S	A	7	223,8	N	N	C	SOR	S	SOR	NA	óbito	209
160	M	73	S	OH	1	76	0	S	B	8	2,3	S	N	C	SOR	Sim	SOR	NA	vivo	888
161	M	71	S	OH	2	30	0	S	B	18	1,8	N	N	A	Tx	N	Nen	N	óbito	312
162	M	38	S	VHB	1	22	0	S	B	14	90,7	N	N	A	Tx	S	RFA	S	vivo	635
163	M	62	S	VHB	3	30	0	S	B	17	223,5	N	N	A	Tx	N	Nen	N	óbito	141
164	M	53	S	VHC	3	23	0	S	B	11	16	N	N	A	Tx	S	TACE	S	óbito	1177
165	M	49	S	OH	1	60	0	S	B	13	217,5	N	N	B	TACE	S	TACE	NA	óbito	506
166	M	63	S	VHC	1	27	0	S	B	12	187	N	N	A	Tx	S	TACE	S	óbito	572
167	M	72	S	VHC	1	175	4	N	B	11	216,5	N	N	D	Nen	S	Nen	NA	óbito	64
168	M	52	S	VHB	3	24	0	N	A	8	3,3	N	N	A	Tx	S	RFA	S	vivo	980
169	M	51	S	VHC	10	110	0	S	B	8	66,8	N	S	C	SOR	N	Nen	NA	óbito	199
170	M	53	S	VHC	1	30	0	N	A	7	168,5	N	N	A	Rx	N	TACE	S	vivo	1030
171	M	80	S	OH	1	26	1	S	B	11	2,4	N	N	C	SOR	N	RFA	NA	óbito	580
172	M	80	S	OH	1	22	2	S	C	24	6	N	N	D	Nen	N	RFA	NA	óbito	400
173	M	67	S	OH	2	150	1	N	A	7	>60500	S	Sim	C	SOR	Sim	SOR	NA	óbito	107
174	M	62	S	OH	2	24	1	S	A	6	2,2	N	N	C	SOR	S	SOR	NA	óbito	787
175	M	28	N	Outra	1	74	0	S	B	15	1,1	N	N	B	TACE	S	TACE	S	vivo	1127
176	M	53	S	OH	5	22	0	S	B	15	16	N	N	B	TACE	S	TACE	N	óbito	471
177	M	71	N	VHC	1	54	0	N	A	6	6,5	N	N	B	TACE	S	TACE	NA	óbito	925
178	M	59	S	VHC	5	32	3	S	B	11	512	N	N	D	Nen	S	Nen	NA	óbito	201
179	F	63	S	VHC	2	55	1	S	A	6	3371	N	N	C	SOR	N	TACE	NA	óbito	339
180	F	64	S	VHC	1	77	0	N	A	7	11,7	N	N	B	TACE	S	TACE	NA	vivo	815
181	F	67	S	VHC	2	50	0	S	A	13	5,1	N	N	B	TACE	S	TACE	NA	óbito	201

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N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
182	F	65	S	VHC	3	60	0	N	A	9	2049	N	N	C	SOR	S	SOR	NA	óbito	391
183	M	55	S	VHC	1	110	1	S	A	8	54672	S	Sim	C	SOR	Sim	SOR	NA	óbito	277
184	M	57	S	OH	1	23	0	S	B	13	9,8	N	N	A	Tx	S	TACE	S	vivo	1238
185	M	59	S	VHB	10	184	2	S	B	14	72,8	N	S	C	SOR	N	Nen	NA	óbito	84
186	M	51	S	VHC	1	30	0	N	A	8	5,9	N	N	A	Rx	S	Rx	NA	vivo	1073
187	F	72	S	NASH	1	140	0	S	A	6	12,7	N	N	B	TACE	N	Rx	NA	vivo	1244
188	F	63	S	NASH	2	100	1	N	A	9	261,9	N	N	C	SOR	N	TACE	NA	óbito	299
189	M	52	S	VHB	4	70	0	S	A	10	33,4	N	N	B	TACE	S	TACE	S	vivo	771
190	M	69	S	OH	1	40	0	S	A	8	5918	N	N	A	RFA	N	TACE	NA	vivo	1043
191	M	59	N	VHC	1	17	0	S	A	8	9,5	N	N	O	Tx	N	RFA	NA	outra causa	433
192	M	65	S	NASH	3	23	2	S	C	18	36,5	N	N	D	Nen	S	Nen	N	óbito	157
193	M	51	S	VHC	2	14	0	S	A	11	6,1	N	N	A	Tx	N	PEI	NA	óbito	598
194	M	72	S	VHB	1	45	0	S	A	9	9,8	N	N	A	Tx	S	TACE	S	vivo	833
195	F	65	S	VHC	1	96	0	S	B	14	6801	S	N	C	SOR	N	Qt	NA	óbito	211
196	F	64	S	VHC	1	26	0	S	A	7	2,5	N	N	A	Tx	N	Rx	NA	óbito	958
197	F	79	S	VHC	1	102	2	S	C	15	104,4	N	N	D	Nen	S	Nen	NA	óbito	70
198	F	69	S	Outra	1	53	1	S	A	8	48,6	S	N	C	SOR	Sim	SOR	NA	óbito	182
199	F	84	S	VHC	2	80	1	S	A	7	5648	S	N	C	SOR	N	Nen	NA	óbito	338
200	F	38	S	Outra	2	50	0	S	B	14	107,1	N	N	B	TACE	N	Nen	NA	vivo	51
201	F	62	S	VHC	1	17	1	S	B	15	484,3	N	N	C	SOR	N	Nen	NA	óbito	265
202	F	72	S	VHC	2	63	0	S	B	11	5323	N	N	B	TACE	N	Nen	NA	óbito	232
203	F	78	S	VHC	5	21	0	S	A	6	62,5	N	N	B	TACE	S	TACE	NA	vivo	1312
204	F	57	S	VHC	2	75	0	S	A	13	213,5	N	N	B	TACE	S	TACE	NA	óbito	256
205	F	71	S	OH	1	30	0	S	A	13	551,1	N	N	A	RFA	N	TACE	NA	óbito	315
206	F	57	S	VHC	3	93	0	S	B	15	23,8	N	N	B	TACE	S	TACE	NA	óbito	364
207	F	58	N	Outra	1	140	1	N	A	7	18,3	N	N	C	SOR	N	Nen	NA	óbito	161
208	F	71	S	VHC	1	100	0	S	A	8	10,4	S	N	C	SOR	Sim	SOR	NA	óbito	72
209	F	61	S	VHC	1	25	0	S	B	15	46,2	N	N	A	Tx	S	RFA	S	vivo	703
210	F	66	S	VHC	1	39	0	S	A	9	98,8	N	N	A	Tx	S	TACE	S	vivo	1160
211	F	62	S	VHB	1	23	1	S	B	11	5,5	N	N	C	SOR	N	RFA	S	óbito	376
212	F	61	S	VHC	5	30	0	S	B	10	221,5	N	N	B	TACE	S	TACE	NA	óbito	206
213	F	60	S	VHC	1	14	1	S	A	9	34,6	N	N	C	SOR	N	Rx	NA	vivo	1387
214	F	73	S	VHC	1	39	0	N	A	6	874,5	N	N	A	Rx	N	TACE	NA	óbito	1021
215	F	68	S	VHC	1	30	0	S	B	16	2019	N	N	A	Tx	N	PEI	N	outra causa	243
216	F	62	S	VHC	1	35	0	S	A	8	7,3	N	N	A	Tx	N	TACE	N	óbito	770
217	F	53	S	VHB	2	84	0	N	A	7	354,1	N	N	B	TACE	S	TACE	S	óbito	278
218	F	54	S	VHC	2	30	1	N	B	18	1,9	N	N	C	SOR	N	TACE	N	óbito	332

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N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
219	M	79	S	VHC	2	55	0	S	A	8	6,8	N	N	B	TACE	S	TACE	NA	vivo	1360
220	M	65	S	NASH	1	22	0	S	A	11	4,3	N	N	A	Tx	S	TACE	S	vivo	1247
221	M	72	S	VHC	1	64	1	S	B	11	3,2	N	N	C	SOR	N	TACE	NA	óbito	264
222	M	56	S	VHC	5	60	0	N	A	7	3528	N	N	B	TACE	S	TACE	NA	óbito	210
223	M	63	S	VHB	1	152	1	S	B	10	85	S	N	C	SOR	N	Nen	NA	óbito	96
224	M	69	S	OH	1	66	0	N	A	7	7,8	N	N	B	TACE	S	TACE	NA	óbito	597
225	F	59	S	VHC	1	18	0	S	A	10	6,2	N	N	0	Tx	S	RFA	S	vivo	841
226	F	65	N	VHC	2	20	0	N	A	7	249,3	N	N	A	Tx	N	RFA	N	vivo	748
227	M	61	S	VHC	1	35	0	S	A	10	5,1	N	N	A	Tx	S	TACE	S	vivo	1426
228	F	59	S	VHC	1	60	0	S	A	8	2193	N	N	B	TACE	S	TACE	NA	óbito	303
229	F	68	S	OH	1	32	1	S	A	7	1584	N	N	C	SOR	N	RFA	NA	óbito	1198
230	M	65	S	VHC	1	52	0	S	A	9	220	N	N	B	TACE	S	TACE	NA	óbito	1222
231	M	79	S	OH	1	130	1	S	A	11	10	N	N	C	SOR	N	TACE	NA	óbito outra causa	413
232	M	78	S	VHC	3	65	2	N	A	11	2,3	N	N	C	SOR	N	TACE	NA	óbito outra causa	388
233	M	72	S	OH	1	32	1	S	B	16	8,2	N	N	C	SOR	N	PEI	N	vivo	1355
234	F	60	S	Outra	3	53	2	S	B	10	58,7	N	S	C	SOR	S	SOR	NA	vivo	661
235	M	68	S	VHC	6	62	1	N	A	10	1165	N	N	C	SOR	N	TACE	NA	vivo	436
236	F	77	S	VHC	1	45	0	N	A	7	1296	N	N	A	Rx	S	Rx	NA	vivo	893
237	M	77	S	OH	1	194	3	N	A	7	>60500	N	S	D	Nen	S	Nen	NA	óbito	75
238	M	63	S	VHC	1	27	0	S	A	11	47,1	N	N	A	Tx	S	PEI	S	vivo	1428
239	F	68	S	VHC	2	29	0	S	B	18	70,1	N	N	A	Tx	N	Nen	N	óbito	199
240	F	74	S	VHC	1	100	1	S	A	6	29,4	S	N	C	SOR	Sim	SOR	NA	óbito	511
241	M	54	S	VHC	1	20	0	S	A	6	1080	N	N	A	Tx	N	TACE	NA	vivo	926
242	M	74	S	VHB	2	76	0	S	A	9	5058	N	N	B	TACE	S	TACE	NA	óbito	351
243	M	70	S	VHC	1	10	0	S	A	7	7,8	N	N	0	PEI	S	PEI	NA	vivo	1215
244	F	24	N	Outra	1	140	2	N	A	9	14080	N	S	C	SOR	S	SOR	NA	óbito	131
245	M	62	S	OH	2	100	2	S	B	12	111,7	S	N	C	SOR	N	TACE	NA	óbito	343
246	M	51	S	VHC	1	120	0	S	A	9	8,3	S	Sim	C	SOR	N	Nen	NA	óbito	194
247	M	63	S	VHC	1	115	1	S	A	9	304,6	N	S	C	SOR	S	SOR	NA	óbito	216
248	M	68	S	OH	1	26	0	S	B	12	2,2	N	N	A	Tx	N	RFA	NA	óbito	388
249	M	58	S	OH	2	39	2	S	C	24	4,1	N	N	D	Nen	S	Nen	NA	óbito	752
250	M	78	S	Outra	1	170	3	S	A	8	32,2	N	N	D	Nen	S	Nen	NA	óbito	192
251	M	59	S	VHC	3	140	0	N	A	6	5,7	S	Sim	C	SOR	Sim	SOR	NA	óbito	417
252	M	47	S	VHC	1	37	0	S	B	15	12,9	N	N	A	Tx	S	TACE	S	vivo	1240
253	M	64	S	VHC	10	25	1	S	A	9	10,6	N	N	C	SOR	N	TACE	NA	óbito	702
254	M	75	S	VHB	1	98	1	N	A	10	>60500	N	N	C	SOR	N	Nen	NA	óbito	140
255	M	53	S	VHC	3	50	0	S	B	9	4,7	N	N	B	TACE	S	TACE	N	óbito	350

continua

continuação

N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
256	M	46	S	VHC	1	43	0	S	A	9	5,4	N	N	A	Tx	N	RFA	N	vivo	930
257	M	44	S	VHB	3	22	0	S	A	7	417	N	N	A	Tx	N	TACE	N	óbito	470
258	M	48	N	VHC	1	81	0	N	A	9	6914	N	N	B	TACE	S	TACE	NA	óbito	1058
259	M	68	S	VHC	1	65	0	N	A	6	15,3	N	N	B	TACE	N	Rx	NA	óbito	235
260	M	52	S	VHC	10	106	2	N	B	8	233,2	N	S	C	SOR	S	SOR	NA	óbito	820
261	M	68	S	VHB	5	45	0	S	A	13	6,8	N	N	B	TACE	S	TACE	NA	vivo	911
262	F	61	S	VHC	1	34	0	S	A	14	18,2	N	N	A	Tx	S	TACE	S	vivo	848
263	F	64	S	VHB	1	23	0	S	A	7	1,4	N	N	A	Tx	S	RFA	S	vivo	1279
264	F	56	S	OH	1	28	0	S	A	7	3,5	N	N	A	RFA	N	TACE	S	vivo	1167
265	F	81	S	Outra	1	20	0	S	A	8	3177	N	N	A	RFA	S	RFA	NA	vivo	1242
266	M	57	S	VHC	2	46	0	S	B	14	154,9	N	N	B	TACE	S	TACE	N	óbito	133
267	M	59	S	VHC	1	75	0	S	A	8	80,9	S	N	C	SOR	N	Nen	NA	óbito	278
268	F	69	S	NASH	3	40	0	S	A	6	10,7	N	N	B	TACE	S	TACE	N	vivo	1303
269	M	61	S	VHC	1	33	0	S	A	11	3,7	N	N	A	Tx	S	RFA	S	vivo	1240
270	M	62	S	OH	1	39	1	S	A	8	1813	N	N	C	SOR	N	TACE	N	óbito	306
271	M	72	S	VHC	1	70	0	S	A	10	3739	N	N	B	TACE	S	TACE	NA	óbito	270
272	M	58	S	VHC	3	27	0	S	B	7	4,1	N	N	A	Tx	N	RFA	NA	óbito	1060
273	M	72	S	VHB	2	16	0	N	A	9	2,6	N	N	A	PEI	S	PEI	NA	vivo	1317
274	M	57	S	VHC	1	176	0	N	A	6	13455	N	S	C	SOR	N	Rx	NA	óbito	307
275	M	70	S	OH	5	37	0	S	B	11	262,2	N	S	C	SOR	N	Nen	NA	óbito	129
276	M	42	S	VHC	1	100	0	S	B	13	16864	N	N	B	TACE	N	Nen	NA	óbito	136
277	F	61	S	VHC	1	43	0	S	B	7	12,7	S	N	C	SOR	Sim	SOR	NA	óbito	474
278	F	40	N	VHB	1	39	0	N	A	6	2,0	N	N	A	Rx	S	Rx	N	vivo	1071
279	M	73	S	VHC	3	21	2	S	B	15	7,5	N	N	C	SOR	N	TACE	NA	óbito	452
280	F	61	S	OH	1	20	0	S	A	10	16	N	N	A	Tx	S	RFA	S	vivo	891
281	F	66	S	VHC	2	22	0	S	A	13	3397	N	N	A	Tx	N	TACE	N	óbito	370
282	M	66	S	VHC	1	11	0	N	A	9	28,3	N	N	0	RFA	S	RFA	NA	vivo	1359
283	M	74	S	OH	1	120	3	S	B	10	24411	N	N	D	Nen	S	Nen	NA	óbito	21
284	M	68	S	VHB	1	100	3	N	B	11	262,4	S	Não	D	Nen	Sim	Nen	NA	óbito	83
285	M	40	S	VHB	10	66	1	S	B	16	60500	N	S	C	SOR	S	SOR	NA	óbito	89
286	M	55	S	VHC	1	62	0	S	A	8	7365	N	N	B	TACE	S	TACE	NA	óbito	1087
287	F	61	S	NASH	1	30	0	S	B	15	12,4	N	N	A	Tx	S	Transplante	S	óbito	293
288	F	71	S	VHC	1	22	0	S	A	9	73,3	N	N	A	RFA	S	RFA	N	vivo	1128
289	M	57	S	VHC	2	46	0	N	A	10	3,2	N	N	B	TACE	S	TACE	NA	vivo	906
290	M	64	N	NASH	1	20	0	N	A	8	8,2	N	N	A	Rx	N	PEI	NA	vivo	1258
291	M	49	S	VHC	2	50	0	S	A	8	31103	N	N	B	TACE	S	TACE	NA	óbito	262
292	M	57	S	NASH	2	70	0	N	A	6	144,2	N	N	B	TACE	S	TACE	NA	óbito	539

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N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
293	M	73	S	VHC	3	90	0	N	A	6	107	N	N	B	TACE	S	TACE	NA	vivo	759
294	M	47	S	VHC	1	190	1	S	B	15	45585	S	N	C	SOR	N	Nen	NA	óbito	81
295	M	60	S	VHC	1	45	1	S	B	12	7,7	N	N	C	SOR	N	RFA	N	óbito	240
296	M	56	S	VHC	10	100	3	N	B	6	1975	N	N	D	Nen	S	Nen	NA	óbito	171
297	M	59	S	VHC	3	30	0	S	A	11	44,6	N	N	A	Tx	N	TACE	NA	óbito	1242
298	M	59	S	VHC	1	35	0	S	A	10	541,8	N	N	A	Tx	S	TACE	S	vivo	1411
299	M	69	S	VHC	1	41	0	N	A	13	3,4	N	N	A	Rx	N	TACE	NA	óbito	570
300	M	56	S	VHC	1	27	0	S	A	13	11,6	N	N	A	Tx	S	Transplante	S	vivo	851
301	M	69	S	NASH	1	26	0	N	A	13	5,6	N	N	A	Rx	N	PEI	NA	vivo	1178
302	M	60	S	VHB	1	49	0	N	A	9	1,7	N	N	A	Rx	S	Rx	NA	vivo	1132
303	M	68	S	VHC	1	80	1	S	A	7	4,348	N	S	C	SOR	N	Nen	NA	óbito	149
304	M	69	S	OH	1	70	0	S	B	15	35,4	N	N	B	TACE	S	TACE	NA	óbito	273
305	M	59	S	VHC	1	27	0	S	B	10	3,3	N	N	A	Tx	N	RFA	NA	óbito	335
306	M	56	S	OH	1	15	0	S	A	11	79,7	N	N	0	Tx	N	RFA	NA	vivo	560
307	F	54	S	Outra	2	26	2	S	C	16	69	N	N	D	Nen	N	TACE	NA	vivo	628
308	F	62	S	VHC	3	20	0	S	A	9	38	N	N	A	Tx	N	TACE	N	vivo	433
309	F	67	S	VHC	4	29	2	S	C	17	3,7	N	N	D	Nen	S	Nen	NA	óbito	402
310	M	59	S	OH	2	40	0	S	B	15	97,9	N	N	B	TACE	S	TACE	N	óbito	338
311	M	68	S	VHB	1	22	0	N	A	6	3869	N	N	A	Rx	N	RFA	NA	óbito	412
312	M	51	S	VHC	2	20	2	S	A	8	459	N	N	C	SOR	N	TACE	N	vivo	461
313	F	61	S	VHC	1	35	0	S	A	8	3,1	N	N	A	Tx	S	RFA	S	vivo	638
314	M	72	S	OH	10	120	3	S	B	10	2,4	S	Não	D	Nen	Sim	Nen	NA	óbito	82
315	M	58	S	VHB	1	120	1	S	A	6	60500	S	N	C	SOR	Sim	SOR	NA	óbito	227
316	M	60	S	VHC	1	45	0	S	A	9	16	N	N	A	Tx	N	TACE	N	vivo	507
317	M	56	S	VHC	1	45	2	S	C	19	2,4	N	N	D	Nen	N	Transplante	S	vivo	1057
318	M	75	S	OH	1	24	0	S	A	7	3	N	N	A	RFA	S	RFA	NA	vivo	643
319	M	71	S	VHC	4	67	0	N	A	8	9145	N	N	C	SOR	S	SOR	NA	vivo	865
320	M	59	S	VHC	1	13	0	S	A	9	100	N	N	0	Tx	N	PEI	NA	vivo	1073
321	M	43	S	VHC	1	23	0	S	A	12	10	N	N	A	Tx	S	RFA	S	vivo	698
322	M	74	S	NASH	2	60	1	S	A	8	2,6	N	N	C	SOR	N	Nen	NA	óbito	399
323	M	83	N	Outra	10	100	3	N	A	8	1830	N	S	D	Nen	S	Nen	NA	óbito	72
324	M	65	S	VHC	3	100	1	S	B	10	20	S	Sim	C	SOR	Sim	SOR	NA	óbito	239
325	F	74	S	VHC	1	50	3	S	B	12	11145	S	Não	D	Nen	Sim	Nen	NA	óbito	168
326	M	65	S	OH	5	23	0	S	A	11	43	N	N	B	TACE	S	TACE	S	vivo	570
327	M	57	S	OH	4	80	0	N	A	9	2409	N	N	B	TACE	S	TACE	NA	vivo	642
328	M	73	S	VHC	1	25	0	S	A	8	205	N	N	A	Tx	N	Rx	NA	óbito	227
329	M	72	S	VHB	1	37	0	N	A	8	2,1	N	N	A	Rx	N	TACE	NA	vivo	588

continua

conclusão

N	Sexo	Idade	Cirrose	Etiologia	Número de nódulos	Tamanho do maior nódulo	ECOG-PS	HP	Child-Pugh	MELD	AFP	IV	Metástase	BCLC	Tratamento proposto	Aderência ao BCLC	Tratamento inicial	Transplante	Status	Sobrevida
330	M	73	N	NASH	4	88	2	N	A	14	2427	N	N	C	SOR	N	Nen	NA	óbito	117
331	M	59	S	NASH	2	69	0	S	B	19	4,8	N	N	B	TACE	S	TACE	NA	óbito	287
332	M	66	S	VHC	5	160	2	S	B	10	3,6	S	N	C	SOR	Sim	SOR	NA	vivo	1373
333	M	52	S	VHC	1	19	1	S	B	12	5,3	N	N	C	SOR	S	SOR	N	vivo	564
334	M	68	S	NASH	2	20	1	S	B	12	4,5	N	N	C	SOR	N	TACE	S	vivo	685
335	M	71	S	NASH	3	100	0	S	A	7	254	N	N	B	TACE	S	TACE	NA	óbito	348
336	M	58	S	VHC	1	58	1	N	A	9	3,8	N	N	C	SOR	N	Rx	NA	vivo	699
337	M	59	S	VHC	1	65	2	S	B	12	8	S	N	C	SOR	N	Nen	NA	óbito	136
338	M	69	S	VHC	2	90	0	S	A	9	6269	S	N	C	SOR	Sim	SOR	NA	óbito	109
339	M	66	S	VHC	1	30	0	N	A	11	27,1	N	N	A	Rx	N	RFA	NA	vivo	515
340	M	50	S	VHC	2	39	0	S	A	11	51	N	N	B	TACE	S	TACE	N	vivo	744
341	M	72	S	VHB	1	51	0	S	A	13	146	N	N	B	TACE	S	TACE	S	óbito	369
342	M	61	S	VHC	1	16	0	S	A	7	169	N	N	0	Tx	N	RFA	NA	vivo	726
343	M	59	S	VHB	1	30	0	S	A	10	29	N	N	A	Tx	S	TACE	S	vivo	582
344	F	62	S	VHC	1	90	2	S	A	10	19	S	N	C	SOR	Sim	SOR	NA	vivo	813
345	F	72	S	VHC	1	38	0	N	A	7	38	N	N	A	Rx	N	TACE	N	vivo	777
346	F	65	S	VHC	2	29	1	S	B	20	17908	N	N	C	SOR	N	Nen	N	óbito	514
347	F	83	S	NASH	1	73	0	S	A	6	5,4	N	N	B	TACE	S	TACE	NA	vivo	661
348	F	60	S	VHC	1	135	1	S	A	11	13096	N	N	C	SOR	S	SOR	NA	vivo	273
349	F	50	S	VHC	2	22	1	S	B	11	5,6	N	N	C	SOR	N	TACE	S	vivo	561
350	F	51	S	VHC	2	60	0	S	A	10	13,2	N	N	B	TACE	N	Nen	NA	vivo	11
351	M	94	N	Outra	1	62	0	N	A	7	0,9	N	N	B	TACE	S	TACE	NA	vivo	725
352	M	79	S	VHC	2	50	3	S	B	11	366	S	Não	D	Nen	Sim	Nen	NA	vivo	66
353	M	55	S	VHC	1	22	0	N	A	7	87	N	N	A	Rx	S	Rx	NA	vivo	703
354	M	53	S	VHC	1	61	0	S	A	8	32	S	N	C	SOR	Sim	SOR	NA	vivo	771
355	M	74	S	OH	4	41	1	S	B	16	263	N	N	C	SOR	N	TACE	NA	vivo	181
356	M	74	S	VHC	4	90	0	S	A	9	8641	N	S	C	SOR	S	SOR	NA	óbito	221
357	M	72	S	VHB	2	113	0	N	A	9	368	S	Sim	C	SOR	Sim	SOR	NA	óbito	62
358	M	52	S	OH	2	250	1	N	B	7	1402	S	Sim	C	SOR	Sim	SOR	NA	óbito	65
359	M	52	S	OH	1	25	0	S	A	9	2	N	N	A	Tx	N	TACE	N	vivo	431
360	M	60	S	VHC	4	49	0	S	A	10	6,7	N	N	B	TACE	S	TACE	NA	óbito	597
361	M	51	S	VHC	1	27	0	S	A	13	4,6	N	N	A	Tx	N	Nen	NA	vivo	700
362	M	62	S	NASH	1	35	1	N	A	6	3,3	N	S	C	SOR	S	SOR	NA	vivo	615
363	M	60	S	VHB	6	55	1	S	B	18	60500	N	N	C	SOR	N	Qt	NA	óbito	271
364	F	54	S	VHC	2	60	0	S	A	8	1394	S	N	C	SOR	Sim	SOR	NA	óbito	865

Apêndice B – Artigos publicados e trabalhos apresentados com parte da casuística deste estudo

ORIGINAL ARTICLE

OPEN

Hepatocellular Carcinoma Management in Nonalcoholic Fatty Liver Disease Patients *Applicability of the BCLC Staging System*

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Background/Aims: Nonalcoholic fatty liver disease (NAFLD) has emerged as an important cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The Barcelona Clinic Liver Cancer (BCLC) system is the preferred staging system to evaluate patients with HCC and links prognosis assessment with treatment recommendation. The aim of this retrospective study was to evaluate whether the BCLC staging system and its treatment algorithm are suitable for patients with HCC arising from NAFLD.

Methods: Forty-two patients with HCC related to either to NAFLD or cryptogenic cirrhosis were retrieved retrospectively from 2 centers in Brazil. Patients were classified according to BCLC staging system. If the proposed HCC therapy could not be applied, the case was considered to represent deviations from the recommended BCLC guideline. Causes of treatment deviations were investigated.

Results: There were 4 patients without evidence of cirrhosis according to liver biopsy and/or clinical evaluation. One (2%), 21 (50%), 10 (24%), 5 (12%), and 5 patients (12%) were classified initially to the very early (0), early (A), intermediate (B), advanced (C), and terminal (D) BCLC stages, respectively. Thirty-five patients (83%) were treated according to BCLC recommendations. There were 3 cases (of 5) of protocol deviation in BCLC C patients. The 1- and 2-year overall survival rates were 81% and 66%, respectively.

Conclusions: The BCLC system is applied in most cases of NAFLD-related HCC cases. Deviation of BCLC is found more frequently in BCLC C stage patients.

Key Words: nonalcoholic fatty liver disease, hepatocellular carcinoma, BCLC staging system, liver cancer, management

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Hepatocellular carcinoma (HCC), which accounts for >5% of cancers globally, is ranked as the sixth most common cancer and the third leading cause of cancer-related death worldwide.¹ Cirrhosis is the main risk factor for HCC development. Most cases are associated to chronic hepatitis B and C infection as well as alcohol consumption.² In recent years, nonalcoholic fatty liver disease (NAFLD) has appeared as an important cause of chronic liver disease, cirrhosis, and HCC. In the absence of effective surveillance strategies, the stage of presentation is often advanced.^{3,4}

HCC is unique because in addition to cancer stage, the underlying liver function substantially affects prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging system was proposed and has been validated by several groups in the United States and Europe and offers the best stage classification and guidance for HCC treatment allocation.^{5,6} BCLC staging system was developed mainly in European populations in which hepatitis C virus infection was dominant. Validation was also done by Asiatic group where hepatitis B virus is dominant.⁷

This system currently recommends radical therapies [liver transplantation, surgical resection, or percutaneous ablation, such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI)] for very early (BCLC stage 0) or early-stage (BCLC stage A) HCC, transarterial chemoembolization (TACE) for intermediate-stage (BCLC stage B) HCC, sorafenib administration for advanced-stage (BCLC stage C) HCC, and supportive care for end-stage (BCLC stage D) HCC.⁸ However, although this staging system was developed using an evidence-based approach, its application can be problematic in NAFLD patients because of different clinical profile of these patients.⁹ There are few reports of BCLC application in NAFLD patients.

Evidence has emerged suggesting that the molecular pathogenesis, clinical features, and the prognosis of NAFLD-related HCC may differ from viral-induced HCC.⁴ Most of HCC cases are described in cirrhotic patients, but HCC is increasing also in the noncirrhotic setting.¹⁰ These findings suggest that hepatocarcinogenesis may be deregulated in early stages of this disease. Some comparative studies suggest that

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NAFLD-related HCC patients are older and present with comorbidities that may limit HCC therapy according to recommended guidelines.^{9,11}

The main objective of this retrospective study was to evaluate whether the BCLC staging system and its treatment algorithm are suitable for patients with HCC arising from NAFLD. We also studied clinical characteristics of NAFLD-related HCC, and aspects related to diagnosis, overall survival, and predictors of survival.

METHODS

Patients

Between January 2010 and December 2012, 42 patients with HCC related either to NAFLD or cryptogenic cirrhosis were retrieved retrospectively from 2 centers in Brazil (Instituto do Câncer do Estado de São Paulo and Universidade Federal do Rio Grande do Sul). The Institutional Review Board of the University of São Paulo approved the study. Part of the included patients comes from an observatory of HCC in NAFLD of the Fatty Liver Inhibition of Progression (FLIP) consortium.¹²

Cirrhosis was diagnosed on histologic features and/or radiologic evidence (imaging studies suggesting chronic liver disease and portal hypertension), laboratory abnormalities such as thrombocytopenia, hypoalbuminemia, prolonged prothrombin time, or clinically decompensated disease (ascites, variceal bleeding, or hepatic encephalopathy). Other causes of chronic liver disease as hepatitis B, hepatitis C, autoimmune hepatitis, α 1-antitrypsin deficiency, Wilson disease, and hemochromatosis were excluded by appropriate laboratory tests. Unless features of the metabolic syndrome were present, or NAFLD was evident from histology, cases were regarded as cryptogenic. Baseline information, including patient demographics; risk factors for NAFLD; serum biochemistries; liver biopsy when available, severity of cirrhosis (Child-Pugh classification and Model for End-Stage Liver Disease score); Eastern Cooperative Oncology Group performance status; cancer stage according to the BCLC staging system; α -fetoprotein level; and treatment modalities were collected at enrollment.

HCC was diagnosed according to noninvasive diagnostic criteria of the American Association for the Study of Liver Diseases updated in 2010 whenever cirrhosis was present.⁸ Liver histology confirmation was performed in all noncirrhotic patients and inconclusive cases by imaging examination.

Staging According to the BCLC

BCLC stages were determined based on tumor size and number, liver function tests, performance status, and cancer-related symptoms.⁸ All patients underwent abdominal dynamic computed tomography or magnetic resonance, chest computed tomography, and a bone scan for staging. Portal hypertension was defined by the presence of esophagogastric varices by upper endoscopy, ascites, or splenomegaly and a platelet count $<100,000/\text{mm}^3$. Patients were classified as 0 (very early), A (early), B (intermediate), C (advanced), or D (terminal) using BCLC staging system.

Study Outcome

A local multidisciplinary team in each center composed of hepatobiliary surgeons, hepatologists, pathologists, oncologists, and interventional radiologists assessed all patients and decided on the best therapeutic option for each particular case, as performed routinely for each patient with HCC. For each

patient the administered treatment strategy was compared with the 1 theoretically recommended by the BCLC stage. The main outcome of the study was to determine whether therapeutic options in agreement with the BCLC classification were applicable or not. In the latter case, we investigated the causes of treatment deviations from BCLC recommendations and analyzed the rate of deviation for each BCLC stage.

Treatment

Curative therapies included surgical resection, liver transplantation, and local ablative therapy such as RFA or PEI.^{8,13,14} Surgical resection was considered in patients with a single tumor, with well-preserved liver function, normal bilirubin, and absence of portal hypertension.¹⁵ This was also the first choice for noncirrhotic patients with a single nodule, regardless of tumor size. Liver transplantation was considered in patients fulfilling the Milan criteria and showed increased portal pressure or bilirubin. During the waiting time on the liver transplant list, patients were treated with percutaneous ablation or TACE as a bridge therapy to liver transplantation.^{8,13-15}

If hepatectomy or liver transplantation were not indicated local ablative therapies such as RFA or PEI were performed depending on the size and number of tumor nodules. In multifocal tumors or large HCCs without extrahepatic spread or vascular invasion, TACE was the treatment of choice.^{8,13-15}

Sorafenib was indicated for patients with advanced HCC. When treatment efficacy was considered limited or treatment-related risk was substantial due to extensive tumor burden, Child-Pugh class C status, or other medical comorbidities, supportive care was given.^{16,17}

Statistical Analysis

Overall survival was measured from the date of diagnosis until death or last follow-up visit. Survival time was estimated using the Kaplan-Meier method and differences in survival between groups were assessed using the log-rank test.

RESULTS

Patients Characteristics

Baseline characteristics of the 42 patients are shown in Table 1. Median age was 66.5 years (range, 25 to 80 y) and male sex predominated ($n=26$; 62%).

Four patients (10%) were classified as cryptogenic cirrhosis because no features of the metabolic syndrome were present, and there was no evidence of NAFLD in liver histology. NAFLD-related HCC were seen in 38 patients. In this group, there were 4 patients without evidence of cirrhosis according to liver biopsy and/or clinical evaluation. In NAFLD group, 24 patients had previous liver biopsy with macrovacuolar and microvacuolar fatty change, zonal distribution, foci of necrosis, portal and perivenular fibrosis, and inflammatory and fibrotic infiltrate with zonal distribution. In NAFLD group, 34 patients (81%) had obesity; 31 patients (73%) had type II diabetes, 29 patients (69%) had arterial hypertension, and 11 patients (26%) had dyslipidemia.

The numbers of patients in Child-Pugh classes A, B, and C were 20 (48%), 15 (35%), and 3 (7%), respectively. HCC was diagnosed based on noninvasive diagnostic criteria of the American Association for the Study of Liver Diseases in 24 patients (57%). Diagnosis of HCC was confirmed by histology in 18 patients (43%).

Twenty-nine patients (69%) had a single tumor and the median diameter of largest tumor was 38 mm (range, 17 to

TABLE 1. Baseline Characteristics of the Study Population

Characteristics	N = 42
Age (median [range]) (y)	66.5 (25-80)
Sex (n [%])	
Male	26 (62)
Etiology (n [%])	
NAFLD	38 (90)
Cryptogenic cirrhosis	4 (10)
Metabolic syndrome	
Obesity (%)	34 (81)
Diabetes (%)	31 (73)
Hypertension (%)	29 (69)
Dyslipidemia (%)	11 (26)
Previous biopsy-proven nonalcoholic steatohepatitis (%)	24 (57)
Liver function (n [%])	
Noncirrhotic	4 (10)
Cirrhotic	38 (90)
Child-Pugh class	
A	20 (48)
B	15 (35)
C	3 (7)
HCC diagnosis (n [%])	
Surveillance	23 (55)
Noninvasive	24 (57)
Liver histology	18 (43)
HCC stage	
Single tumor (n [%])	29 (69)
Tumor size (median [range]) (mm)	38 (17-150)
Vascular invasion (n [%])	5 (12)
Extrahepatic spread (n [%])	3 (7)
α -Fetoprotein level (median [range]) (ng/mL)	11 (1-20,000)
BCLC stage (n [%])	
0	1 (2)
A1/A2/A3/A4	5/7/3/6 (50)
B	10 (24)
C	5 (12)
D	5 (12)

BCLC indicates Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; NAFLD, nonalcoholic fatty liver disease.

150 mm). Five patients (12%) had macrovascular invasion and 3 (7%) extrahepatic spread. The median α -fetoprotein value was 11 ng/mL (range, 1 to 20,000 ng/mL).

Classification of BCLC Stage

Noncirrhotic patients were incorporated to BCLC staging system because, in the real-life, they are practically treated with BCLC algorithm. One (2%), 21 (50%), 10 (24%), 5 (12%), and 5 patients (12%) were classified initially to the BCLC 0, A, B, C, and D stages, respectively. Among 42 patients, HCC was diagnosed in a screening program in 55% (there was 1 noncirrhotic patient). Patients with HCC diagnosed outside of a surveillance program (n = 19) were mostly not candidates to curative therapies (73%) ($P = 0.002$) (Table 2).

Allocation of Treatment According BCLC Stages

Curative treatments, which included resection, local ablative therapy, and liver transplantation, were performed in 23 (55%) patients, whereas palliative treatments such as TACE or sorafenib were given in 11 (26%) patients. Eight (19%) patients received only the best supportive care. Table 3 summarizes the detailed treatment modalities used for patients classified according to the BCLC staging system.

TABLE 2. BCLC Stage According to Surveillance Program

	BCLC ($P = 0.002$)	
	0/A	B/C/D
Surveillance (n)		
Yes	17	6
No	5	14

BCLC indicates Barcelona Clinic Liver Cancer.

Liver resection was the first choice therapy in all noncirrhotic patients, based on the decision of the multidisciplinary team as the best therapeutic option in each case. The first patient had 1 nodule of 37 mm. The second patient had 1 nodule of 109 mm. The other 2 patients had >2 nodules, but in the same liver segment. All noncirrhotic patients survived >2 years after treatment.

Most patients (85%) in BCLC stage A were treated according to BCLC recommendations. Liver resection was performed in 4 patients, liver transplant in 7 patients, and local ablation therapy in 7 patients. There were 3 protocol deviations in this group. Two patients were treated with TACE and 1 received best supportive care.

Most patients at the BCLC stage B were treated with TACE. In this group of 7 patients, 1 could be included in the liver transplant list after fulfilling Milan criteria. Only 1 patient presented a BCLC protocol deviation (ie, could not be administered TACE) because of significant comorbidity (heart failure) and received only best supportive care. Two patients in this group were treated with resection, because they were noncirrhotic.

Most cases of protocol deviation were found in BCLC C patients (3 of the 5 BCLC C patients). Two patients were initially treated with sorafenib (one of them was included in a clinical trial with brivanib plus sorafenib). One patient was treated with liver resection and 1 received TACE. These 2 cases of protocol deviation had preserved liver function (Child-Pugh A) and were classified as BCLC C because of macrovascular invasion at a segmental branch level. This was an attempt to a more curative therapy in these 2 cases. The third patient presented with rapid deterioration of general status and liver decompensation and received best supportive care.

All patients in BCLC D stage received best supportive care exclusively. There were 3 patients that received only best supportive care and were included in the group of protocol deviation because they were classified as BCLC A, B, and C staging system. The reason for not treating these patients is the association of poor liver function, compromised general status and advanced age. On the other side, the others patients who did not follow BCLC algorithm presented a very compensated liver function and a more aggressive therapy was attempted in each case. Two patients were classified as BCLC B, but without signs of liver cirrhosis and resection was indicated by the multidisciplinary group. The other 2 patients were those classified as BCLC C because of macrovascular invasion, but the multidisciplinary team decision was for resection in one case and TACE in the other case before indicating sorafenib.

Survival

During the follow-up period (median, 11 mo; range, 0 to 85 mo), 12 patients died of tumor progression or cirrhosis-related complications. The 1- and 2-year overall survival rates were 81% and 66%, respectively (Fig. 1). All noncirrhotic

TABLE 3. Allocation of Treatment Modalities According BCLC Staging Systems

	BCLC Staging System				
	Stage 0 (n = 1)	Stage A (n = 21)	Stage B (n = 10)	Stage C (n = 5)	Stage D (n = 5)
Resection	—	4	2	1	—
Liver transplant	—	7	—	—	—
Local ablation therapy	1	7	—	—	—
Transarterial chemoembolization	—	2	7 (1*)	1	—
Sorafenib	—	—	—	2	—
Best supportive care	—	1	1	1	5

*One patient could be included in the liver transplant list after fulfilling Milan criteria.
BCLC indicates Barcelona Clinic Liver Cancer.

patients were alive after 2 years of follow-up. Child-Pugh A cirrhotic patients presented a better overall survival rate ($P=0.02$) than Child-Pugh B and C patients. BCLC stage 0 and A patients had a better survival compared with BCLC B, C, and D patients, but it was not statistically significant.

DISCUSSION

HCC is the main cause of death in patients with cirrhosis. The BCLC system is the preferred staging system to evaluate patients with HCC as it takes into account the characteristics of the tumor, the degree of liver impairment, and the physical performance.^{5,7} Moreover, it is the only one that links prognosis assessment with treatment recommendation. NAFLD is a well-recognized etiology of HCC. Although clinical profile and hepatocarcinogenesis of these patients may be different from viral hepatitis infected patients, the BCLC could be applied in most cases of HCC arising in the context of NAFLD.

In this study, we characterized the outcome of patients with HCC arising on NAFLD or cryptogenic liver disease. Patients enrolled in a regular surveillance program were more often diagnosed at an early stage. Surveillance in patients with established cirrhosis and nonalcoholic steatohepatitis (NASH) is part of international recommendations. Recently, a Japanese group observed that in 28% of NAFLD patients, HCC

developed in less advanced stages of fibrosis.¹⁸ In the present study, we observed HCC in 4 noncirrhotic patients that were treated with liver resection. However, recommendation of surveillance in this subgroup of patients can not be generalized and must be made with caution because it is estimated that in the United States, NAFLD can affect 30% of the general population.¹⁹

Recently, 166 new cases were collected over 22 months in the FLIP consortium and the demographic aspects found in our study were similar to this larger database.¹² However, in the FLIP study, 59% patients were symptomatic and consequently BCLC stage C or D, whereas in the present study, 47% were BCLC stage 0 and A. Besides, applicability of the BCLC system was not evaluated in FLIP study. Another difference was the larger proportion of noncirrhotic patients in the FLIP study (43%) compared with 10% in our study. Preliminary data show that almost all noncirrhotic cases occurred in steatohepatitis rather than steatosis alone in both studies.¹²

The majority of studies describing HCC in the context of NAFLD usually focus on risk factors for liver carcinogenesis. Very little information is available on tumor stage and treatment of HCC after diagnosis. Besides, several factors affect the choice of treatment options and as the BCLC staging system is based on clinical and radiologic findings, it is not possible to determine exact stage in some patients.⁷

In our study, there were 4 noncirrhotic patients who were treated with liver resection. Most cases of protocol deviation were found in BCLC C stage (advanced stage) patients that sorafenib was the treatment of choice in these cases.⁸ One patient was treated with liver resection despite the presence of vascular invasion because it affected a segmental branch. The other patient who was classified as BCLC C was not evaluated initially by multidisciplinary team approach and received TACE in a private setting. This patient showed a very good tumor control response with TACE sessions besides the presence of segmental vascular invasion. These facts are problematic for the BCLC staging system not only in NAFLD patients, but in all types of HCC because its recommended treatment options are dependent on tumor stage. In another Korean study, applicability of the BCLC staging system to patients with HCC demonstrated that donor shortage, financial problems, the relatively limited efficacy of molecular targeting agents, and the presence of an indeterminate nodule were the main causes of deviation from BCLC recommendations.²⁰

In the other side, there are many concerns about HCC treatment in NAFLD patients. Comparative studies demonstrated that these patients are older, have higher body mass index, and are more likely to be diabetic, obese, or hypertensive.^{9,21} All these factors may difficult treatment schedule

FIGURE 1. Overall survival of 42 patients.

according to BCLC guidelines. They may be older to be candidate to liver transplant or have more renal dysfunction to TACE or have too many comorbidities to surgical resection. In our study, only 1 patient from BCLC A did not receive HCC therapy due to his comorbidities. Another patient did not follow BCLC guideline and received TACE because of technical contraindication to others procedures. In general, protocol deviation was not associated to age or presence of comorbidities. Deviations were associated to the presence of a good liver function allowing a more aggressive oncologic treatment.

Liver transplant was performed in 8 patients. United Network for Organ Sharing database showed that the frequency of liver transplant in NASH patients is increasing in the last decades and it is projected that NASH would likely overtake hepatitis C virus as an indication of LT by the year 2020. Besides age and risk factors, NASH patients had an excellent outcome (5-y survival of 80% to 85%) after liver transplantation.²¹ Survival after resection was also comparable with viral hepatitis patients ($P=0.391$), but patients with NAFLD showed better disease-free survival on univariate ($P=0.048$) and multivariate ($P=0.020$) analyses.⁹

NAFLD is recognized as a risk factor for the development of HCC. Most cases are believed to develop in a background of cirrhosis. However, an increasing number of NAFLD-related HCC arising from a noncirrhotic liver has been reported.¹⁰ In the present study, 4 of 42 (10%) patients who developed HCC in the context of NAFLD or cryptogenic liver disease had a noncirrhotic liver. In all the cases, HCC diagnosis was confirmed by liver histology. All patients in this subgroup were treated with surgical resection even with tumors >50 mm (50%) or >1 nodule (50%). In this context, a more aggressive HCC therapy was possible because of absence of liver dysfunction and portal hypertension. All patients were alive after 2 years of follow-up. However, in the literature, the BCLC guideline is recommended for cirrhotic patients. In non-cirrhotic patients, a more aggressive oncology treatment should be performed.⁸

The main limitation of this study is the small sample size and the short period of follow-up. A better overall survival and progression-free survival of patients who were treated aggressively than those in the same stage that followed the BCLC algorithm could not be performed due to these limitations.

CONCLUSIONS

The BCLC system is applicable in most cases of NAFLD-related HCC cases. Deviation from BCLC-based therapeutic recommendations is found more frequently in BCLC C stage patients. In noncirrhotic patients, a more aggressive oncology treatment should be performed, preferably with liver resection.

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Laparoscopic Resection of Hepatocellular Carcinoma: When, Why, and How? A Single-Center Experience

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Abstract

Purpose: The aim of this study was to evaluate short- and intermediate-term results of laparoscopic liver resection in selected patients with hepatocellular carcinoma (HCC).

Patients and Methods: Eighty-five patients with HCC were subjected to liver resection between February 2007 and January 2013. From these, 30 (35.2%) were subjected to laparoscopic liver resection and were retrospectively analyzed. Special emphasis was given to the indication criteria and to surgical results.

Results: There were 21 males and 9 females with a mean age of 57.4 years. Patients were subjected to 10 nonanatomic and 20 anatomic resections. Two patients were subjected to hand-assisted procedures (right posterior sectionectomies); all other patients were subjected to totally laparoscopic procedures. Conversion to open surgery was necessary in 4 patients (13.3%). Postoperative complications were observed in 12 patients (40%), and the mortality rate was 3.3%. Mean overall survival was 29.8 months, with 3-year overall and disease-free survival rates of 76% and 58%, respectively.

Conclusions: Laparoscopic treatment of selected patients with HCC is safe and feasible and can lead to good short- and intermediate-term results.

Introduction

HEPATOCELLULAR CARCINOMA (HCC) is the most common primary liver cancer and the fifth most common malignancy worldwide.^{1–3} In about 90% of the cases, it occurs in patients with chronic liver disease,^{2,4} and, in the last few years, there has been a clear increase in prevalence, especially in Western countries, that is directly related to hepatitis C virus infection.^{4,5} Curative therapeutic options available are surgical resection and liver transplantation. The choice between transplantation and resection is controversial, and there are no controlled trials comparing these modalities. The best potential curative procedure seems to be liver transplantation because it can treat simultaneously the tumor and the underlying liver disease.⁶ On the other hand, the best results are achieved in patients within a strict selection criterion set known as the Milan criteria.⁶ Moreover, in a context of a lack in liver grafts availability seen worldwide and the increasing prevalence of HCC, the number of donors is much lower than necessary to meet the

organ needs. The disproportion between the growing number of transplant candidates on the waiting list and the shortage of donors leads to a long waiting list time, raising the risk of tumor progression and causing a significant number of dropouts.⁷

Resection, a therapeutic alternative that can be performed readily and with lower costs compared with liver transplantation, has become a safe procedure in the last years with mortality rates in specialized centers lower than 5%.^{8,9} In selected cases, good long-term results can be achieved (50%–70% 5-year overall survival). However, resection is followed by high rates of morbidity and mortality in patients with chronic liver disease, being possible only in patients with preserved liver function.¹⁰

Despite the controversy between resection and transplantation, groups specializing in both liver surgery and liver transplantation, in the context of a long waiting list for transplant (more than 6–9 months), have advocated resection for the treatment of solitary HCC in patients with preserved liver function. It has also been shown that in patients within

the Milan criteria, the long-term outcome of those listed for liver transplantation (intention-to-treat analysis) was similar when compared with patients who underwent resection.¹¹ There are many other arguments other than the avoidance of a long waiting list favoring liver resection for HCC: immediately applicability, lower mortality rate, the availability of a surgical specimen for histological and molecular evaluation, and good long-term results.¹²

Most of the groups that deal with patients with liver diseases use a screening program to detect early HCC, thereby increasing the number of patients diagnosed with small HCC nodules in the last few years.^{13,14} It has already been shown that laparoscopic liver resection (LLR) for HCC, especially when indicated for solitary, small, and peripheral tumors in patients with preserved liver function, is safe and can lead to good short- and long-term results.¹⁵ The enthusiasm for minimally invasive treatment of HCC led to the publication of many case series showing very good results.¹⁶⁻¹⁹ Recent meta-analyses showed that laparoscopic resection led to shorter hospital stay, decreased blood loss, and lower rates of postoperative morbidity (less ascites) compared with open liver resection.^{8,20,21}

The aim of this study was to evaluate short- and intermediate-term results of LLR for selected patients with HCC. The authors also present their guidelines for the treatment of HCC.

Patients and Methods

From a prospective hepatobiliary surgical database, 85 patients with HCC were subjected to liver resection in our unit between February 2007 and January 2013. From these patients, 30 (35.2%) were subjected to LLR and were retrospectively analyzed. All patients were subjected to clinical evaluation and liver function laboratory tests. Preoperative workup included helicoidal computed tomography (CT) scan or magnetic resonance, thoracic CT, and bone scintigraphy. Diagnosis was based on image characteristics; none of the patients was subjected to liver biopsy. In patients in whom CT or magnetic resonance imaging depicted signs of portal hypertension, upper digestive endoscopy was performed. Radiological studies were reviewed in a multidisciplinary meeting held weekly.

Treatment guidelines for HCC in our unit are shown in Figure 1.

The selection criteria for the laparoscopic approach were as follows:

- Solitary nodule, smaller than 5 cm in diameter
- Preserved liver function (Child-Pugh Class A)
- Peripheral location on the liver
- Resection of up to two segments of the liver
- Platelet count of >100,000/mL
- American Society of Anesthesiologists score lower than 3
- Patients with portal hypertension and esophageal varices Grade 1 or 2 (with platelet count of >100,000/mL) in Child Class A patients were not excluded.

In brief, all patients were positioned in a supine French position with the surgeon positioned between the legs. For right lateral resections, the patient was placed in a left lateral (45°) position. Pneumoperitoneum was set at 12 mm Hg, and intraoperative staging was performed. Parenchyma transection was performed with the use of a Harmonic® scalpel (Ultracision®; Ethicon Endosurgery, Cincinnati, OH) or LigaSure™ (Valleylab, Boulder, CO). For the resection of a segment or

FIG. 1. Guidelines for the treatment of single hepatocellular carcinoma (HCC) within the Milan criteria. LLR, laparoscopic liver resection; OLT, orthotopic liver transplant; RFA, radiofrequency ablation; PVE, portal vein embolization.

section, the transection of the portal pedicle and hepatic veins was done with the use of vascular staplers. Specimen removal was done inside a plastic bag through the umbilical or a suprapubic incision. During parenchyma transection all patients were maintained with low central venous pressure levels (between 3 and 5 cm H₂O). No routine drainage was used.

In the last 2 patients with tumors located in the right posterior section, a hand-assisted procedure was performed through a small upper midline incision.²²

Liver resections were defined according to the Brisbane 2000 classification.²³ Intraoperative and immediate postoperative data collected included perioperative transfusions, conversions to open procedure (hybrid procedure), surgical margins, postoperative complications, length of hospital stay, and mortality. Postoperative complications were classified according to the Clavien-Dindo classification.²⁴ Postoperative follow-up was performed every 4 months, including clinical, laboratory, and radiological evaluation. Data collected included disease recurrence and mortality.

Continuous variables were expressed as median (range) and were compared by means of the Mann-Whitney test. Categorical variables were compared by the chi-squared test or Fisher's exact test. Survival and recurrence-free survival were measured from the date of operation to the time of death or at the time when a recurrent tumor was first diagnosed, respectively. Survival analysis was estimated by the Kaplan-

Meier survival method, and the differences in survival between the groups were compared by the log-rank test. Differences were considered as statistically significant when the *P* value was <0.05 .

Results

There were 21 males and 9 females with a mean age of 57.4 years (ranging from 28 to 77 years). The etiology of liver cirrhosis is depicted in Table 1. All patients presented a solitary nodule with a mean size of 3.7 cm (range, 2–5 cm). In 21 patients nodules were peripheral or located in a lateral position within liver parenchyma.

Patients were subjected to 10 nonanatomic resections and 20 anatomic resections (14 left lateral sectionectomies, 4 segmentectomies 6/7, 1 right hemi-hepatectomy, and 1 left hemi-hepatectomy). One patient without any comorbidity with a 5-cm nodule located in the middle of the right hemi-liver was subjected to a right hepatectomy. All surgical margins were free of tumor for at least 1 cm.

Two patients were subjected to hand-assisted procedures (right posterior sectionectomies); all other patients were subjected to totally laparoscopic procedures.

Conversion to open surgery was performed in 4 patients (13.3%) because of bleeding in 3 patients and staple failure in the other. Intraoperative transfusion was performed in 6 (20%) patients. The median and mean length of hospital stay was 6 days and 7.8 days, respectively (range, 2–24 days).

As seen in Table 1, postoperative complications were observed in 12 patients (40%); these included ascites in 5 patients, nondiabetic acute renal failure in 2, encephalopathy in 1, biliary fistula in 1, postoperative ileus in 1, colonic perforation

in 1, and sepsis due to pneumonia in 1 (right hepatectomy). An unidentified colonic perforation was diagnosed after 7 days, leading to re-operation, multi-organ dysfunction, and death after 24 days, leading to a mortality rate of 3.3%.

During long-term follow-up 1 patient developed an umbilical hernia that was surgically treated with good outcome. Ten of 29 patients (34.4%) had recurrent disease as follows: liver-only in 6, lung in 2, adrenal gland in 2, and epigastric port site in 1. Of the 6 patients with liver-only recurrence, 4 were subjected to intra-arterial embolization or radiofrequency ablation as a bridge to liver transplantation. Two of these patients were subjected to orthotopic liver transplant with good outcome.

The other 2 patients with liver-only recurrence were subjected to palliative intra-arterial embolization, whereas 2 patients with lung metastasis underwent systemic treatment with sorafenib. One patient with adrenal metastasis was subjected to adrenal laparoscopic resection, and the other one with abdominal wall recurrence was subjected to local resection.

Mean overall survival was 29.8 months with a 3-year survival of 76% and 3-year disease-free survival of 58% (Fig. 2).

Discussion

LLR is gaining worldwide acceptance recently because of the excellent results shown by expert surgeons in specialized centers. The feasibility and safety of LLR even for major resections have also been confirmed.²⁵ However, when dealing with patients with HCC, issues such as liver function, size of the remnant liver, bleeding control during a diseased parenchyma section, surgical margins, and postoperative morbidity have to be considered.

Recent series of laparoscopic resection of HCC published by very skilled surgeons have shown excellent results not only when morbidity and mortality were evaluated, but also long-term results.^{16,20,21,26–29} These enthusiastic results have led to a discussion of the real place of LLR in the treatment algorithm for HCC. In our group, beginning in 2006 we proposed a guideline for the curative treatment of HCC based on a case-by-case multidisciplinary discussion.

TABLE 1. DEMOGRAPHIC, PREOPERATIVE, AND SURGICAL DATA OF PATIENTS WITH HEPATOCELLULAR CARCINOMA WHO UNDERWENT LAPAROSCOPIC LIVER RESECTION

	n	%
Gender		
Male	21	70
Female	9	30
Cirrhosis etiology		
HCV	17	56
HCB	6	20
NASH	3	10
Alcohol	3	10
Unknown	1	3
Type of resection		
Anatomical	20	66
Nonanatomical	10	33
Blood transfusion		
Yes	6	20
No	24	80
Postoperative complication (by Clavien–Dindo classification)		
No	18	60
Yes	12	40
Grade I	9	
Grade II	1	
Grade IVb	2	

HCV, hepatitis B virus; HCB, hepatitis C virus; NASH, nonalcoholic steatohepatitis.

FIG. 2. Overall survival and disease-free survival curves for patients with hepatocellular carcinoma subjected to laparoscopic liver resection.

As liver function is considered the most important determinant of postoperative morbidity and mortality following liver resection, resection should be reserved for Child-Pugh Class A patients, with those being Child-Pugh Class B or C referred for transplantation. Fan et al.³⁰ have shown that for Child Class A patients within the Milan criteria, resection can lead to the same results independently of the presence of normal liver parenchyma, chronic hepatitis, or cirrhosis. According to the European and American guidelines for the treatment of HCC, the presence of portal hypertension is considered as a contraindication for liver resection because of the higher risk of liver dysfunction and mortality; however, this statement is not widely accepted.³¹ Capusotti et al.³¹ showed that for Child-Pugh Class A patients, the presence of portal hypertension did not affect survival following liver resection. Indeed, Cucchetti et al.³² also stated that the presence of portal hypertension should not exclude from surgery patients who could potentially benefit from curative resection. In our series, all patients had a preserved liver function and small nodules and, with the exception of 1 case, were subjected to limited resections; thus, the presence of small varices in patients with platelet counts >100,000/mL did not lead to an increase in morbidity or mortality.

Owing to the improvement of screening programs in patients with chronic liver disease, small HCC (early-stage) cases have been more frequently diagnosed. Patients with preserved liver function and small tumors are the best candidates for laparoscopic treatment. There are three different approaches for LLR: totally laparoscopic, hand-assisted, and hybrid resections. Our group prefers the totally laparoscopic approach except in patients with tumors located in the posterior segments of the right hemi-liver (segments 6 and 7), where a hand-assisted or a hybrid procedure seems to be easier and faster.^{22,33} Koffron et al.³⁴ presented their experience with a laparoscopic-assisted method (hybrid method) where liver mobilization and hilar dissection are done laparoscopically with hand assistance and the small hand port is used for liver transection; this maneuver turns a tedious and slow right liver mobilization into a simple, fast, and safe procedure. Nitta et al.³⁵ have also shown the usefulness of the laparoscopy-assisted technique for major liver resections.

A point of discussion is the type of resection for HCC. Anatomical surgery, where one or more entire segments with their portal pedicle are resected, has been advocated as the ideal treatment for HCC. It is well known that for HCC the main tumor pathway spread is through the portal vein; thus the *en bloc* resection of the tumor and its portal vein territory may lead to better oncological results.³⁶ However, in patients with chronic liver disease and cirrhosis, parenchyma-sparing procedures are mandatory to avoid postoperative liver failure. Thus, the choice between a nonanatomic wedge resection and an anatomic resection should be individualized. In our series, we tried to perform anatomical resections except in cases with small peripheral subcapsular nodules or in patients with signs of portal hypertension.

The optimal resection margin for HCC resection is still controversial. In a randomized trial comparing a wide 2-cm margin with a margin aiming at 1 cm, Shi et al.³⁷ found lower postoperative recurrence rates and better survival in the wide margin group. However, it is accepted that a 1-cm disease-free margin is adequate for the majority of patients with HCC.³⁷ Shi et al.³⁷ have recently shown that marginal re-

section (free margins smaller than 1 mm) did not negatively affect postoperative recurrence-free survival. In our series, all patients had free margins larger than 1 cm, and no recurrence at the operation site was observed. In a recent meta-analysis, Zhou et al.³⁸ showed no differences in surgical margins when comparing the open liver resection group with the LLR group.

The potential risk of intraoperative bleeding during laparoscopic liver resection in patients with HCC remains a matter of concern. However, most series have shown less bleeding and necessity of transfusion compared with open surgery. Aldrighetti et al.¹⁹ emphasized the hemostatic effect of the pneumoperitoneum and the advantage of image magnification to reduce blood loss during LLR. The improvement of energy devices and staplers used for liver transection is also an important factor for bleeding control.¹⁹ In our series, fewer than 20% of the patients required blood transfusion, and the Pringle maneuver was used in 4 patients in whom conversion to open surgery was necessary. In a multi-institutional European series with 163 LLRs, 9.2% of the procedures were converted to open or hand-assisted surgery, mostly because of bleeding or technical difficulties.¹⁸

LLR presents the advantages of a minimally invasive procedure such as less postoperative pain, fast recovery, and early return to work. Although there are no controlled trials comparing LLR and open resection for the treatment of HCC, most case-control studies and small series of patients have shown advantages over the open approach in well-selected cases. In a recent meta-analysis, operative blood loss, blood transfusion, and length of hospital stay were significantly lower in the LLR group.²⁰ Moreover, lower incidences of postoperative ascites were observed compared with the open procedure in almost all series of LLR, probably as a consequence of the preservation of the abdominal wall and umbilical round ligament collateral venous circulation.^{12,16,18,19,27,29,39-41} Another potential advantage is the avoidance of adhesions in patients subjected to LLR with recurrent disease and candidates for a rescue future liver transplant.¹² Two of our patients presented with postoperative ascites; however, both were easily controlled with medical treatment (sodium restriction and diuretics). No other signs of postoperative liver failure such as jaundice or encephalopathy were observed.

The major drawback of liver resection for HCC is the high recurrence rate of about 40% in the first year. Despite a higher recurrence rate after resection, most authors have shown that those patients can be subjected to salvage liver transplantation. Belghiti et al.⁴² showed that patients subjected to salvage transplantation present the same long-term results as those subjected to transplantation as the primary treatment. Indeed, Cherqui et al.⁴³ have shown that among their patients with recurrent HCC following LLR, 77% were transplantable (within the Milan criteria). The same group indicated that LLR when compared with open liver resection for HCC had decreased morbidity after salvage liver transplantation.¹² In our experience, 8 patients had recurrence only in the liver; 6 of them (75%) were transplantable and were subjected to bridge procedures for liver transplantation. Two patients were subjected to liver transplantation without any significant difficulty.

In our series, 3-year overall survival and disease-free survival were 76% and 58%, respectively. Belli et al.,⁴⁴ in a case-control study, presented similar overall and disease-free

survival rates comparing the conventional approach with LLR, showing that from an oncological point of view that the minimally invasive approach was comparable to open surgery. In a recent article with 65 patients subjected to LLR for HCC, the same authors showed long-term results comparable to the open procedure.¹⁶ Other well-balanced case-control series showed similar overall and disease-free survival rates.^{9,28,45} Zhou et al.,²¹ in a recent meta-analysis, have also shown similar overall and disease-free survival rates comparing open with LLR.

Thus laparoscopic treatment of selected patients with HCC is safe and feasible and can lead to good long-term results. LLR can be considered as a curative therapy for a significant number of patients or, for those with recurrence, as a bridge procedure for curative liver transplantation. But, above all, LLR should be part of the therapeutic armamentarium for the curative treatment of HCC.

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Disclosure Statement

No competing financial interests exist.

Author Contributions

P.H. designed and wrote the manuscript. M.V.P. and F.F.C. revised the manuscript and did the statistical analysis. G.M.F. and F.deL.M.L. performed research on the patient database and revised the manuscript. J.A.P.K., R.M.L., and I.C. revised the manuscript.

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Percutaneous radiofrequency ablation for early hepatocellular carcinoma: Risk factors for survival

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HCC by computed tomography (CT) or magnetic resonance imaging (MRI) (single nodule of ≤ 5 cm, or multi- (up to 3) nodules of ≤ 3 cm each) and who underwent RFA treatment with curative intent between January 2010 and August 2011 at the Instituto do Câncer do Estado de São Paulo, Brazil were enrolled in the study. RFA of the liver tumors (with 1.0 cm ablation margin) was carried out under CT-fluoro scan and ultrasonic image guidance of the percutaneous ablation probes. Procedure-related complications were recorded. At 1-mo post-RFA and 3-mo intervals thereafter, CT and MRI were performed to assess outcomes of complete response (absence of enhancing tissue at the tumor site) or incomplete response (enhancing tissue remaining at the tumor site). Overall survival and disease-free survival rates were estimated by the Kaplan-Meier method and compared by the log rank test or simple Cox regression. The effect of risk factors on survival was assessed by the Cox proportional hazard model.

RESULTS: A total of 38 RFA sessions were performed during the study period on 34 patients (age in years: mean, 63 and range, 49-84). The mean follow-up time was 22 mo (range, 1-33). The study population showed predominance of male sex (76%), less severe liver disease (Child-Pugh A, $n = 26$; Child-Pugh B, $n = 8$), and single tumor (65%). The maximum tumor diameters ranged from 10 to 50 mm (median, 26 mm). The initial (immediately post-procedure) rate of RFA-induced complete tumor necrosis was 90%. The probability of achieving complete response was significantly greater in patients with a single nodule (*vs* patients with multi-nodules, $P = 0.04$). Two patients experienced major complications, including acute pulmonary edema (resolved with intervention) and intestinal perforation (led to death). The 1- and 2-year overall survival rates were 82% and 71%, respectively. Sex, tumor size, initial response, and recurrence status influenced survival, but did not reach the threshold of statistical significance. Child-Pugh class and the model

Abstract

AIM: To evaluate outcomes of radiofrequency ablation (RFA) therapy for early hepatocellular carcinoma (HCC) and identify survival- and recurrence-related factors.

METHODS: Consecutive patients diagnosed with early

for end-stage liver disease score were identified as predictors of survival by simple Cox regression, but only Child-Pugh class showed a statistically significant association to survival in multiple Cox regression analysis (HR = 15; 95%CI: 3-76 mo; $P = 0.001$). The 1- and 2-year cumulative disease-free survival rates were 65% and 36%, respectively.

CONCLUSION: RFA is an effective therapy for local tumor control of early HCC, and patients with preserved liver function are the best candidates.

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Key words: Hepatocellular carcinoma; Radiofrequency ablation; Overall survival; Disease-free survival

Core tip: Radiofrequency ablation (RFA) is widely recognized as an effective therapy for early stage hepatocellular carcinoma (HCC) in patients who are not suitable candidates for surgical resection, such as those with decompensated liver function or portal hypertension. Reports from Brazil of clinical experience with RFA management of HCC are rare. This study evaluated 34 consecutive patients with early HCC treated with RFA at a single Brazilian hospital. RFA was efficacious for promoting local tumor control and positive outcome was related to preserved liver function. Careful evaluation of liver function may help to identify the best candidates for this procedure.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequently diagnosed primary hepatic malignancy, with the majority of cases occurring in patients with liver cirrhosis^[1,2]. The increased practice of ultrasonography (US)-based surveillance of high-risk patients, such as those with chronic liver disease, has promoted the rates of HCC diagnosis at the early stage when therapeutic intervention is more likely to be effective and less extensive. While surgical resection remains the preferred curative treatment method, patients with decompensated liver function or portal hypertension are contraindicated for this procedure and may require liver transplantation; however, the substantially complicated nature of organ transplantation and lack of donors has led researchers to seek alternative methods for local tumor control, and

percutaneous ablation therapy has emerged as a particularly promising treatment for such patients^[3].

Percutaneous tumor ablation has been shown to promote tumor necrosis and preserve liver function^[3,4]. Radiofrequency ablation (RFA) is currently considered the most effective modality of percutaneous ablation therapy, with demonstrated efficacy and safety profiles for early HCC cases of both single lesion (1 nodule, ≤ 50 mm) and multi-lesion (up to 3 nodules, ≤ 30 mm each)^[3,4]. RFA is a physical thermal ablation technique by which energy is introduced directly into the tumor tissue through an active electrode. The electric current is converted into heat in a closed circuit and the ionic agitation of molecules caused by intracellular movement of alternating electrical current at the needle tip results in friction-generated heat; temperatures around and above 60 °C cause coagulation necrosis^[4].

Meta-analyses of the randomized controlled trials carried out to investigate the efficacies and outcomes of various tumor ablation techniques have shown RFA to be superior to ethanol injection for achieving complete tumor ablation and in survival rates^[5,6]. A recent meta-analysis of studies investigating the efficaciousness of RFA *vs* hepatic resection also indicated that the two procedures produced similar short-term therapeutic efficacies in early HCC cases^[7]. The accumulated evidence of RFA efficacy has promoted its popularity among physicians for treating unresectable early HCC.

The majority of studies on RFA outcomes in HCC patients have been conducted with Asian and European populations^[8-11]. Few reports of clinical experience with this particular interventional technique have been reported for early HCC patients in Latin America. The study reported herein was carried out to assess the outcome of potentially curative RFA therapy in patients with early HCC treated at a large metropolitan hospital in Brazil and to identify the related risk factors for survival and tumor recurrence.

MATERIALS AND METHODS

Study design and patient selection

This study was designed as a single-center retrospective analysis and was carried out with pre-approval by the local institutional review board (Registration ID: 368/12; Instituto do Câncer do Estado de São Paulo (ICESP), Brazil) according to the ethical guidelines of the Declaration of Helsinki.

The hospital's prospective database was searched for patients diagnosed with early HCC who underwent RFA treatment with curative intent between January 2010 and August 2011. Patients who were subject to RFA without curative intent (as recommended by multidisciplinary team evaluation) were excluded from analysis, regardless of whether a clinically effective outcome had been achieved. However, patients who had been awaiting liver transplantation and received RFA as bridge therapy were included in the study.

HCC diagnosis and staging

Prior to the RFA treatment, all patients had been evaluated by imaging analysis (including US, contrast-enhanced dynamic computed tomography (CT), magnetic resonance imaging (MRI), and/or chest CT), physical examination, and laboratory testing. The Child-Pugh and model for end-stage liver disease (MELD) scoring systems were applied to determine liver function status. HCC was diagnosed according to dynamic CT or MRI findings showing hyperattenuation in the arterial phase with washout in the portal venous phase^[12,13]. In cases with inconclusive imaging findings, tumor biopsy was performed to confirm the HCC diagnosis.

For all patients, the RFA treatment was selected after consideration of the tumor parameters (*i.e.*, site, size, and number), the functional reserve of the liver, and the general health status. In particular, the following criteria were applied to determine a patient's candidacy for RFA: (1) ineligibility for or refusal of surgical resection; (2) US-detected tumor; (3) a single nodule ≤ 50 mm in diameter, or up to three nodules with a maximum diameter of 30 mm each; (4) Child-Pugh A or B cirrhosis; and (5) international normalized ratio of < 1.6 and platelet count of $> 50 \times 10^9/L$. The following conditions were considered contraindications for RFA: (1) hepatic hilum proximal to the tumor; (2) abundant ascites; (3) decompensated encephalopathy; and (4) extrahepatic tumor spread and/or macrovascular invasion.

RFA

At ICESP, the RFA routine is standardized, and all procedures were performed by one of three trained physicians (one having record of at least 5-years of experience with percutaneous ablation therapy) using the Cool-Tip 200-W RF generator (Covidien, Mansfield, MA, United States). The procedure was performed on an in-patient basis with general endotracheal anesthesia or conscious sedation, depending on the target location and anticipated complexity. Prior to needle insertion, the point of entry was planned to ensure a safe trajectory and end position. CT-fluoro scan and US image guidance was used to precisely place the ablation probes percutaneously within the tumor. The tumor size, location, and geometry were considered when selecting whether a single 17-gauge or triple cluster 17-gauge needle electrode will be applied in the RFA procedure. The tumor ablation was carried out in overlapping sessions, with the intent of ablating the entire tumor along with a 1.0 cm ablative margin.

Immediately after the procedure, a contrast-enhanced CT was performed in the interventional suite and detection of residual tumor tissue necessitated an additional needle insertion and ablation routine.

Follow-up

The efficacy of RFA was evaluated at one month after the procedure. CT or MRI imaging analysis was carried out and the response to RFA was classified as complete response (absence of enhancing tissue at the tumor site)

or incomplete response (enhancing tissue observed at the tumor site). Patients showing incomplete response were given an additional RFA procedure. After achievement of complete response, patients were followed-up at 3-mo intervals, until April 2013. The follow-up evaluations included clinical testing (including liver function testing) and CT or MRI. Tumor recurrence was diagnosed upon imaging detection of an enhancing area within or at the periphery of the ablated lesion. The recurrence was defined as distant if one or more of the detected tumor(s) were > 1 cm beyond the primary site. Patients with recurring HCC tumors were treated with additional RFA, if the same initial criteria for RFA candidacy remained satisfied. For those patients with recurrent HCC that showed contraindications to additional RFA, alternative therapies (such as transarterial chemoembolization (TACE) or sorafenib) were considered and applied.

All major complications that occurred during the follow-up period were recorded. Major complications were defined as complications resulting in hospital admission for interventional therapy, unplanned increase in the routine level of medical care, prolonged hospitalization, permanent adverse sequelae, or death.

Statistical analysis

Continuous data were expressed as median and range. The Lausen (1994) method was used to identify cutoff points of tumor size and MELD score necessary to maximize the subsequent log rank statistical analysis^[14]. Fisher's exact test was carried out to identify variables associated with initial complete response.

Overall survival was defined as the interval between treatment and death or date of last follow-up. Probability of disease-free survival was defined as the interval between treatment and the date of local or distant HCC recurrence. Survival rates were estimated by the Kaplan-Meier method and compared by log rank or simple Cox regression analyses. The effect of risk factors on survival was assessed by the Cox proportional hazard model, according to the calculated hazard risk (HR) and 95%CI. All statistical analyses were performed by the R statistical computing package (version 2.15.2; The R Project for Statistical Computing). A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Demographic, clinical and RFA treatment characteristics of early HCC patients

Of the total 395 patients with HCC who were evaluated for potential clinical management at ICESP during the 20-mo study period, 38 (12%) were treated with RFA. Four patients that received RFA without curative perspective were excluded from analysis. The baseline characteristics of the 34 RFA-treated patients are shown in Table 1. This patient population showed predominance of males, low-grade liver dysfunction (Child-Pugh A),

Table 1 Baseline characteristics of the 34 patients with early hepatocellular carcinoma treated with radio frequency ablation *n* (%)

Characteristics	No. of patients (<i>n</i> = 34)
Sex, male/female	26/8
Age in years median, range	63, 49-84
Etiology,	
HCV	24 (70)
HBV	1 (3)
Alcohol	6 (18)
Others	3 (9)
Child-Pugh class	
A	26 (76)
B	8 (24)
MELD points median, range	9, 6-16
Cutpoint by Lausen method	11
Portal hypertension, <i>n</i> (%)	27 (79)
ECOG-PST, 0/1 %	85/15
BCLC stage, 0/A %	18/82
Alpha-fetoprotein in ng/mL median, range	10.7, 1.4-12.7
Tumor size in mm, median, range	26, 10-50
Cutpoint by Lausen method	35
Tumor stage, <i>n</i> (%)	
Single	22 (65)
≤ 20 mm	6
21-30 mm	8
> 30 mm	8
Multinodular	12 (35)
Initial response (<i>n</i> = 32)	
Complete	29 (90)
Partial	3 (10)
Recurrence (<i>n</i> = 32)	
No	17 (53)
Yes	15 (47)
Local tumor recurrence	6
Distant recurrence	9

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; MELD: Model for end-stage liver disease.

Figure 1 Overall survival of the 34 patients with early hepatocellular carcinoma treated with radio frequency ablation.

single tumor status, and larger tumor size (only 17% had tumors ≤ 2 cm).

A total of 38 RFA sessions were performed in the 34 patients. Only three patients showed incomplete initial response, but complete response was achieved in all after additional RFA sessions (2 sessions, *n* = 2; 3 RFA sessions, *n* = 1). The median follow-up period was 22 mo

(range, 1-33) for all patients; two patients were lost to follow-up.

Overall survival rates of RFA and related factors

The 1- and 2-year overall survival rates were 82% and 71%, respectively (Figure 1). No deaths occurred among the female patients during the follow-up period. Overall survival time was significantly higher for patients with tumors ≤ 35 mm in diameter (3 years *vs* > 35 mm: 2 years, *P* = 0.08). All patients that achieved complete response had a single tumor, while 27% of the patients with multinodular HCC never achieved complete response (*i.e.*, partial response); the probability of achieving complete tumor ablation was significantly greater in patients with a single nodule (*vs* multiple tumors, *P* = 0.04).

Overall survival rate was higher in patients with complete response (HR = 0.22, 95%CI: 0.04-1.22), but the difference from patients with incomplete response did not reach the threshold for statistical significance (*P* = 0.83). Preserved liver function was associated with a significantly better overall survival time, as shown by patients with MELD score ≤ 11 (HR = 14.00, 95%CI: 2.8-70.0 mo; *vs* ≥ 12, *P* = 0.001) and patients classified as Child-Pugh A (HR = 15.00, 95%CI: 3.0-76.0 mo *vs* Child-Pugh B, *P* = 0.001). Patients with recurrence during follow-up showed a trend towards better survival, but this result may reflect the different (longer) follow-up times of certain patients (Figure 2). In multiple Cox regression analysis, only the Child-Pugh class was found to be associated with survival at a statistically significant level.

Outcomes of RFA bridge treatment in patients with substantial liver dysfunction

Sixteen of the RFA-treated patients were on the liver transplant waiting list in the beginning of their follow-up period. Four of those patients received orthotopic liver, and the median time to transplant was 12 mo. Five of the patients who did not receive a donor-match died from liver failure, and all showed no signs of HCC progression. At the end of follow-up, seven patients remained on the liver transplant list and met the Milan criteria. Explant analysis of the four transplanted patients showed that although the main nodule was completely necrotic in two of the cases and partially necrotic in the other two cases, small HCC foci (nodules < 10 mm) were present in all of the explanted liver specimens.

Disease-free survival rates of RFA and factors related to recurrence

At the end of follow-up, tumor recurrence had been detected in 15 (47%) of the total 32 patients. The 1- and 2-year cumulative disease-free survival rates were 65% and 36%, respectively (Figure 3). Tumor recurrence during follow-up was influenced by survival; log rank test indicated that patients with better survival rates (Child-Pugh A, MELD ≤ 11, and female) were at risk for recurrence.

Both local recurrence (*n* = 6) and distant recurrence

Figure 2 Cumulative survival rates of hepatocellular carcinoma patients following radiofrequency ablation treatment. Comparisons are presented between the following patient sub-groups: A: Male and female; B: Tumor size of ≤ 35 mm and > 35 mm; C: Child-Pugh A and B; D: Model for end-stage liver disease score ≤ 11 and > 11 ; E: Complete and partial initial response; F: With tumor recurrence and without tumor recurrence.

($n = 9$) occurred. Among the patients that experienced distal recurrence, three showed macroscopic vascular invasion at the time of recurrence detection and one experienced nodal recurrence. Treatment for recurrence included RFA ($n = 6$), percutaneous ethanol injection ($n = 2$), TACE ($n = 5$), and sorafenib ($n = 2$).

Major complications of RFA

Two patients experienced major complications fol-

lowing the RFA sessions. One patient developed acute pulmonary edema and was transferred to the intensive care unit; the patient fully recovered and was discharged to home without further incident occurring during the remaining follow-up. Another patient experienced intestinal perforation and died 31 d after the RFA procedure.

Of the total 12 patients (34%) that died during the follow-up period, only one death was attributed to HCC progression. The majority of deaths (50%) were related

Figure 3 Cumulative disease-free survival of the 34 patients with early hepatocellular carcinoma treated with radio frequency ablation.

to complications of underlying cirrhosis and liver failure. Three deaths were attributed to other causes unrelated to tumor, liver failure, or the RFA treatment. None of the patients that survived to the end of follow-up presented any clinical signs of worsening liver function.

DISCUSSION

In the past two decades, RFA has become recognized worldwide as an efficacious and safe treatment modality for patients with early HCC^[12,13]. In Brazil, more than one-third of newly diagnosed HCC cases are classified as early stage^[7], and clinicians face the same clinical challenges for treating these types of patients with concomitant portal hypertension or decompensated liver function (contraindications for surgical resection)^[3]. To expand our knowledge of RFA application and outcome in Brazil, this study evaluated the initial (immediate post-procedural) and short-term (1-2 year follow-up) clinical experience with RFA in a single treatment center with experienced staff. The 38 RFA procedures performed with curative intent on a total of 34 patients with early HCC showed high anti-tumor effect, providing complete response in 90% of the patients. Moreover, the overall survival rate was found to be significantly associated with liver function in these patients.

After selection of tumor variables (number and size), our results showed a great discrepancy in terms of overall survival after RFA depending on liver function. Specifically, the 1-year survival rates for patients with Child-Pugh A and B score were 96% and 37%, respectively. Similar findings were reported by other groups examining clinical efficacy of RFA^[15-17]. Because most HCCs arise in the context of liver cirrhosis, the established liver impairment may already represent a general poor prognosis for these patients. Indeed, for Child-Pugh C patients, HCC treatment has no effect on outcome^[12,13]. For Child-Pugh B patients, however, HCC treatment can be beneficial, but the outcome is not consistent. Asymptomatic HCC patients with minor laboratory changes and without decompensated cirrhosis are categorized within the same group as patients with ascites, encephalo-

lopathy, and/or important coagulopathy. Recent recommendations for TACE treatment candidacy emphasize careful selection from among those patients with Child-Pugh B^[18]. The data from the current study also indicate that liver function is an important consideration for RFA candidacy. Child-Pugh B patients comprised 24% of the study population and most of these patients had MELD scores > 11 as well as a previous episode of ascites or encephalopathy which was compensated before the RFA treatment (data not shown).

RFA was very successful in promoting tumor control in the current study population, in general. Achievement of complete response was detected in the initial evaluation for all patients with single nodule HCC. Achievement of initial complete response after RFA has been reported as an important predictor of survival, due to its association with significant improvement in disease outcome^[15,19]. The impact of extensive tumor necrosis on survival has also been reported for TACE^[20], and researchers have considered features of this alternative treatment modality in hopes of developing improved strategies for RFA. Multiple electrode insertion was proposed to facilitate generation of a sufficient safety margin, and iterative RFA was shown to promote achievement of complete and durable ablation^[9]. TACE has also been applied as an adjunct therapy to RFA and improves the treatment-induced tumor necrosis. Occlusion of arterial flow during RFA significantly enlarges the zone of coagulation, which may underlie the improved effects on tumor control that are achieved when RFA is used in combination with transarterial therapies, such as TACE. Indeed, supplementing RFA with TACE has been shown to improve survival in some HCC patients, but the precise benefit of this association must be validated^[21-23].

Recurrence of tumors treated with RFA occurred in 47% of the patients in the current study. Despite imaging analysis detecting no viable neoplastic tissue at post-procedural and follow-up exams, residual nests of tumor cells contributed to local tumor recurrence in 40% of these cases. The cases of distant recurrences (60% of recurrences) was not surprising due to the multicentric nature of HCC in cirrhosis. Recurrent HCC is not uncommon after RFA nor is it specific to this modality of therapy. Even patients treated with hepatic resection show recurrence rates > 70% at five years after the surgical therapy^[24,25]. Unfortunately, no adjuvant therapy has demonstrated a significant improvement in disease-free rates after potentially curative therapies (such as RFA) for early HCC either.

Most of the published data on RFA effectiveness has come from studies conducted with Eastern cohorts of patients and generalization to Western patients may not be feasible because of the known etiologic differences of these populations^[26,27]. The largest study to date on RFA outcome demonstrated that etiology of liver disease is an important predictor of long-term survival and distant intrahepatic recurrence, and identified a role for chronic infection with hepatitis C virus (HCV) in patient

survival^[10]. In another study, patients with HCV-related cirrhosis who achieved sustained virological response to antiviral therapy were shown to have a substantially lower rate of HCC recurrence and accompanying higher survival rate^[9]. In the current study, up to 70% of the patient cohort were HCV-positive (data not shown) and this may have played a role in the high recurrence rate.

RFA is a well-established bridge therapy for patients awaiting liver transplant. The results from explant analysis of the transplanted patients supported the finding that RFA is very efficacious in promoting tumor necrosis; the treated lesions remained necrotic in all cases. However, very small (< 1 cm) HCC lesions were found in all explant specimens. Thus, RFA appears to be a good choice for bridge therapy of patients with compensated liver function while awaiting donor liver to become available for transplantation^[28]; those patients with decompensated liver function, however, may not be suitable candidates for RFA, and liver transplantation should remain the treatment of choice. In our hospital, the average wait time for a donor liver was approximately 12 mo^[29]; living-donor transplant may also be an excellent curative therapy and should be explored as a feasible alternative for some HCC patients, such as those not suited to surgical resection or RFA.

One RFA-related death that of gastrointestinal perforation, occurred in the current study's cohort. Risk of this type of procedure-related complication is increased when the target nodule is located adjacent to the intestine, and the risk is even higher when the patient has a previous history of gastrointestinal surgery. The reported frequency of gastrointestinal perforation in RFA is 0.3% per treatment^[29]. Our patient had no history of gastrointestinal surgery and we performed an intraperitoneal infusion technique, by which 500-1000 mL of 5% glucose solution was injected before and during the ablation routine for the purpose of creating space between the lesion and the intestine. The RFA procedure itself was uncomplicated and the patient was discharged to home afterwards. Ten days later, the patient returned to clinic with acute abdominal pain and immediately underwent laparotomy and colostomy. Nonetheless, the patient died 31 d after the RFA procedure.

The current study has several limitations inherent to its study design that must be considered when interpreting its results. While the small sample size reflected the normal volume for this procedure in a reference HCC center in Brazil, it may have been the reason why no significant differences were observed for some of the well-known predictors of survival and recurrence. Furthermore, the current study's findings were gained from a single-center cohort and cannot be compared to clinical experiences from other treatment centers, due to heterogeneity of selection and patient management, physicians' expertise, indication of additional treatments, and the institution's volume of care. Liver transplantation is considered the optimal treatment for early HCC patients with decompensated liver function, and these

patients are not good candidates for the alternative minimally invasive therapies. Inclusion of patients with more advanced liver dysfunction (Child-Pugh B patients) in the current study's cohort may have compromised the overall survival rate. However, this cohort composition was considered an accurate reflection of the actual profile of patients seeking HCC treatment, and the results may help to refine selection criteria for RFA candidates in our hospital in the future.

In summary, RFA was a safe and effective therapy to achieve local tumor control of early HCC in Brazilian patients. The best candidates for RFA were patients with early HCC and well preserved liver function. Careful follow-up with imaging analysis should be conducted after RFA, as the rate of recurrence remains high. Yet, most cases of recurrence can be effectively treated with additional RFA or other standard therapies. Finally, RFA ablation was shown to be an effective bridge therapy during the wait for a donor liver, but mainly benefited patients with well compensated liver function.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is a frequent complication of chronic liver disease and is the main cause of death in patients with compensated liver cirrhosis. Prospective surveillance of cirrhotic patients has improved the diagnosis rates of HCC in early stage, when patients are candidates for potentially curative therapies. In this scenario, radiofrequency ablation (RFA) has emerged as a promising alternative therapy.

Research frontiers

RFA is the standard of care for patients with early HCC who are not candidates for surgical resection. RFA is considered safe and effective due to its demonstrated ability to promote tumor necrosis without deterioration of liver function. This study identifies risk factors for survival and disease recurrence following RFA treatment, and the results are expected to improve patient selection for this procedure.

Innovations and breakthroughs

The publicly available literature includes few reports of clinical experience and analyses of RFA in HCC patients from Brazil and Latin America. Selection and patient management, physicians' expertise, indication of additional treatments, and the institution's volume of care can be institution specific and may influence RFA outcome. This study of a Brazilian patient cohort from a hospital with clinical expertise in RFA confirms the importance of careful liver function evaluation when considering a patient's candidacy for RFA.

Applications

RFA is a very effective therapy to promote local tumor control. Patients with well-preserved liver function were shown to have better survival rates following RFA treatment of HCC. For patients classified as Child-Pugh B, liver transplantation should remain the first choice for therapy.

Terminology

RFA is a physical thermal ablation technique that introduces energy directly into target tissue (such as a tumor lesion) through an active electrode. HCC is a primary malignant tumor that frequently occurs in patients with chronic liver disease. Decompensated liver function occurs when the liver can no longer function normally. Overall survival denoted the chance of staying alive after the treatment for HCC. Tumor recurrence was defined as the return of HCC after treatment and after a period of time during which the cancer could not be detected by routine imaging analysis.

Peer review

This study analyzed data from Brazilian patients with early HCC who underwent RFA with curative intent. A rate of 90% complete tumor necrosis was obtained at initial (immediate post-procedural) evaluation. The 1- and 2-year overall

survival rates were 82% and 71%, respectively. Child-Pugh class was the only independent predictor for survival following RFA. The results of this study agree with those from similar studies in ethnically and geographically different cohorts that have been previously published, and provide novel insights into the unique clinical experience of a Latin America-based population. Although this was a preliminary study and used only a small amount of cases, the results may be useful to treating physicians in selecting candidates for RFA treatment.

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Abstract Submission for ILCA 2012

Epidemiology, staging and prognosis

ILCA2012-1124

Stage, Treatment Approach And Viral Genotype In Chronic Hepatitis B Patients With Hepatocellular Carcinoma (Hcc) Followed Up In São Paulo, Brazil

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Presentation Method: Oral or Poster presentation

Introduction: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the burden of this devastating cancer is expected to increase further in coming years. Risk factors for the development of HCC in patients with chronic hepatitis B virus (HBV) infection are being elucidated. As most HCCs arise after liver cirrhosis (LC), it was suggested as the most important risk factor for HBV-related HCC. There is also growing evidence suggesting that viral genotypes may influence the clinical outcome of HBV infection including the risk for HCC. In Brazil there are not any previous studies reporting HBV genotypes found in HCC cases. The aim of this study was to characterize the viral genotypes circulating among HCC patients and ascertain the characteristics of patients with incidental HCC diagnosis.

Methods: Thirty-one HBV/HCC patients were enrolled for this study. All patients were forwarded to a referee oncological center ICESP with or without symptoms. Demographic, clinical and tumoral characteristics, 1st treatment approach and eligibility for transplantation were recorded. For HBV genotyping, a fragment of 1,306 bp partially comprising the DNA polymerase and the HBsAg genes (S/POL) was amplified, sequenced and genotyped by phylogenetical analysis using reference sequences obtained from the GenBank. They were aligned using Muscle software and edited with the SE-AL software. Bayesian phylogenetic analyses were conducted using the Markov Chain Monte Carlo (MCMC) simulation implemented in BEAST v.1.5.3. The maximum credibility tree (MCCT) was constructed with the TreeAnnotator v1.5.3 and then visualized with the FigTree v1.1.2 software.

Results: Among thirty-one HCC patients, 96.7% were cirrhotic patients, 64.5% were Caucasians, 80.6% men and mean age was 56.5 years (range 39-85 years). The mean values of clinical variables were: Alpha-fetoprotein (AFP): 2505.8 ng/mL; Alkaline phosphatase (ALP): 134 U/L; Aspartate aminotransferase (AST): 58.9 U/L; Alanine aminotransferase (ALT): 44.4 U/L; Gamma glutamyl transferase (GGT): 134 U/L; Platelets: 137.3 mil/mm³; Albumin 3.64 g/dL and Bilirubin 1.32 mg/dL. HCC tumors were identified by: Screening program – 22.6%, Causal Finding – 16.1% and Symptoms – 61.3%. From 7 cases included within screening program, 28.5% presented an early stage HCC (single nodule <2 cm). The majority of patients were BCLC early stage (BCLC-A – 54.8%) and applicability of TACE and resection treatments was more frequently: 38.7% and 22.5%, respectively. Furthermore, tumors in BCLC-B and BCLC-C stages were detected in patients with symptoms. The frequency of HBV genotypes among HCC patients was A1 (41.6%), C2 (16.6%), D3 (16.6%), A2 (8.3%), F2a (8.3%) and D1 (8.3%).

Conclusion: HBV subgenotype A1 and male sex were more prevalent in these patients. HBV subgenotype C2, commonly found in Asia, was the second most prevalent genotype. These results agreed with the distribution of HBV genotypes circulating in Brazil, where A1 subgenotype is the most prevalent, being predominant in the Northern and Northeastern states. Furthermore, according to the patients profile, data demonstrate that the majority of HCC patients are diagnoses within symptoms stage that limits the chance for precocious diagnosis and effective therapy. However, the screening program showed a positive result for detection of very early tumors in HBV patients. Thus, according to this result obtained in this reference center, we concluded that it is necessary to invest in the adherence of patients to the screening program.

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Disclosure of Interest: None Declared

Abstract Submission for ILCA 2012

Epidemiology, staging and prognosis

ILCA2012-1359

Management Of Hepatocellular Carcinoma According To Barcelona Clinic Liver Cancer Staging - Survival Analysis Of 395 Patients In Brazil

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Presentation Method: Oral or Poster presentation

Introduction: Hepatocellular carcinoma (HCC) develops in the context of liver cirrhosis in the majority of cases in Brazil and hepatitis C virus infection is the main etiology. Few data are available regarding efficacy of HCC management in Brazil. The Barcelona Clinic Liver Cancer (BCLC) staging offers prognostic stratification and treatment allocation for HCC. We conducted this retrospective study to assess overall survival of HCC patients according to BCLC staging system and efficacy of different treatment options.

Methods: From May-2010 to March-2012, 404 patients with HCC diagnosis were evaluated at Instituto do Câncer do Estado de São Paulo (ICESP), Brazil. Nine patients were excluded because of missing data. A multidisciplinary team, composed by hepatologists, surgeons, radiologists, pathologists and oncologists, choose HCC therapy according to liver function, tumor stage and performance status. Survival rate and median survival times associated with different treatment options and BCLC classification were compared using the Kaplan–Meier method and log-rank test.

Results: A total of 395 patients were included. Overall survival rates were 79% and 59% at 1 and 3 years. At 1 year, survival rates were 90%, 92%, 78%, 52% and 6% for BCLC 0, A, B, C and D, respectively. Surgical resection was employed in 43 patients and offered a survival rate of 95% and 82% at 1 and 3 years, respectively. Percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) was used in 54 and 38 patients, only in very early and early stages (BCLC 0 and A). PEI offered a survival rate of 96% at 1 year and 82% at 3 year. Survival rates for RFA were 88% and 78% at 1 and 2 year. Liver transplant was performed in 32 cases. In most cases, a bridge therapy was necessary to avoid tumor progression. Transarterial chemoembolization (TACE) was the most frequent initial HCC therapy in early and intermediate stages and offered a survival rate of 85% and 63% at 1 and 3 year. Thirty patients were treated with sorafenib and survival rates were 62% and 18% at 1 and 2 year. All patients BCLC D (n=23), received only supportive care.

Conclusion: In our center, most cases of HCC evaluated were in very early and early stages. Liver resection and PEI offered the best survival rates. Liver transplantation still benefits a limited number of patients with early HCC in the period studied. Chemoembolization is the most employed therapy in early and intermediate stages. Sorafenib was indicated in almost half of patients with advanced HCC. Efficacy of each treatment cannot be compared because patients selection varied according to liver function, tumor stage and performance status. The BCLC classification offers a prognostic stratification of patients with HCC in this cohort of patients.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2012

Diagnostic imaging and local regional therapies

ILCA2012-1362

Initial Tumor Response Evaluation According To Mrecist Criteria Predicts Survival In Patients With Hepatocellular Carcinoma Treated With Tace-Drug Eluting Beads

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Presentation Method: Oral or Poster presentation

Introduction: Transarterial chemoembolization (TACE) is efficient in reduce tumoral growth and increase survival in patients with hepatocellular carcinoma (HCC). Drug eluting beads (DEB) is an embolizing device that slowly releases chemotherapy to decrease systemic toxicity during TACE. Initial studies showed that TACE-DEB is superior to conventional TACE regarding tumor response and toxicity. The aim of this study is to evaluate tumor response according to mRECIST criteria in patients with HCC treated with TACE-DEB and survival rate after 1-year follow-up.

Methods: In the period of the study, 52 patients with HCC were treated with 64 sessions of TACE-DEB loaded with doxorubicin 50mg. Tumor response was evaluated one month after the procedure with CT or MRI according to mRECIST criteria.

Results: Median age was 62 years and 74% were male. The majority of the patients were cirrhotic (90% - CHILD A 62% e CHILD B 38%). Etiology of liver disease was HCV in 26/52 (50%), HBV in 8/52 (15%), alcohol in 10/52 (19%) and NASH in 3/52 (6%). According to BCLC staging system, 46% was BCLC A and 54% was BCLC B. Most patients had one nodule (66%). No patient presented with extrahepatic metastasis or macroscopic vascular invasion. Complete response was reached in 12/52 (23%), partial response in 19/52 (37%), stable disease in 4/52 (8%) and progressive disease in 17/52 (32%).

Overall survival rate after TACE-DEB was 74% at 1 year. According to BCLC stage, survival rate was 95% and 56% in BCLC A and B group, respectively. Presence of objective response (complete response + partial response) according to mRECIST criteria was predictor of better survival in 1 year (83% vs 60%, p<0.05).

Conclusion: In patients with HCC submitted to TACE-DEB, BCLC A and presence of objective response according to mRECIST criteria were predictor of better survival at 1 year. Further studies are necessary to evaluate other predictors of survival and if evaluation of tumor response may be predictive of higher long-term survival.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2012

Epidemiology, staging and prognosis

ILCA2012-1271

Hepatocellular Carcinoma (HCC) In Brazilian Nafld Patients

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Presentation Method: Oral or Poster presentation

Introduction: The connection between non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) has been well established but the exact mechanisms leading to development of HCC in patients with NASH remain unclear. Our objective was to characterize patients with HCC and active, histologically defined steatohepatitis.

Methods: From January 2006 to April 2012, 30 patients with HCC in the setting of NASH in the absence of chronic liver disease of any other cause, imbibing less than 100 g alcohol/week were evaluated at two Brazilian centers (Department of Gastroenterology of Clinic Hospital of University of São Paulo School of Medicine, São Paulo and Department of Internal Medicine, Universidade Federal do Rio Grande do Sul). All were negative for other liver diseases such as hepatitis C, hepatitis B, autoimmune hepatitis, Wilson disease, and hemochromatosis.

Results: The patients [23 (76,7%) males and 7 (23,3%) females, age $64,5 \pm 9,3$ years] had normal BMI (10,3%), overweight (51,7%) or obese (38%); 63,3% were diabetic and 23.3% had dyslipidemia. Cirrhosis was present in 89,3% of the cases, but 10,7% had HCC in the setting of NASH without cirrhosis. Among our NASH-related HCC patients, 65,5% had a single tumor nodule with a median diameter of 27 mm (2-150 mm). The BCLC stage were: A (55,1%), B (27,5%), C (10,5%) and D (6,9%). Among the patients who had tumor biopsy the majority were moderately differentiated HCC. Treatment for NASH-related HCC consisted of surgery in 11 patients (36,7%) (6 transplantation; 5 resection), transcatheter arterial chemoembolization in 11 patients (36,7%) and percutaneous ethanol instillation in 8 patients (26,6%). No patient was underwent radiofrequency ablation.

Conclusion: Cancer in our NASH patients preceded clinically advanced disease and could be diagnosed in the early stage in a screening program. Moreover, the association of NASH with HCC is not limited to patients with NASH-related cirrhosis. We observed HCC in 10,7% of patients without cirrhosis by multiple parameters including repeated biopsy, radiographic imaging and direct surgical inspection. Further investigation of these relationships is warranted to determine relative risk and the possible need for more aggressive screening in NASH patients.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2013

Epidemiology, staging and prognosis

ILCA2013-1218

Trends Of Hepatocellular Carcinoma (Hcc) In Hiv-Infected Patients Over Time, 1995 - 2011

Ting-Yi Chen^{1,7}, Luciana Kikuchi², Beatriz Mínguez³, Maribell Ventura³, Eugenia Vispo⁴, Marianne Harris⁵, Mamta K. Jain⁶, Emma Page⁷, Lynn E. Taylor⁸, Kristen Marks⁹, Marina Núñez¹⁰, Maria D. Hernández¹¹, Ziba Jalali¹², Erica Palys¹³, Nazia Qazi¹⁴, Rena K. Fox¹⁵, Ayse Aytaman¹⁶, Judith A. Aberg¹, Norbert Bräu^{17,18}, Liver Cancer in HIV Study Group¹⁹

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Presentation Method: Oral or Poster presentation

Would you like this abstract to be considered for the ILCA Junior Investigator Award?: Yes

Introduction: The incidence of HCC overall has been rising worldwide. Cases of HCC in HIV-positive patients have only recently been reported, and their frequency over time as well as trends over time is unknown.

Methods: HIV-infected patients with HCC (AASLD criteria) were retrospectively identified from 1992-2011 in 38 centers in North and South America, Europe, and Australia. Time of diagnosis was divided into earlier (1995-2005) and later years (2006-2011).

Results: Among 221 HIV-infected patients with HCC, the number of cases rose steadily between 1995 and 2011. Compared to diagnosis pre-2006 (n=102), patients with a diagnosis 2006 or later tended to be diagnosed through screening more often (63% vs. 52%, p=0.097), were on antiretroviral therapy more often (90% vs. 79%, p=0.022), and had lower HIV viral load (mean, 1.98 vs. 2.80 log copies/mL, p<0.001), higher median CD4+ cells (356 vs. 272 per mm³, p=0.001), and lower median AFP levels (87 vs. 727 ng/mL, p=0.001). They also tended to have effective HCC therapy more often (64% vs. 51%, p=0.053), mostly because of more frequent use of surgical resection (16% vs. 5%) and of sorafenib, which became available in 2007 (12% vs. 0%). There was no difference in age (mean, 51 years), etiology of HCC (HCV, 77%; HBV, 22%, non-viral, 1%), and tumor staging (BCLC stages C&D, 56% vs. 54%). Survival was significantly longer 2006-2011 (median, 16.2 vs. 7.4 months, p=0.004). In multi-variable Cox regression analysis, only screening, log HIV viral load, AFP <200 ng/mL, BCLC staging, and effective HCC therapy were independently predictive of survival but not year of diagnosis before or after 2006.

Conclusion: In HIV-infected patients with HCC, a diagnosis in 2006-11 was associated with better survival than one in 1995-2005. This was explained by better HIV viral control, more frequent HCC diagnosis through screening, more frequent HCC therapy, as well as a lower AFP level.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2013

Epidemiology, staging and prognosis

ILCA2013-1142

Impact Of Screening On Staging And Survival Of Hepatocellular Carcinoma (Hcc) In Hiv/Hcv-Coinfected Patients

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Presentation Method: Oral or Poster presentation

Would you like this abstract to be considered for the ILCA Junior Investigator Award?: Yes

Introduction: Current recommendations for HCC screening in HCV-infected patients with cirrhosis (liver sonography every 6 months) are based on expert opinions. No data are available for the effectiveness of HCC screening in HIV/HCV-coinfected patients.

Methods: HIV/HCV-coinfected patients with HCC (AASLD criteria) were retrospectively identified from 1992-2011 in 38 centers in North and South America, Europe, and Australia. Patients were considered screened if they initially presented with an abnormal AFP level or imaging study and not screened if they presented with symptoms.

Results: Among 167 HIV/HCV-coinfected patients with HCC, 95 (57%) were screened and 72 (43%) were unscreened. Screened patients were younger than unscreened subjects (mean, 51 vs. 54 years, $p=0.015$), abused alcohol less often (33% vs. 49%, $p=0.032$), and had a lower mean Child-Turcotte-Pugh score (6.8 vs. 7.7, $p=0.002$). They more often had HIV RNA < 400 copies/mL (77% vs. 53%, $p=0.001$) and had a higher median CD4+ cell count (340 vs. 273/mm³, $p=0.015$). Screened patients also had a smaller median tumor size (3.0 vs. 5.0 cm, $p<0.001$), more commonly met Milan criteria for liver transplantation (67% vs. 27%, $p<0.001$), and less often had portal vein thrombosis (12% vs. 28%, $p=0.008$) or extrahepatic metastases (8% vs. 26%). They also presented less frequently with advanced Barcelona-Clinic-Liver-Cancer (BCLC) stages C+D (39% vs. 67%, $p<0.001$) and more often received effective HCC therapy (75% vs. 36%, $p<0.001$). With adjustment for lead time of 8.1 months, screened patients had a longer median survival (14.1 vs. 3.9 months, $p<0.001$). In multi-variable Cox regression analysis, screening was independently associated with survival (H.R., 2.37; 95% C.I., 1.5 – 3.8; $p<0.001$) together with HCC therapy, BCLC staging and AFP level. Over time, the rate of patients diagnosed through screening improved, it was 48% in 1995-2001, 53% in 2002-2008, and 71% in 2009-2011.

Conclusion: Many HIV/HCV-coinfected patients with HCC had not been screened. Yet, screening was associated with earlier HCC stages, more HCC therapy, and independently predicted survival. In recent years, more patients with HCC were diagnosed through screening

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2013

Epidemiology, staging and prognosis

ILCA2013-1218

Trends Of Hepatocellular Carcinoma (Hcc) In Hiv-Infected Patients Over Time, 1995 - 2011

Ting-Yi Chen^{1,2}, Luciana Kikuchi², Beatriz Mínguez³, Maribell Ventura³, Eugenia Vispo⁴, Marianne Harris⁵, Mamta K. Jain⁶, Emma Page⁷, Lynn E. Taylor⁸, Kristen Marks⁹, Marina Núñez¹⁰, Maria D. Hernández¹¹, Ziba Jalali¹², Ayse Aytaman¹³, Erica Palys¹⁴, Judith A. Aberg¹, Norbert Bräu^{15,16}, Liver Cancer in HIV Study Group¹⁷

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Presentation Method: Oral or Poster presentation

Would you like this abstract to be considered for the ILCA Junior Investigator Award?: Yes

Introduction: The incidence of HCC overall has been rising worldwide. Cases of HCC in HIV-positive patients have only recently been reported, and their frequency over time as well as trends over time is unknown.

Methods: HIV-infected patients with HCC (AASLD criteria) were retrospectively identified from 1992-2011 in 38 centers in North and South America, Europe, and Australia. Time of diagnosis was divided into earlier (1995-2005) and later years (2006-2011).

Results: Among 221 HIV-infected patients with HCC, the number of cases rose steadily between 1995 and 2011. Compared to diagnosis pre-2006 (n=102), patients with a diagnosis 2006 or later tended to be diagnosed through screening more often (63% vs. 52%, p=0.097), were on antiretroviral therapy more often (90% vs. 79%, p=0.022), and had lower HIV viral load (mean, 1.98 vs. 2.80 log copies/mL, p<0.001), higher median CD4+ cells (356 vs. 272 per mm³, p=0.001), and lower median AFP levels (87 vs. 727 ng/mL, p=0.001). They also tended to have effective HCC therapy more often (64% vs. 51%, p=0.053), mostly because of more frequent use of surgical resection (16% vs. 5%) and of sorafenib, which became available in 2007 (12% vs. 0%). There was no difference in age (mean, 51 years), etiology of HCC (HCV, 77%; HBV, 22%, non-viral, 1%), and tumor staging (BCLC stages C&D, 56% vs. 54%). Survival was significantly longer 2006-2011 (median, 16.2 vs. 7.4 months, p=0.004). In multi-variable Cox regression analysis, only screening, log HIV viral load, AFP <200 ng/mL, BCLC staging, and effective HCC therapy were independently predictive of survival but not year of diagnosis before or after 2006.

Conclusion: In HIV-infected patients with HCC, a diagnosis in 2006-11 was associated with better survival than one in 1995-2005. This was explained by better HIV viral control through antiretroviral therapy, more frequent screening and HCC therapy, as well as a lower AFP level.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2014

Epidemiology, staging and prognosis

ILCA2014-1197

External Validation Of Art Score (Assessment Of Re-Treatment With Tace): A Single-Centre Cohort Study

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Presentation Method: Oral or Poster presentation

Would you like this abstract to be considered for the ILCA Junior Investigator Award?: Yes

Introduction: Recently, the ART score (assessment for re-treatment with transarterial chemoembolization) has been published to guide the decision for a second TACE in patients with hepatocellular carcinoma (HCC). Patients with an ART score of 0-1.5 points gained survival benefit from a second TACE session, while patients with an ART score ≥ 2.5 points did not. This study aimed to evaluate the prognostic performance of the ART score in an independent cohort of HCC patients.

Methods: A cohort of 49 patients, diagnosed with early and intermediate stage HCC and treated with at least two TACE sessions between November 2011 and December 2012 at the Instituto do Câncer do Estado de São Paulo, Brazil, was used for validation of the ART score. The ART score prior to the second TACE session was assessed in comparison the TACE naïve liver. The model's performance was assessed using Kaplan-Meier survival curves and log-rank test.

Results: Patients in the cohort had a median age of 63 years and 67% were men. Hepatitis C virus infection was present in 55% and 87% had a Child-Pugh class A. Most patients had multifocal HCC (65%), median tumor size was 37 mm and 61% was classified as intermediate stage (BCLC B). The ART score was 0-1.5 points in 65%.

Overall survival rates after 6 months was 90% vs 62% in patients with ART score 0-1.5 vs ≥ 2.5 points. But this difference was not statistically significant after one year (HR 1.52; CI 95% 0.62-3.72; p=0.36) (Figure). The overall survival in 1 year was 64%. The absence of prognostic differentiation may be explained by the better survival observed in our cohort for patients with ART score ≥ 2.5 points in comparison to the original cohort.

Image:

Conclusion: An ART score of 2.5 prior the second TACE does not identify patients with a dismal prognosis in our cohort. The sequential assessment of the ART score may improve in identifying patients with dismal prognosis prior to TACE sessions in our cohort.

References: 1. Sieghart W, Huckle F, Pinter M, Graziadei I, Vogel W, Müller C, Heinzl H, Trauner M, Peck-Radosavljevic M. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. *Hepatology*. 2013 Jun;57(6):2261-73.

Disclosure of Interest: None Declared

Abstract Submission for ILCA 2014

Epidemiology, staging and prognosis

ILCA2014-1198

Deviation From BclC Guideline And Influence On Survival Rate

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Presentation Method: Oral or Poster presentation

Would you like this abstract to be considered for the ILCA Junior Investigator Award?: Yes

Introduction: The Barcelona Clinic Liver Cancer (BCLC) staging system recommends first-line therapy for each tumor stage. We evaluated the effect of compliance with BCLC treatment allocation on the prognosis of patients with hepatocellular carcinoma (HCC). We have evaluated the applicability of the BCLC staging system and the effect of treatment allocation according to BCLC on the survival rate and prognosis in patients with HCC.

Methods: Treatment allocation for 364 consecutive, newly diagnosed HCC patients referred to our center were retrospectively analyzed during a 2-year period. For each stage, survival was compared according to whether treatment matched the BCLC recommendation. The survival rate was calculated using the Kaplan Meier method and compared using the simple Cox regression by stratum.

Results: Patients distribution according to BCLC staging system was: 9 patients (2%) in very early (O), 121 (34 %) in early (A), 85 (23%) in intermediate (B), 115 (32%) in advanced (C) and 34 patients (9%) in terminal stage (D). Only 189 patients (52%) were treated according to BCLC. Adherence to BCLC recommendations varied according to stage: 44%, 78%, 42% were adherent in BCLC 0/A, B and C/D stage, respectively. The overall survival rate in stage 0 and A was higher for patients adherent to BCLC guidelines in comparison with non-adherent patients (90% vs 58% in 2 years, $p < 0.05$ or HR 0,08 CI 95% 0,08-0,39 $p < 0.05$). However, this difference was not observed in patients BCLC B, C and D.

Conclusion: Deviations from BCLC recommendations occur in 48% of patients with HCC. Non-compliance to BCLC guidelines results in a decreased survival of patients diagnosed with HCC in BCLC stage 0 and A.

Disclosure of Interest: None Declared