上の高値，9例では1.5～1.9倍の高値がみられた。20例（13.1%）は治療前値の2倍以上のビリルビン上昇がみられた。

III. 肝癌治療法別にみた予後の比較

これまで，肝癌治療法別にそれぞれの治療法の優劣を比較した報告がみられる。外科治療と経皮的治療との比較に関しては，Kotoh ら[1]，Livraghi ら[2]が小型単発肝癌の治療ではPEIは肝切除との成績は同等であったとしている。Ryu ら[3]は3,225例の多施設多数例をretrospective studyで検討し，3 cm以下3個以内の肝癌で臨床病期I期の症例では，肝切除とPEIとで予後の差はなかったが，同様の肝癌で臨床病期II期の症例ではPEIの予後が良好であったとしている。日本肝癌研究会全国集計のデータ解析から，Arii ら[4]は臨床病期I期の2 cm以下単発肝癌，2 cmを超える単発肝癌，および臨床病期II期で2 cmを超える2個の多発肝癌の症例では，肝切除が選択された症例の予後が良好で外科治療の意義を報告している。Yamamoto ら[5]は，小型肝癌に行った肝切除とPEIの比較で，後者が再発率・生存率とも不良であるが，無作為化試験を行わないと評価は難しいとしており，これまでのretrospective studyと同様の結論となっている。

また，TAEを含む治療の比較では，Ryu ら[3]は，3 cm以上の肝癌で肝機能良好であれば肝切除がPEI・TAEより良いことを示唆し，Arii ら[4]も同様TAEの根治性が低いことを示している。Livraghi ら[6]はまた，RFAとPEIとの比較で，前者では完全壊死率が高く，多くの腫瘍に適応があるが，副作用が多かったとしている。Ikeda ら[7]もRFA治療はPEIよりも少ない治療回数で完全壊死が得られ，重大な副作用はなく推奨すべき治療としている。

IV. 再発形式からみた肝切除後の治療成績

RFA治療ではわずかながら局所治療部位からの再発が認められる。種々の肝癌治療法の中で，肝移植を除いて最も根治的（[illegible]取り除くことができる）治療は，[illegible]である。慢性肝疾患の背景疾患が[illegible]広い適応を持たない治療であり，[illegible]再発の率が高いことも事実である。[illegible]期の肝癌」を根治的に切除した成績[illegible]再発形式を通じて肝癌の治療法選択[illegible]考になると考えられる。

1980年代の切除例を主とした[illegible]例の研究[8]では，5 cm以下の肝[illegible]心性発癌は2.4%しかなく，肝内[illegible]発がほとんどであると記載して[illegible]能の十分でなかった時期であり，[illegible]「見落とし」に由来する結論か[illegible]

最近の報告では，精度の高い画[illegible]で高い技術で外科切除された[illegible]く，肝内転移再発が多かったと[illegible]い。Sugimoto ら[9]らは，177例の[illegible]再発のうち転移再発は35例に[illegible]例は細径針腫瘍生検の結果と異[illegible]られた。さらに，彼らは異時性[illegible]発の予後が不良であると述べて[illegible]ら[10]は，480例の切除後長期予後[illegible]例の3分の1は多中心性が考え[illegible]例の予後は良好であったが，短[illegible]襲度によることが多いとしてい[illegible]の報告も同様で，1年未満の早期[illegible]険因子は肝癌破裂・脈管侵襲であ[illegible]1年以後の晩期再発46例では肝[illegible]あったとし，早期に肝内転移，[illegible]の再発が多いと分析した。

Nakano ら[12]も，病理学的被[illegible]下・高分化・脈管侵襲なし・被[illegible]癌では，多発であっても多中心性[illegible]切除後予後も比較的良好であった[illegible]Kubo ら[13]も高分化型肝癌切除[illegible]発は，再発肝癌組織は一部に高分[illegible]ており，全例多中心性再発であ[illegible]いる。

最近ではウイルス学的側面を含[illegible]えている。Miyagawa ら[14]は，HC[illegible]

は多中心性発生の多発例が多いが，予後は HBV と HCV で変わらなかったとしている。Yamamoto ら[15]は，B 型で異時多発した肝細胞癌 8 例について再発腫瘍の clonality を検討したところ，6 例が多中心性，2 例が肝内転移と判断している。Maeda ら[16]らは，B 型で *de novo* 発癌が多い傾向があり，また分化度が低いことを指摘し，HBV と HCV で発癌過程に相違があることを推定している。

以上のように，肝癌治療後の再発は，局所再発と他部位再発に分けて考えることが必要であり，さらに後者は肝内転移再発と多中心性再発に分けて考えることが必要である。臨床的にこれらの区別を行うことは容易でないことも多いが，再発の少ない治療を選択し，再発抑制治療をいかに構築していくかという立場からは再発様式の理解は避けて通れない。

V．肝癌に対する経皮的局所療法と今後

肝癌は主としてウイルス性肝硬変を発生母地とするため，肝癌の治療に際しては，肝機能をできるだけ温存することが必要である一方，肝内転移や脈管侵襲をきたした結節を根治的に治療する目的からは十分に広い範囲の除去が必要である。外科的肝切除は後者を重視し現存する肝癌細胞をより十分に除去しようとするものであり，内科的局所治療は将来の新規の肝癌発癌に備えて，より肝機能の温存を図ろうとして発達してきた。1980 年代の PEI の時代にはともすると，肝機能温存を重視するあまり肝癌根治性の点では肝切除より劣る場面もみられた。しかし，PMCT を経て RFA が加わった現在，直径 25～30 mm までの肝癌であれば内科的局所療法で肝癌根治性と肝機能温存の両面で満足のいく治療ができる時代となった。

RFA が治療手段の一つに入ることにより，従来は肝癌が多発であるからという理由で，TAE・肝動脈抗癌剤動注などの interventional radiology にとどまっていた症例の一部は，より根治的な治療効果を目指す段階に引き上げることができた。これに伴って，RFA は「予後規定結節」という概念を実地臨床の場でより具体的なものとするであろう。実際にわれわれの病院で行われた RFA は多発例・再発例が多く，多発例では肝動脈塞栓が奏功しなかった結節のみを対象として行われる場合が少なくない。小型肝癌に対して少数回の治療で良好な壊死効果が得られる事実は，5 個以上の多発肝癌においても，最も生存を脅かす「予後規定結節」のみを治療するという考え方で，積極的な生存期間延長を図ることもできると考えられる。

また RFA の導入は，従来は多発結節で困難としていた肝切除の適応の場面で，大型の肝癌のみを外科切除するというふうに，外科医の考え方を柔軟なものに変化させつつある。

ウイルス性慢性肝疾患，特に肝硬変を基礎疾患とした肝癌症例では，根治的に肝癌治療を行っても，再発をきたすことが多く，異時性多発が避けられない。このため，異時的に種々の治療を組み合わせて行う症例は極めて多い。この慢性肝疾患・肝癌発癌の呪縛がある限り，集学的治療の中枢に RFA が位置することになろう。

強力な発癌母地であるウイルス性肝硬変から発生し，高率な発癌予測のもとに早期発見される特異な癌腫である肝癌は，他の癌とは異なったアルゴリズムによる診療形態が必要である。

本稿では主として，初発の肝癌に対する治療方法選択について述べたが，今後は肝内転移と多中心性発生とのさらなる鑑別の努力と治療方針の洗練，初発・再発病変の効率的な早期発見，発見された肝癌に対しては熟練した手技による集学的治療の洗練，信頼性の高い治療効果判定が求められる。慢性肝疾患が存在する以上，再発が不可避であることを認識し，発癌および再発抑制治療に努力は向けられるべきである。そして，再発率ではなく，良好な quality of life の上に立った生存率というものがより頻繁に治療効果判定に用いられると思われる。種々の modality の治療法を有効に採用するためにも，個々の治療方法がさらに客観的に比較されることが望まれる。

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2．ラジオ波熱凝固治療法各機種の比較

池田　健次

オ波凝固療法とマイクロ波凝固療法との違い

ジオ波凝固療法(RFA)は，周波数 460～480 kHz
波ラジオに近い周波数帯の電磁波を使用した熱凝
法であるが，同じく電磁波を使用したマイクロ波
療法(MCT)とはいくつかの点で異なっている．第
ラジオ波周波数帯は，生体を導電体とみなし体内
流を流すことができるのに対し，マイクロ波の周
帯の 2,450 MHz では，生体を絶縁体とみなし電圧
けることにより仕事をすることが大きな相違となっ
る．前者は抵抗加熱(ジュール熱)で組織加熱を行
に対し，後者は誘電加熱による熱凝固療法を達成
いる．このことは，後者が電流を流さないで何ワッ
仕事をするという表現しかしないのに対し，RFA
電流やインピーダンス(交流電流に対する抵抗値)
表現が可能で，RFA 機器では電流・インピーダン
よる凝固壊死過程がモニター可能である．第二に，
生のメカニズムとも関連して RFA と MCT とでは
固範囲の大きさが異なることがあげられる．一般
FA では種々のデバイスの工夫とともに大型の壊死
が得られやすく，MCT の治療効果より優れている．
に，MCT は，極性分子である水分子の振動により
加熱を行う原理に基づくが，これに伴う水分子の
の変化・解離電流の必要性などを考慮せねばなら
ことが RFA 機器を扱う点で異なる事項となってい

の他，MCT ではバイポーラ電極を用いるために，
RFA で用いられている下肢などに貼付する大型の
板(対極板)が必要ない点が有利で簡便な理由となっ
る．しかし，RFA でもバイポーラ電極は可能で，
針など電極形状の工夫で一本の電極針に絶縁部分
り二極間に電流を流すことは可能である．

熱発生の観点からみたラジオ波凝固治療

体組織に電流を流すことによるジュール熱発生は，
そのものに起こる変化であり，電極を熱すること
る熱凝固ではない．点電極から発する電流であれ
局所的に集中した電流(すなわち電流密度が高い)となるため，当該部位の細胞の水蒸気爆発に次いで組織の炭化を起こすため組織の絶縁化を経て，それ以上の電流発生が起こらなくなる(すなわち組織の切開作用)．結局，電気メス型の点電極を用いた場合には小範囲の炭化にとどまり，期待する大きさの組織壊死が得られないことになる．電流密度を低くし組織の過剰な温度上昇を起こさない電磁波的な工夫として，連続通電の代わりに間歇通電(パルス通電)を行うことも広い熱凝固範囲を得るための条件である．

このことを解決するために，RITA・RTC システムでは，複数の電極が傘型に展開する形状として，電流密度が高くなりすぎることを防いでいる．Cool-tip 電極では，非展開型の単針の電極を用いているが，電極内の冷却装置により電極付近の組織の高熱化・炭化を防ぐとともに，その周囲に発生した熱が遠方に伝導しやすい物理学的特徴を備えている．

熱発生は，電極に与えた電圧と組織(肝癌部および周囲の非癌部肝組織)に流れた電流の積に比例し，さらに通電時間を乗じ，これを熱容量(比熱×組織質量)で除した値となる．言い換えれば，与えられた組織の比抵抗が一定として考えると，熱発生は電流の二乗に比例し熱容量に反比例する形となる．RFA で使用されている電極は形状が異なるものの全て棒状電極であり，電極からの距離が 2 倍になれば，電流密度は 1/2 になり，温度上昇は 1/4 に低下することがわかる．

最終的には，蛋白凝固を起こすに十分な温度を一定以上の時間持続するか，凝固の結果として起こる組織のインピーダンス上昇を確認することが，ラジオ波治療の目標になる．現行のラジオ波凝固治療は，電磁波発生の観点からは組織での蒸気爆発防止のために棒状電極を用い，組織の炭化防止・壊死範囲拡大の観点からは出力制御を行い，また凝固終了の監視のために温度または組織のインピーダンスをモニターするという各点において，3 機種共通のコンセプトのもとに作られている[1,2]．

の門病院消化器科

わが国で使用されているラジオ波機器の特性

(1) RITA(Radiofrequency interstitial tissue ablation, RITA Medical System, USA)

電極は展開型針で，電極先端部に電子的な温度計が装着されており，熱凝固過程が組織の温度上昇でモニターできることが特徴になっている．一定以上の温度上昇(80°C，105°Cなど)が一定以上の時間持続することを目標にして，組織内温度により出力制御が行われる．すなわち，組織の凝固達成度(水分の枯渇状態すなわちインピーダンス上昇)よりは組織の加温状態持続をモニターすることで電磁波出力を制御する唯一の機種である．現在は3 cmの凝固域を目的とするmodel 70と，5 cmに対応するmodel 90とが使用可能で，ジェネレータは最大150 Wの出力を有している．

(2) RTC(Radiofrequency tissue coagulation, Boston Scientific社，USA)

形状記憶金属を使用した展開型針(LeVeen針)でもっともシンプルな構造からなっている．アルゴリズムに従った電気出力の段階的な上昇を行い，組織が急速で不均一な熱凝固を防ぎつつ組織壊死を広げるものである．電磁波出力は，全展開針から得られる組織のインピーダンス全体を持続的にモニターすることで行い，組織の凝固が達成(インピーダンスの急上昇：「roll-off」)できると電流が流れない状態となり，出力を停止する．RITAでのモニターが凝固温度維持であるのに対し，RTCでは凝固達成による組織状態の変化を捉える形式である．組織の凝固過程は，時間経過に伴い各展開針先端部より起こり，これが順次電極近位部に及ぶことが実験的に確認されているが，目的とする凝固を達成するには比較的高出力を要する．当初より製造者側から提案されている出力アルゴリズムでは，3 cm以上の展開針でroll-offが達成できない頻度が少なくなく，電流密度が低すぎることに由来すると考えられている．良好な凝固達成は，電極の段階的展開法で解決でき，総出力が低く抑えられるとともに，治療時間も短くてすむ[3]．

(3) Cool-tip RFシステム(Cool-tip radiofrequency system, Tyco Healthcare Group LP, USA)

唯一，電極に展開針を用いない形状である．単針の内部に冷却水灌流のための管が内蔵されており，熱凝固の仕事を行う電極先端が加熱してしまわない工夫がなされている．熱伝導的には電極自体の加熱が起こらないために，熱が遠くまで伝達しやすい特性を示しており，非展開型で表面積の小さな電極で大きな凝固範囲を達成する大きな理由[illegible]電磁波出力の制御は組織のインピーダ[illegible]基本で，凝固過程が進むと組織にかか[illegible]ことにより出力を低下させ，電極周囲[illegible]固・炭化を防ぐ．冷水により電極温度[illegible]や，熱凝固過程の確認のために温度を[illegible]とが可能である．

展開型・単針型による治療適応と[illegible]

肝内治療部位に穿刺した電極が呼吸[illegible]のずれが起こる場合には，展開針を使用[illegible]状となった電極がこれを防ぐために[illegible]な治療が可能である．肝表面などの腫瘍[illegible]に肝癌に対して微妙な穿刺手技が必要[illegible]針先のずれ防止には有用な形状である[illegible]的に展開する電極の全てが超音波では[illegible]め，一本一本の針が肝外に突出したり大[illegible]たりする可能性があり，腫瘍の存在部位[illegible]術的に注意せねばならない．

単針のCool-tip電極では，穿刺した[illegible]接の肝内の構造を損傷することはない．[illegible]治療でも肝外に展開針が突き出ることが[illegible]全ではあるが，熱伝達による周囲組織[illegible]るわけではないので注意を怠ってはなら[illegible]電極では，治療後に肝癌の肝内播布が多い[illegible]かとの報告も見られたが，多数の報告例[illegible]体として展開針との差はないと考えられ[illegible]

凝固過程のモニターの方法によ[illegible]

温度モニターにより治療過程が進む[illegible]RF[illegible]ピーダンス変化を捉えて治療を行うRTC[illegible]式では，治療に関してのコンセプトがわず[illegible]温度モニターでは「凝固努力反映」的であ[illegible]インピーダンスモニターは「凝固成果反映」[illegible]これは両者のいずれかに優劣があることを[illegible]のでもなく，逆にいずれの方式にも弱点が[illegible]認識すべきである．十分な組織温度上昇が[illegible]凝固・組織凝固が起こるが，数点のサンプ[illegible]温度上昇の起こりにくい部分が把握でき[illegible]近傍，脂肪組織の存在，被膜の存在などが[illegible]る温度上昇に影響する因子である．一方[illegible]ンス上昇は，組織温度上昇の結果，組織[illegible]発し，乾燥した電流の流れない組織に変化[illegible]示している．インピーダンス上昇は「成果[illegible]はあるが，組織変化が電極近傍に起こっ[illegible]

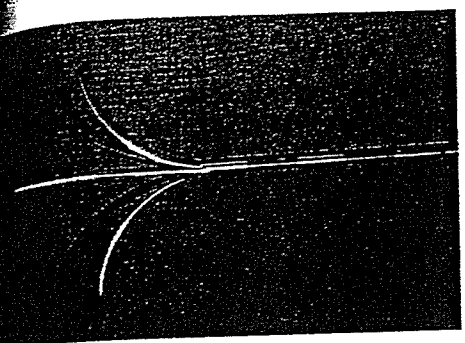

図1　直径5 cm 凝固対応の RITA 針(model 90)

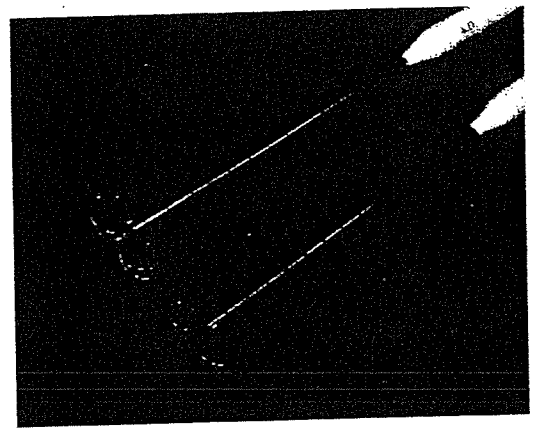

図2　30 mm 凝固針と並べた 40 mm 凝固用 LeVeen 針(RTC)

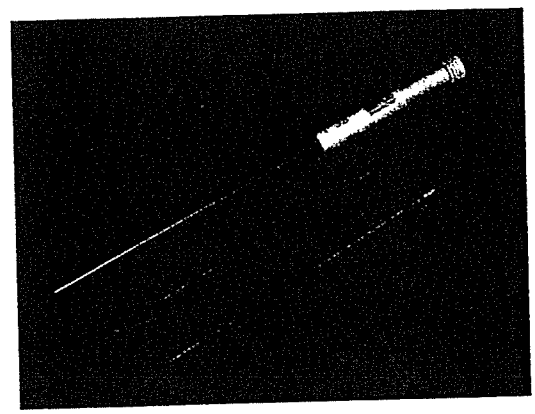

図3　専用外筒針とこれに対応した LeVeen 針(CoAccess Needle Electrode)

れないし，期待する球形ではなく不整形の凝固域
成されただけかもしれない．インピーダンス上昇
局所の炭化，末梢展開電極周囲の大型血管の存
血流状態が影響する．

ラジオ波機器と合併症

ラジオ波治療中の疼痛は，一般的に出力エネルギー
きさに比例する．大型血管によるラジエータ効果
こらない良好な部位に穿刺された RITA 針では，
上昇が良好となるため，凝固進行中の出力エネル
が抑えられ，疼痛は軽い．同様に RTC でも cool-
でも，マニュアル操作で出力を抑えつつ緩徐に治療
うと疼痛は軽減する．

開針で懸念されている，超音波で必ずしも把握で
いような「3 次元的に展開した電極針による合併症」
報告はほとんど見られない．胆管手術の既往，Oddi
の機能不全による胆管系合併症は，肝門部のみなら
比較的肝臓末梢部の凝固治療を行っても起こりうる
併症であり，RFA の治療適応は厳密に決定する必要
る．

機種全てが熱凝固に基づく腫瘍壊死を目指すもので
，熱発生に伴って起こる肝臓近傍の臓器障害，と
胆のう炎・消化管穿孔などのリスクは同様である．

大型肝癌に対する各 RFA 機器の対応

一世代」の RFA 機器は，いずれも 3 cm 以下の腫
の制御を目的として開発されている．その後は 3 機
もに，より大型の肝癌に対応できるデバイスを開
ており，実際に使用可能となってきている．

ITA・Model 90(図 1)は，直径 5 cm の腫瘤の凝固
可能となるように展開径が 5 cm となる大型電極であ
一定温度を達成し，大きな凝固径を作るために電
波出力は最大 200 ワットまで高める設定が必要であ
る．

RTC では，40 mm の展開針(図 2)と 200 ワット出力が可能なジェネレータ(RF-3000)の組み合わせで 4 cm の凝固ができる．さらに 30～35 mm の細径タイプの電極針と専用外筒針との組み合わせ(図 3)で，凝固前に複数の外筒針を穿刺しておくことで，大きな腫瘍全域に計画的に電極針を配置・凝固することが可能である．

Cool-tip システムでは，早くから cluster 針タイプ(図 4)が発表されている．これは 1 本針の電極を 3 本束ねた形状のもので，直径約 5 cm の凝固域を達成する．3 本の電極を同時に刺入していくため，外側区域であれば心窩部から刺入が容易であるが，右葉であれば 1 cm 以上の幅が確保できる広い肋間が必要である．

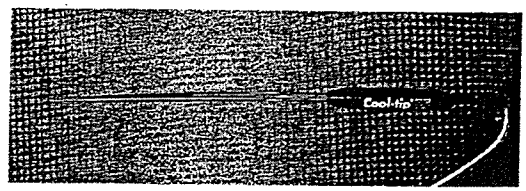

図4　直径5 cm凝固に対応するCool-tip型電極

これまでに，肝癌内に液体などを注入する方法，肝動脈塞栓術を併用する方法，ラジオ波凝固中に肝動脈をバルーンで閉塞する方法など他のインターベンションを組み合わせることで，ラジオ波凝固の壊死域を拡大させる工夫がさまざまに行われてきたが[7〜10]，実際にはラジオ波機器のデバイスの工夫によりその多くが解決されつつある．デバイスの大型化・高出力化に伴い大型の壊死域が得られるようになったが，凝固域は必ずしも期待される球形のものではなかったり，胆管損傷や肝臓内外の合併症の可能性が増加したりする一方，対象腫瘍が大型化していることに由来する再発率の高さなどが問題として残されており，外科的肝切除の適応上の棲み分け，合併症を避けるための機器以外での工夫が今後の課題として残されている．

いずれにせよ，RFAが小型肝癌の標準的治療の一つとなった現在，RFAを臨床で100%以上活用していくためには，個々のジェネレータとデバイスの特性を十分に把握し，長所と弱点とを理解したうえで技術的な研鑽をすることが必要である．

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胆管細胞癌の病因としてのC型肝炎ウイルス感染

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肝細胞癌の病因は、化学物質やB型肝炎ウイルス(HBV)・C型肝炎ウイル(HCV)など、その原因・背景病変の90％以上が判明している。これに対し原発性肝癌の1割を占めるといわれる胆管細胞癌の病因についての研究進んでおらず、危険因子や背景病変は不明であった。ここでは疫学的動向ともに胆管細胞癌のリスク要因について述べたLazaridisらおよびShaibらの報告を紹介する。

胆管細胞癌は世界的に増加傾向にある

肝内胆管細胞癌と肝外胆管細胞癌解剖学的な部位によって分類する従来の方法は、さまざまな点で臨床的に有用であることから汎用されてきた。Lazaridisらは、アメリカにおいて胆管細胞癌が増加傾向にあり、このうち肝外胆管細胞癌は減少傾向であるのに対し肝内胆管細胞癌は明らかな増加傾向にあることを報告している[1]。具体的には、人口10万人あたりの肝内胆管細胞癌患者が1975～80年の0.32人から1995～2000年の0.85人へと増加したとしている。しかし、一方で肝外胆管細胞癌患者は1.08人から0.82人へと減少したとしている。

そのほかにも世界的に胆管細胞癌の発生数は増加しているとの報告がある。わが国では「厚生の指標」に死因分類・癌腫分類が記されているが、原発性肝癌として一括されているために、胆管細胞癌の実際の発生頻度は不明である。最も新しい肝癌研究会による全国調査(2000～01年)では、胆管細胞癌の発生数は724人(原発性肝癌の3.63％)とされ、10年前の調査(1990～91年)の322人(同2.7％)から増加している。

胆管細胞癌の危険因子

Lazaridisらは、近年のアメリカでの胆管細胞癌の増加を受けて、その発症の背景因子をレビューしている。

そこでは以前から知られていた胆管細胞癌の危険因子について、「65歳以上の高齢者」という一般的なリスクを除くと、「肝・胆道系疾患(原発性硬化性胆管炎)」「肝吸虫」「Caroli病」「総胆管嚢胞」「胆管腺腫」「胆道系乳頭腺腫症」「肝内胆石」などをリスク要因としている。

次いで、「トロトラスト」「ダイオキシン」「塩化ビニル」などの化学物質や環境汚染物質を挙げ、最後にHCVが肝内胆管細胞癌に関連するとした最近の報告が紹介されている。

Lazaridisらは、依然として「胆管系の炎症病態」が胆管細胞癌の原因であるとしたが、これらは肝外胆管細胞癌のリスクになることが多く、肝内胆管細胞癌のリスクとしてはHCV感染を挙げたにとどまっている。

Shaibらは、population-based の症例対照研究により、これまでに報告されてきた胆管細胞癌の危険因子と新たに明らかになった危険因子を検討している[2]。以前から知られていた胆管細胞癌の危険因子としては、「胆管炎」「先天的胆管拡張」などが挙げられるが、これらは主として「肝外胆管細胞癌」との関連が想定されるものである。Shaibらがここで検討したのは、625例の胆管細胞癌症例と90,834例の非癌対照である。この症例対照研究では、65歳以上の胆管細胞癌症例に対して、年齢と性別を合致させた対照を集めたのではなく、同時期に同じ情報量のある同地域在住の65歳以上の「非癌対照者」であったことに留意すべきであろう。

検討の結果、胆管細胞癌患者では対照に比して「2歳高齢(p=0.02)」で「男性が多い傾向(p＜0.001)」であったことが背景の違いとしてまず挙げられている。

また、「年齢」「性別」「人種」「居住地」などを補正した多変量解析(表)では、①非特異的肝硬変(補正オッズ比27.2、p＜0.0001)、②アルコール性肝硬変(同7.4、p＜0.0001)、③HCV感染(同6.1、p＜0.0001)、④HIV感染(同5.9、p=0.003)、⑤糖尿病(同2.0、p＜0.0001)、⑥炎症性腸疾患(同2.3、p=0.002)、などが胆管細胞癌症例に有

意に多い背景要因であったとしている。

Shaibらは、本研究の検討結果が胆管細胞癌のどれだけの症例を説明できるかは別として、結論的に「HCV感染」「HIV感染」「肝硬変」「糖尿病」が発癌に強く関連していると述べている。このうち、胆管細胞癌の原因として比較的特異的といえるものは、「肝硬変」「アルコール性肝硬変」「HCV感染」「炎症性腸疾患」であり、高危険群の設定に必要な要因になりうると考えられる。

HCVと胆管細胞癌の関連についてのわが国での研究

慢性肝疾患やHCV感染が胆管細胞癌と関連していることは、すでにわが国で報告されており、このうちYamamotoらは胆管細胞癌切除50例の症例集積研究で、16例(32%)がHCV抗体陽性であることを示している[3]。Kobayashiらは600例のC型肝炎による肝硬変のレトロスペクティブなコホート研究で、7.2年間に14例の胆管細胞癌発癌がみられたとしている。また、彼らは初めて「胆管細胞癌発癌率曲線」を示し、いずれもHCVと胆管細胞癌との強い関連性を述べている[4]。最近では、Yamamotoらも症例対照研究で、HCV抗体陽性例では6.02のオッズ比で胆管細胞癌のリスクがあるとしており、この分野でのわが国の研究が一歩進んでいることを示した[5]。

胆管細胞癌の病因と今後の課題

最近の研究では、肝内胆管細胞癌の原因として、「HCV感染」「慢性肝疾患(肝硬変)」が最も関連する「基礎疾患」であり、これに次いで、「炎症性腸疾患」「B型肝炎感染」が挙げられている[6]。これら「特異的な基礎病態」に加えて、「加齢」「糖尿病」「HIV感染」など、癌化を促進する非特異的な要因が加わっているというのが現在の胆管細胞癌の原因病態分析の結果である。今後は、肝内胆管細胞癌と肝外胆管細胞癌という分類の妥当性の検討、そしてこれらそれぞれについてさらに特異的な病態・病因分析が行われることが必要であろう。加えて高リスク群設定が胆管細胞癌の早期発見に役立つか、C型肝炎感染者からの胆管細胞癌発癌予防が実証されるかなどの課題が残されている。

表　肝内胆管細胞癌発癌に関連する危険因子
(「年齢」「性別」「人種」「居住地」を患者登録法で背景を合致させた多変量解析)

	補正オッズ比	95%信頼限界	p値
慢性非感染性肝疾患			
非特異的肝硬変	27.2	19.9～37.1	＜0.0001
アルコール性肝硬変	7.4	4.3～12.8	＜0.0001
ヘモクロマトーシス	1.1	0.3～4.3	0.9
感染性			
HBV	0.8	0.1～5.9	0.8
HIV	5.9	1.8～18.8	0.003
HCV抗体など	5.2	2.1～12.8	＜0.0001
HCV(非特異的肝炎を含む)	6.1	4.3～8.6	＜0.0001
胆管病変			
胆管炎	8.8	4.9～16.0	＜0.0001
総胆管結石	4.0	1.9～8.5	0.0004
胆汁うっ滞	6.7	2.7～21.6	＜0.0001
先天性胆管異常	3.0	0.4～21.6	0.3
その他の危険因子			
喫煙	1.8	1.2～2.7	0.007
糖尿病	2.0	1.6～2.4	＜0.0001
炎症性腸疾患	2.3	1.4～3.8	0.002

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Quarterly Review

Locoregional therapy for hepatocellular carcinoma

KENJI IKEDA, HIROMITSU KUMADA

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide, with an annual incidence reaching one million new cases.[1,2] In about 90% of patients, HCC is a late complication of cirrhosis.[3] The 5-year incidence of HCC in cirrhosis is 15%-20%.[4,5] The risk of developing HCC has been reported to be 0.5% per year for hepatitis B and 5% per year for hepatitis C.[5,7] Accordingly, the incidence of HCC directly correlates with the epidemiology of the causes of cirrhosis, which is essentially from alcoholic and viral origins.[3] Chronic hepatitis B and C infection appears to be the most important risk factor for HCC. There is, however, a heterogeneous geographical distribution because of its association with chronic viral hepatitis.

In high-risk areas such as Southeast Asia, China and sub-Saharan Africa the prevalence is > 100/100,000 population. Although less common is Western countries, the annual incidence increased from 1.4/100,000 in the period 1976-80 to 2.4/100,000 between 1991 and 1995.[8] In the particular case of the hepatitis C virus (HCV), it takes up to 20 years to develop HCC from chronic viral infection, so that the massive dissemination of this virus in the 1970s and 1980s is now beginning to induce a marked rise in of the incidence of HCC in Western countries. HCC is now emerging as a major health concern for the next decades.[8-11]

The hepatitis B virus has a specific oncogenic action by integration in the host DNA causing chromosomal rearrangements. Another mechanism is inflammation and repeated cycles of necrosis and regeneration associated with chronic inflammation and cirrhosis. Chronic hepatitis C infection, although less prevalent than hepatitis B infection, is another major causative factor for HCC. Alcoholic cirrhosis, hemochromatosis, primary biliary cirrhosis, and autoimmune cirrhosis also increase the risk of developing HCC, with alcohol-induced cirrhosis playing a particularly important role in Western countries.[12,13]

Most patients develop few symptoms while the tumour is small and often present late with multifocal disease. The natural course of HCC is progressive tumor growth compromising hepatic function, intrahepatic metastases and spread to distant sites. In general HCC has a poor prognosis, with a median survival of 3-6 months after the onset of symptoms.[14]

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Nowadays, an increasing number of HCCs are discovered at an early stage because of increasing awareness and screening of asymptomatic patients with cirrhosis.[15] Percutaneous locoregional therapy became a therapeutic option for a small HCC associated with cirrhosis during the last decade, because of poor liver function reserve and a high recurrence rate after surgical resection.

GENERAL CONSIDERATION FOR LOCAL ABLATION THERAPY

A careful clinical, laboratory, and imaging assessment has to be performed on each individual patient by a multidisciplinary term to evaluate eligibility for percutaneous ablation. Cirrhotic patients with a small HCC nodule are candidates for surgery and percutaneous ablation.[16] Multiple percutaneous image-guided therapies currently are available for thermal ablation of localized solid tumors. Thermal sources for these treatment modalities include high-intensity ultrasound, laser, microwave, and radiofrequency.[17,18]

Radiofrequency ablation (RFA) is a safe, predictable, and inexpensive option and has emerged as the thermal modality that most easily can create large volumes of tissue necrosis. The predictability of RFA is adequate to limit collateral damage and complications, however, is limited by biologic and anatomic variability of tissue. The tumor to treat by RFA must be focal, nodular-type lesion. The presence of a clear and easy-to-detect target for needle placement is crucial for the outcome of treatment. Tumor size should be preferentially smaller than 3 to 5 cm in greatest dimension. When using thermal methods of tissue destruction, some additional points are considered. Treatment of lesions adjacent to the gallbladder or to the hepatic hilum risks thermal injury of the biliary tract. Lesions located along the surface of the liver can be considered for thermal ablation, although their treatment requires experienced hands and may be associated with a higher risk of complications. A careful assessment of the coagulation status is mandatory before percutaneous ablation. A prothrombin time ratio (normal time/patient's time) greater than 50% as well as a platelet count higher than 50,000/microliter are required to keep the risk of bleeding at an acceptable low level.

Percutaneous ethanol injection (PEI) is a well-established technique for tumor ablation.[19] PEI induces local tumor necrosis as a result of cellular dehydration, protein denaturation, and chemical occlusion of tumor vessels. It is best administered by using ultrasound guidance because real-time control allows for a faster procedure, precise centering of the needle in the target, and continuous monitoring of the injection. Fine non-cutting needles, with either a single end hole or multiple side holes, are commonly used for PEI. PEI is usually performed under local anesthesia on an out-patient basis. The treatment schedule typically includes a few to several sessions performed once or twice weekly. The number of treatment sessions, as well as the amount of ethanol to inject, may vary greatly according to the size of the lesion, the distribution of the injected ethanol within the tumor, and the compliance of the patient. Several studies have shown that PEI is an effective treatment for small (3 cm or less), nodular-type HCC. HCC nodules have a soft consistency

and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively, leading to complete tumor necrosis in about 70% of the small lesions.[20]

CRYOSURGERY

Cryotherapy was the first technique employed for localized thermal ablation. The use of cryotherapy for treating liver tumors was first described by Cooper in 1963.[21]

Cryotherapy is a method of tumor ablation that uses cooled probes to freeze and destroy areas of tissue measuring up to 8 cm in diameter.[22] The ablative process is carried out by delivering the subfreezing temperature (-20 to -30 degree centigrade) to the target lesion via a penetrating vacuum cryo-probe. The resulting freeze/thaw process causes irreversible cellular damage by different mechanisms. First, the intra- and extracellular ice formation during the freezing process causes direct physical damage by cellular compression, membrane rupture and protein denaturation.[23,24] Second, the freezing process increases the intra- and extra- cellular electrolytes concentration. This, in turn, results in lipoprotein denaturation and, during the thawing process, the highly concentrated cytotoxic free radicals are released. Third, cells are later killed by post-thaw ischemia and infarction as a result of microvascular thrombosis.[25,26]

The procedure is currently predominantly performed intra-operatively, because probes measuring 3 mm in diameter or large are necessary to deliver optimal quantities of liquid nitrogen to the probe tip. Cryo-probes measuring 3-10 mm are usually used. Larger probes tend to produce large areas of tissue destruction (6-8 cm), whereas smaller 3 mm probes produce approximately 3-3.5 cm of tissue destruction. However, as for other methods of minimally-invasive therapy, the proportion of patients who might be usefully treated with this technique is not yet well established. Although cryo-ablation is not seriously considered as a minimally invasive therapeutic option for HCC, several investigators have reported the use of cryoablation for HCC. Zhou et al.[27] reported the use of cryosurgery for the treatment of 60 patients with primary liver cancer, in 1970. Survival at 1, 2, 3, 4, and 5 years was 52%, 34%, 21%, 16% and 11%, respectively. Among the 21 patients with tumor nodules less than or equal to 5 cm in diameter, survival was increased to 76%, 62%, 50.0%, 41% and 38%, respectively. In 1993 Zhou et al.[28] reported a larger series of 113 patients with hepatic cancer, including 107 patients with primary liver cancer and 6 patients with hepatic metastases, who were treated with cryotherapy using similar technique. The 5-and 10-year survival rates were 22% and 8%, respectively, for the 107 with HCC and 49% and 17%, respectively, for the 32 patients with small (< 5 cm) tumors.

LASER THERMAL ABLATION (ILT)

Laser ablation or interstitial laser photocoagulation is another method for inducing thermally mediated coagulation necrosis that has been used for percutaneous tumor ablation. Interstitial laser therapy has been used to treat liver tumors since 1985.[29] Laser is a monochromatic, collimated and coherent radiation with a wavelength of 1024 nm produced by a Nd:YAG generator, which concentrates extremely high energy in small localized areas. It may be transmitted inside the tumor by single or multiple quartz optical fibers inserted through fine needles (21 gauge), thus converting the intense light energy to tissue heating. The laser provides sufficient energy to allow for significant heat deposition surrounding the fiber tip, inducing protein denaturation and cellular death.[30] Thermal profiles have been demonstrated to correlate well with the extent of coagulation necrosis observed histopathologically,[31,32] as well as with ultrasound[32,33] and T1-weighted MR images.[34,35]

Tumors of 1.5-2 cm size can be treated with a single fiber, while larger nodules require the splitting of the laser beam with the insertion of multiple fibers (up to four) by 20 to 21 gauge fine needles, whose precise positioning may be technically difficult. Laser ablation has been mainly used in the treatment of liver metastases,[36-38] while data available on the laser treatment of HCC is limited. Gilliams et al.[39] reported an 86% 1-year survival of 55 patients with colorectal liver metastases and that the mean survival from the detection of metastases was 18 months. Vogl et al.[40] fond that Laser is effective for small liver tumors, with a local control rate of 44% in 1 year. A subsequent study by the same group of authors was performed on 88 patients with colorectal liver metastases.[41] There was a 95% tumor response rate and the mean survival was 35 months. This encouraging result was further supported by a recent study on 676 consecutive patients with malignant liver tumors.[42]

Few studies published to date have long-term follow up of patients. To date, there are few data on the clinical efficacy of laser for HCC.[43-46] Giorgio et al.[43] treated 85 patients with HCC of 1-6.6 cm with one to four laser fibers inserted and single or multiple sessions, obtaining a complete necrosis in 82%. In the study of Pacella et al.[45] 92 patients with HCC of 4 cm were treated with multiple fiber insertion, with an average of 1.3 sessions per tumor. Complete necrosis was obtained in 97%, while a mean follow-up of 25 months showed a local and elsewhere recurrence of HCC in 6% and 49%, respectively. The same investigators treated 30 large HCC (3.5-9.6 cm) by laser thermal ablation followed by segmental transarterial embolization at 30-90 days, obtaining complete tumor necrosis in 90%, with cancer-free survival rate at 1- and 2-years of 74% and 34%, respectively.[46]

Nevertheless, the major limitation of interstitial ablation therapy is the small volume of tumor ablation, although the current new devices may help to overcome this limitation. In practice, laser ablation is not indicated for large liver tumors.

ETHANOL INJECTION

Intra-tumoral injection of ethanol causes dehydration, intracellular coagulation, necrosis, vascular occlusion, and fibrosis of the tumor; it may benefit patients with small tumors and underlying liver disease that limits resectability.

Although there have not been any prospective randomized trials comparing PEI and surgical resection, several series have shown that the long-term outcome of selected PEI-treated patients was similar to that of patients who had undergone resection, with 5-year survival rates of 35-59%.[47-51] A large series from Japan indicated that patients with small (<5 cm) tumors treated with this approach had a 3-year survival rate of 53%. These results are similar to those reported for surgical

resection and are better than those for chemoembolization.[52] Patients with lesions less than 3 cm in diameter had a survival rate of 94% at 1 year, 63% at 3 years, and 29% at 6 years. Survival is better for patients with Child-Pugh stage A or B cirrhosis than for those with stage C. Reported recurrence rates are 29% within 1 year and 63% within 3 year after treatment.[53]

Side effects include mild to moderate pain after needle withdrawal, and fever (>38 degree C°) starting on the day of the procedure and lasting for 2 to 3 days.[53] While PEI is a low-risk procedure, severe complications, including cases of tumoral seeding, have been reported.[54]

The major limitation of PEI, besides the uncertainty of tumor ablation and the long treatment time, is the high local recurrence rate, that may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3cm.[55,56] These high rates of recurrence suggest that this approach treats only the injected lesions and not microscopic or multi-focal liver disease or metastasis.

The injected ethanol does not always accomplish complete tumor necrosis because of its inhomogeneous distribution within the lesion -especially in the presence of intratumoral septa- and the limited effect on extracapsular cancerous spread. Also, PEI is unable to create a safety margin of ablation in the liver parenchyma surrounding the nodule, where satellite nodules are most frequently located.[57]

MICROWAVE COAGULATION (MCT)

Microwave thermal tissue coagulator emits 2,450 MHz electromagnetic radiation. Alternating radiofrequency current agitates ions in the tissue surrounding the needle, creating frictional heat, which denatures and destroys tissue at predictable temperatures, in a relatively predictable volume. Microwave coagulation therapy has been studied mainly in patients with HCC, whereas there are only a few reports of MCT for liver metastasis.[58,59] Percutaneous MCT is applicable for a small HCC (<3 cm).

In an early series, Seki et al.[60] reported complete ablation in 18 patients with small HCC of <2cm, and there was neither any complication nor local recurrence after a short follow-up period of 11-33 months. The response rate of small HCC (<3 cm) to percutaneous MCT is up to 70%, but is only 55% for large HCC (>3 cm).[58] Recently, a larger series has been published, including 50 patients with 107 HCC (mean size 2.7 cm) treated with single or multiple microwave sessions. Complete necrosis was attained in 98% of nodules < 2 cm and in 92% of nodules > 2 cm, with a recurrence rate at 1 year of 45%.[61] Well-differentiated HCC and those superficially located on the liver surface are associated with better prognosis after percutaneous MCT.[58,59,60,62]

Laparoscopic MCT allows effective ablation of large HCC (up to 5 cm) on the liver surface, as it can be safely performed under direct visual guidance as well as with laparoscopic ultrasonography.[63] Using minimally invasive surgery techniques, Seki et al.[64] advocated laparoscopic MCT under local anesthesia and reported complete tumor ablation in 87.5% of patients with small HCC (mean size=2 cm). Another endoscopic technique of MCT using the thoracoscopic trans-diaphragmatic approach has been suggested by Yamashita et al.[65] to treat HCC located just below the diaphragmatic dome, for which percutaneous MCT is impossible and open MCT requires a large incision. Open MCT can be used to ablate large HCC (maximum of 6.5 cm) and tumors whose location is unfavorable for percutaneous or laparoscopic MCT.[66] However, open MCT is contraindicated in tumors at the liver hilum or close to the diaphragm, as injury to bile ducts and/or the diaphragm is possible.

Although the short-term efficacy of MCT appears to be encouraging, there are limited reports on long-term survival. The overall 3-year survival rate reported was 73-86%.[61,67,68] In addition, Itamoto et al.[68] reported a 48.6% overall 5-year survival rate and a 50% overall 4-year survival rate for patients with primary and recurrent HCC, respectively. Disease-free survival depends on local as well as distant tumor recurrence.

The complications of microwave coagulation therapy include abscess formation, biloma, bleeding, hepatic failure and intraperitoneal dissemination of cancer cells.[59,69]

Shimada et al.[59] found that the complication rate in microwave therapy was significantly higher in patients with large (>4 cm) and more advanced tumors and the authors recommended MCT be reserved for liver tumors < 4 cm. With the available technology, microwave ablation seems to be effective in tumors of 2 cm, but requires the insertion of multiple large needles and repeated treatment sessions in case of tumors more than 2.5 cm in diameter.

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) is a relatively new technology that allows for focal coagulation necrosis of hepatic tumors by producing thermal energy with an alternating electric current generator at a radiofrequency of 200 to 1,200 kHz. Percutaneous thermal tissue ablation using radiofrequency current is performed, by keeping the patient in an electrical circuit with adhesive grounding pads on the thighs or back. A needle with a plastic-insulated shaft is usually placed into the tumor percutaneously with imaging guidance, under local anesthesia. It may also be used at laparoscopy or at laparotomy. Complete ablation can usually be achieved in one to two sessions.

Major progress in RF technology was achieved with the introduction of modified electrodes. The devices most frequently used are made by three companies: Radiotherapeutics, Sunnyvale, Calif.; RITA Medical Systems, Mountain View, Calif.; and Radionics, Burlington, Mass.[70,71] Each of the devices uses a different needle design, watt and algorithms. The first two devices use an expandable electrode, which, once positioned in the tumor, opens out into seven to twelve retractable, curved electrodes around the target like an umbrella. The technique determines a reproducible area of necrosis approximately 3-4 cm in diameter. The third device utilizes a cold perfusion electrode with a diameter of 1.2 mm and the tip exposed for 2-3cm.[70,71] By avoiding early increments of impedance linked to carbonization, such electrodes permit application of a greater power with respect to conventional electrodes. To obtain cooling, a physiological solution is circulated within two coaxial lumens situated in the electrode. The technique determines a reproducible area of necrosis of 2 to 4 cm.[72]

A recently constructed electrode with three cooled tips,

permitting a higher current deposition, determines more than 4.5 cm of coagulation necrosis.[73]

To obtain a large and effective ablation area, Kobayashi et al.[74] arranged an algorithm of tumor heating with expandable electrodes. To increase the final necrotic area obtained with the aforementioned techniques, interruption of the tumor arterial supply by means of occlusion of either the hepatic artery with a balloon catheter or the feeding arteries with gelatin sponge particles was recently proposed.[75] These techniques enabled a substantial and reproducible enlargement of the volume of thermal necrosis produced with a single needle insertion, and prompted the start of clinical application of RF ablation.

Several results of early experiences and pilot studies of RFA therapy for HCC were published from 1998 to 2001[76-83] (Table 1). HCCs of 3cm or less were principal candidates for the therapy and almost all authors described a complete response rate of more than 90% after ablation. The majority of these recurrences could be treated by repeated RFA. Livraghi et al.[84] compared the effectiveness of RFA with that of PEI in 112 patients with HCC less than 3 cm. With RFA, complete necrosis was achieved in 90% of tumors (mean, 1.2 sessions), versus 80% complete necrosis (mean 4.8 sessions) for PEI. Microwave has also been compared with radiofrequency ablation in a randomized controlled trial including 94 HCC of 1-3.7 cm in size, reporting equivalent therapeutic effects and complication rates, but fewer treatment sessions for radiofrequency.[85]

The mortality rate following hepatic RFA is less than 1% in the published reports. The morbidity rates associated with hepatic RFA are generally low. Major treatment-related complication arises in only 2% of all patients undergoing RFA.[76-83] Major complications following RFA are frequently associated with thermal injury to bile duct and surrounding structures, including the colon, stomach, and diaphragm, hemorrhage requiring surgical intervention, and portal vein thrombosis. Complication due to bile duct induces varied degrees of biliary tree dilation, bile duct fistula, jaundice, biloma, and liver abscess. Table 2 summarizes the case reports about major and minor complications of RFA therapy for liver malignancy.[86-107] Rhim et al.[95] described an incidence of major complications (2.4%) found in 1139 patients in a multicenter study. The most common complications were hepatic abscess (0.66%), peritoneal hemorrhage (0.46%), biloma (0.20%), ground pad burn (0.20%), pneumothorax (0.20%), and vasovagal reflex (0.13%). Livraghi et al. [108] also reported details of complications encountered in a total of 2320 patients with RFA therapy performed in 41 Italian hospitals: Six deaths (0.3%) were noted, including two caused by multiorgan failure following intestinal perforation; one case each of septic shock following Staphylococcus aureus-peritonitis, massive hemorrhage following tumor rupture, liver failure following stenosis of right bile duct; and one case of sudden death of unknown cause, 3 days after the procedure. Fifty (2.2%) patients had additional major complications. The most frequent of these were peritoneal hemorrhage, neoplastic seeding, intrahepatic abscesses, and intestinal perforation.

COMBINED THERAPY AND LAPAROSCOPIC APPROACH

Although recent clinical studies have shown success in the use of these strategies for single HCC less than 3 cm in diameter, it is clear that further developments are necessary to achieve complete eradication in larger diameter tumors. Similarly, different minimally invasive strategies are better suited for varying disease presentations. While percutaneous therapies are more effective for single tumors, embolization or transarterial chemotherapy is more appropriate for multifocal disease. Therefore, combining several modalities of treatment to achieve complete tumor cell death must not be neglected. A similar, multidisciplinary approach including surgery, radiation, and chemotherapy should also be applied for the treatment of the tumor. Several investigators have explored combination therapies to achieve successful treatment results in primary liver malignancies, including various arrangements of PEI, thermal ablation, transcatheter arterial chemotherapy, vascular occlusion, and chemoembolization.

Table I. Efficacy of radiofrequency ablation therapy for hepatocellular carcinoma

Author (ref)	Year	No. of patient	Liver tumor	Tumor size	Needle device	Observation period	Complete Necrosis (%)	Major Complicatin (%)
Rossi [76]	1998	23	HCC	23-35mm	expandable	15 M	90	0
Livraghi[77]	1999	42	HCC	< 30 mm	cooled tip	10 M	98	2.4
Curley[78]	1999	48	HCC	< 30 mm	expandable	15 M	98	0.8
Francica[79]	1999	15	HCC	10-43mm	cooled tip	15 M	90	6.7
Jiao[80]	1999	8	HCC+Meta*	6pts>3cm	cooled tip	9.4 M	88	0
Allgaier[81]	1999	12	HCC	3.2 ± 1.3cm	cooled tip	4.8 M	100	0
Lencioni[82]	1999	54	HCC	1-3cm	both	23 M	91	0
Llovet[83]	2001	32	HCC	<5cm	cooled tip	10 M	65(76% for< 3cm)	9.4

*Meta - Metastasis
M - Months

Table II. Case reports of complications after radiofrequency ablation therapy for liver tumor.

Complications	(Reference)
Major complications	
Hemobilia, intrahepatic hematoma	(86)
Rapid progression of HCC	(87)
Tumor seeding	(88)
Bleeding requiring transfusion	(89)
Hepatic abscess	(89)
Colonic perforation	[91]
Bacterial peritonitis	[92]
Intrahepatic pseudoaneurysm	[93]
Portal vein thrombosis	[94]
Biloma	[95]
Secondary hemocholecyst	[96]
Diaphragmatic perforation	[97]
Hypertensive crises	[98]
Bilioenteric anastomosis	[99]
Acute renal insufficiency	[100]
Abdominal wall necrosis	[101]
Minor complications	
Arteriovenous shunt	[102]
Perihepatic hemorrhage	[102]
Pneumothorax	[102]
Skin injury	[103]
Hyperkalaemia	[104]
Hemolysis	[105]
Elevation of body temperature	[106]
Sarcomatous change	[107]
Hemoperitoneum	[100]

Combination of Laser Thermotherapy and Arterial Chemoembolization

Laser thermotherapy is a local effective therapy with low morbidity for a few numbers of HCC of 5cm or less in diameter.[109] The radionale for combination of transcather arterial chemoembolization (TACE) and laser ablation is based on the fact that laser therapy can reduce the volume of viable tissue and improve the lesion within the range of TACE effectiveness. Pacella et al.[110] achieved complete response with a single segmental TACE session in 21 (70%) of the 30 patients and reported that the 1 year local recurrence rate was 7% in large HCC. Laser thermotherapy seems to be more beneficial and advisable in combination with TACE for treating patients with relatively larger and multiple HCCs.

Combination of TACE and PEI

Allgaier et al.[111] treated 132 HCC patients with combination TACE/PEI to achieve a median survival of 25 months. Similarly, Bartolozzi et al.[112] treated 86 patients with single HCC tumors (mean diameter, 5.3 cm) with TACE followed by PEI (mean, 6.8 sessions) to achieve complete necrosis in 82%. Overall 1-, 3-, and 5-year survival rates were 92%, 69%, and 47% respectively. A few authors also reported significant increases in survival with combination therapy over TACE alone.[113,114] In 97 patients with recurrent HCC after surgical treatment, Ishii et al.[113] reported a relative risk of cancer death of 0.32 for patients receiving combination therapy. Koda et al.[115] reported reduced local recurrence and lower incidences of new intrahepatic disease in patients receiving combination TACE/PEI. Embolization alone combined with PEI also demonstrated increases in complete necrosis (20-83%) and better 1- and 3-year survival over TAE alone.[116] Combined TACE and PEI is a therapeutic option that has been proposed to overcome the weakness of each of the two procedures in the treatment of large HCC.[115,117,118]

Combination of TACE and MCT

The combined therapy of MCT applied within 1-2 days of TACE can effectively treat HCC>2.0 cm but < 3.0 cm in dimension. Less number of microwave electrode insertions and lower amount of energy for microwave irradiations are needed when both treatment are combined.[119] Ishikawa et al. suggested that MCT destroyed the peripheral part of the tumour that might remain viable after TAE, but combination therapy with TACE is preferable, especially when a viable part existed within tumours. [120] However, larger scale clinical trials are required to define the role of this combined therapy.

Combination of TACE and RFA

RFA achieves complete tumour necrosis for small HCC ($\leq$3.5 cm in diameter) with fewer treatment sessions compared with PEI, and can also create large volumes of tumour necrosis in a shorter period of time than either laser or microwave therapy.

The combination of TACE and RFA induces larger coagulation necrosis areas than RFA alone. Buscarini et al.[121] treated 14 patients with HCC (3.8-6.8 cm; mean diameter, 5.2 cm) with hepatic segmental transcatheter arterial embolization followed by RF ablation. Mean follow-up lasted 13.2 months with 11 patients disease-free at the time of reporting, indicating that larger hepatomas could be treated with this combination of therapies. Bloomston et al.[122] reported that one-year survival was greater in patients undergoing TACE and RFA than TACE alone (100% vs. 67%, P=0.04). Mean survival was longer after TACE with RFA compared with TACE alone (25.3 months $\pm$15.9 vs.11.4 months $\pm$ 7.3, P<0.05). No patients suffered significant complications in that study. Similarly, Lencioni et al.[123] reported success in 82% of patients with HCCs (diameter, 3.5-8.5 cm) treated with TAE before RF ablation.

For multifocal recurrence, RFA can be useful as a complementary technique for lesions not completely treated by TACE.[124] Goldberg et al.[125] conducted a pilot study in 10 patients with liver tumors, including 4 patients with HCC, and were able to attain 25% to 30% increases in coagulation volume by administering liposomal doxorubicin 24 hours before RF application. More importantly, follow-up imaging studies demonstrated that this particular from of adjuvant therapy resulted in more complete tumor kill as coagulation progressed over time to include residual tumor foci and patent intratumoral blood vessels.

Laparoscopic Approach

The percutaneous approach is least invasive, carries a lower morbidity and complication rate, and is cheapest and most widely used. In the radiology department US, CT, MR guidance or a combination of these approaches can be used. The laparoscopic approach has been used when tumor is adherent

to structures that would be damaged by thermal ablation e.g. tumour adherent to stomach, colon or duodenum. Some centers prefer the laparoscopic approach where there is poor tumor visualization transcutaneously and also for large hepatocellular carcinoma requiring multiple punctures.[126,127] A study that failed selection criteria[128] reported that laparoscopic ultrasonography detected unsuspected extrahepatic disease in 12% and previously unidentified hepatic lesions in 33% of patients. Consistent with this observation, studies of percutaneous radiofrequency ablation without laparoscopic ultrasonography with 10 months' follow-up, reported relapses elsewhere in the liver for 24% to 38% of patients. Data were insufficient to compare outcomes of laparoscopic or open approaches to those of percutaneous ablation. Comparisons between approaches should be made on the basis of "intention to treat".

EVALUATION OF TREATMENT EFFECTS

Contrast-enhanced CT and dynamic MRI are regarded as reliable modalities for evaluation of early responses after radiofrequency ablation and early detection of tumor recurrences.[129-132]

Findings of plain CT show the area after ablation as a low-density area occupying the entire volume of original tumor. In an HCC associated with cirrhosis, radiofrequency heat may be concentrated within a well-encapsulated tumor, and therefore, a successful radiofrequency ablation area tends to be the same size as the original tumor. On contrast-enhanced CT, the ablation area is expected to be nonenhancing. However, a recent ablation area may have an enhancing rim related to hyperemia from thermal injury.[129-131] This is more typically present on the arterial dominant phase but may be present on the portal dominant phase or both phases. Discrete nodular noncircumferential enhancement, especially at the ablation margin, is suspicious for residual or recurrent tumors. Differentiation of reactive hyperemia from residual tumors is often difficult.

The characteristic MRI signals of coagulation necrosis after RFA are intermediate to high signal-to-liver parenchyma on T1-weighted and low signal on T2-weighted images. A T2 hyperintense rim around the ablation area is a possible finding, likely related to edema when thermal ablation is performed. Any discrete areas of T1-hypointense and T2-hyperintense signal should raise the possibility of residual or recurrent tumor. However, a recent ablation area may have heterogeneous signal on both T1- and T2-weighted images because of non-uniform evolution of inflammation and necrosis,[130] resulting in difficulty in the interpretation of unenhanced MRI. Gadolinium-enhanced MRI is therefore routinely used to maximize the accuracy of the study.

Dromain et al.[133] reported a higher sensitivity in early detection of local recurrence on MRI than on CT but without significant differences. A baseline study should be obtained within the first week after the procedure. Subsequent follow-up should be performed every 3 months for 1 year, and every 6 months thereafter. In equivocal cases, follow-up may be more frequently performed.

Lesions adjacent to major vessels have a higher risk of incomplete ablation because of a "heat sink" effect.[134] Because radiofrequency heat cannot easily traverse vessels, the ablation extent is usually limited by major vessels and may not provide the desired ablated margin.

Evaluation of long-term follow-up imaging (>6 months) is generally easier than after ablation, because of the resolution of inflammation. On CT, the RF ablation areas and tracts become sharp and decrease in size, without arterial enhancement. Signs of tumor recurrence include development of noncircumferential nodular enhancement and increase in lesion size. On MRI, the ablation area shows more homogeneous T1 hyperintense and T2 hypointense signal. Signs of recurrence include new enhancement, increase in size of lesion, and development of T1 hypointense and T2 hyperintense signal areas.

FUTURE PERSPECTIVE OF LOCAL ABLATION THERAPY

Recent development of locoregional ablative therapies has expanded the range of tools for treating HCC. The main characteristic of these therapies is the localized tumor destruction in situ, with maximal preservation of non-cancerous part of liver parenchyma, in contrast to the significant liver damage caused by other interventional therapies, such as TACE and intra-arterial chemotherapeutic infusion.

Although a complete tumor ablation rate of over 90% was achieved with RFA, the efficacy of the therapy should be critically assessed with randomized controlled trial to compare it with other local regional therapies or even surgery.

Future studies from the technical viewpoint should be focused on (1) the development of optimal ablation techniques that can increase the volume of tissue destroyed, (2) varied efforts to reduce side effects (most favorable analgesic therapy, avoidance of biliary tree complication), (3) the assessment of efficacy of multimodal and combined treatment, and (4) the development of new and less invasive ablation modality such as extracorporeal high intensity focused ultrasound. Furthermore, chemopreventive therapy should be established to decrease hepatocellular carcinogenesis rate in chronic liver diseases and to reduce recurrence after locoregional therapy.

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HEPATOLOGY

Significance of hepatitis B virus DNA clearance and early prediction of hepatocellular carcinogenesis in patients with cirrhosis undergoing interferon therapy: Long-term follow up of a pilot study

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Abstract

Background and Aim: Because the anti-carcinogenic effect and mechanism of interferon (IFN) in patients with hepatitis B virus (HBV)-related cirrhosis have not been elucidated, quantitative analysis of HBV-DNA concentration was carried out sequentially.

Method: Of 60 consecutive patients with cirrhosis who began IFN therapy between 1986 and 1990, 57 patients were completely observed for the appearance of hepatocellular carcinoma (HCC). All patients underwent intermittent administration of IFN for a median period of 18 months. HBV-DNA was quantified using transcription mediated amplification and hybridization protection assay. A HBV-DNA count <3.7 log-genome equivalent (LGE)/mL (equivalent to $10^{3.7}$ or 5000 copies/mL) was considered to be a negative value.

Results: Of 25 patients who had HBV-DNA loss after IFN therapy, nine lost HBV-DNA during the therapy and 16 lost HBV-DNA after cessation of the therapy. The other nine patients showed a transient loss of HBV-DNA, and the remaining 23 retained persistently positive HBV-DNA during and after therapy. Although HCC developed in two (8.0%) of the 25 patients with HBV-DNA loss, carcinogenesis was found in 11 (34.4%) of 32 patients without HBV-DNA loss (Fisher's exact test, $P = 0.026$). In the two exceptional patients, HCC was detected at 1.2 and 3.6 years after loss of HBV-DNA, respectively. When the HBV-DNA concentration decreased by 2 LGE/mL (decrease to 1/100) at 6 months after initiation of interferon, HBV-DNA became negative eventually in 15 (60.0%) of 25 patients.

Conclusion: A significant decrease or loss of serum HBV-DNA prevents development of HCC, and sequential analysis of HBV-DNA could be very useful in both the prediction and the early detection of small HCC.

Key words: cancer prevention, carcinogenesis, DNA, hepatitis B virus, hepatocellular carcinoma, interferon, liver cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of death in many parts of sub-Saharan Africa and Asia.[1,2] It is also one of the most common neoplasms in Japan. Abundant epidemiological and molecular biological evidence shows that the hepatitis B virus (HBV) is an important factor in the development of HCC,[3–6] but the precise role of HBV-DNA viruses in the oncogenesis of HCC is still unknown. Although increasing evidence indicates that the HBV plays an important role in the development of HCC, particularly after the discovery of integrated forms of HBV,[7,8] current serological and virological markers are still insufficient for establishing this relationship. Because a really curative therapy is not available for HCC at present, the accurate prediction

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and early detection of HBV-related HCC is essential in the current situation. Needless to say, a cohort of patients with HBV-related cirrhosis has a significantly high risk for the development of HCC,[6,9] but the degree of risk of carcinogenesis in an individual patient cannot be predicted as yet. Hepatocellular carcinogenesis in patients with HBV infection may be associated with persistence of aminotransferase, concentration of HBV-DNA, or merely the severity of the liver disease.

Interferon (IFN) has been reported to be effective in patients with HBV-related chronic hepatitis, which, on early control studies,[10–12] decreases serum HBV-DNA concentration and improves biochemical data and subsequently suppresses disease progression to cirrhosis.[13,14] Although the various effects of IFN in HBV infection have been well investigated from the virological, biochemical, and medico-economical viewpoints,[15–17] the influence of IFN on the long-term outcome for liver cirrhosis and on hepatocellular carcinogenesis is still controversial.[18–23] In order to clarify the mechanism of the anticarcinogenic activity of IFN, if any, we analyzed HBV-DNA concentration serially in a cohort of 60 patients with cirrhosis.

The purposes of this study are: (i) to elucidate the relation of hepatocellular carcinogenesis to longitudinal clinical courses of consecutive cirrhotic patients with IFN therapy; and (ii) to investigate a prediction of cancer preventative activity by early HBV-DNA elimination.

METHODS

Patients

Of 189 patients who were diagnosed as having HBV-related cirrhosis using peritoneoscopy and/or liver biopsy from 1983 to 1990 in our hospital, a total of 60 patients underwent IFN therapy from 1986 to 1990. Because three patients were lost to follow up, the remaining 57 patients (95.0%) were analyzed for virological outcome, carcinogenesis, and eventual prognosis: the reason for the dropout from the observation in the three patients was simply relocating house.

Table 1 shows the demography and laboratory data of the consecutive 57 patients who began IFN therapy from 1986 to 1990. There were 45 men and 12 women, with an age range from 19 to 60 years and a median of 41 years. Median values of bilirubin and albumin were 0.9 mg/dL and 4.1 g/dL, respectively. All the patients had a high HBV-DNA concentration of 3.7 log-genome equivalent (LGE)/mL or more at the time of IFN therapy.

Interferon treatment

IFN-α was administered in 35 patients (61.4%) and IFN-β in the remaining 22 patients (38.6%). The daily quantity of IFN was three million units in 22 (38.6%) and six million units in 35 (61.4%), twice a week administration was carried out in 54 (94.7%) and three times a week administration in three (5.3%). All patients received intermittent IFN therapy for a median of 18 months (range, 2–132 months), but the duration of the IFN therapy was arbitrary in this pilot study. Although the daily dose of IFN and the duration of the therapy varied in this study, 52 (91.2%) of the 57 patients received IFN for 6 months or longer.

Table 1 Demography and laboratory data of 57 patients with hepatitis B virus-related cirrhosis undergoing interferon therapy

Demography	
Men : women	45:12
Age (median, range)	41 (19–60)
Decompensated cirrhosis	3 (5.3%)
Past alcohol consumption of 500 kg or more	3 (5.3%)
Laboratory data (median, range)	
Bilirubin (mg/dL)	0.9 (0.4–2.6)
Albumin (g/dL)	4.1 (3.0–4.9)
Aspartic transaminase (IU/L)	65 (16–404)
Alanine transaminase (IU/L)	74(12–586)
Platelet count ($\times 10^3$/mm^3)	125 (68–332)
Antibodies to hepatitis C virus positive	0
Hepatitis B e antigen positive	41 (71.9%)
Hepatitis B virus DNA (LGE/mL)	7.2 (3.9–> 8.7)
Observation period (year)	13.6 (6.5–16.1)

LGE/mL, log-genome equivalent, expressed as 10^n copy/mL.

Follow up of patients and diagnosis of HCC

Follow up of the patients was made on a monthly basis after diagnosis of liver cirrhosis using monitoring virological, hematological, and biochemical data, including α-fetoprotein. All results for these laboratory tests, including HBV markers, were obtained throughout the observation period in each patient. Patients were classified into four groups according to patterns of serial concentration of HBV-DNA: type A, disappearance of HBV-DNA during and after IFN therapy; type B, loss of HBV-DNA after cessation of IFN administration; type C, transient loss of HBV-DNA only during IFN administration; type D, persistently positive HBV-DNA during and after the therapy. Clinical courses of alanine aminotransferase (ALT) fluctuation were also classified into four groups according to normalization of the ALT value.

Imaging diagnosis was made two or more times per year for each patient using computed tomography (CT), ultrasonography (US) or magnetic resonance imaging (MRI). HCC was diagnosed using typical hypervascular characteristics on angiography in addition to certain features of CT, US and MRI. Pathological confirmation of surgically resected specimens was carried out in six (46.2%) of 13 patients with HCC development.