的確に判断し，そして何らかのprophylaxisあるいはpost transplant treatmentのstrategyを確立することが急務となってきた．

本稿ではHCV陽性肝移植レシピエントの欧米の報告をまとめ，わが国における臨床成績を比較し，わが国におけるHCV陽性レシピエントに対する考え方を述べることとする．

I HCVの再感染と肝炎発症

肝移植手術の数時間後から，HCVのダイナミックな複製が開始することが知られている[8]．すなわち，術中無肝期を除き，day 1には多くのレシピエントで血中HCV RNAの陽性が判明している．その後，組織学的には一週間目から肝炎の所見が見出されるような例も認める[9]．その病理学的特徴はacidophilic bodyやpiecemeal壊死などが挙げられる[10]が，臨床の現場では，必ずしも拒絶反応と，この肝炎の組織診断，鑑別診断が容易になされているとは到底思えない．

一番大切なことは，プロトコール肝生検ではないので，HCVの再感染という現象とHCVによる肝炎発症とがそれぞれ明確に成されず，その臨床的区別がはなはだ困難であるということである．なぜならば，血中トランスアミナーゼ値の動揺は薬剤性肝障害，拒絶，感染症などで認められ，それらに起因するものか，再発性ウイルス肝炎によるものかは組織診断でないと確定診断が成されないものである．臨床的に顕著となったHCV再感染による肝炎といわゆる他の要因がオーバーラップした無症候性HCVキャリーの区別は肝移植後の臨床の場では，明確に区別することが困難である．

II HCVレシピエントの肝移植後の臨床経過

肝移植後のHCV陽性レシピエントは以下の4群に分けられる．①再感染後，トランスアミナーゼ値の動揺は軽微で，通常みられるC型慢性肝炎と同様の臨床経過をたどる例と，②短期間に肝硬変に進展し，早期に非代償性肝硬変まで進行する例[2)4)11)12)]が存在し，5年間で8～25%は肝硬変へ進展する[13]群が存在するとされている．さらに，③肝移植後，早期にHCVの顕著な増殖とともに胆汁うっ滞と進行性の線維症をみるfibrosing cholestatic hepatitis（FCH）や重症型肝炎の像を呈する例などにその臨床経過は分けられる．そして，④数パーセントの症例であるが，何ら対処しなくても感染から免れる例も僅かながら存在する[14)15)]．

欧米の報告をまとめると，通常，肝移植後，肝硬変へ進展する頻度は5年間で20～30%[16]と極めて高率である．さらに，平均45カ月の観察で約半数が肝炎の再発を認め，3分の1が肝硬変へ進展した[17]とする報告もある．特に，ドナーの年齢40歳以下と50歳以上で線維化の進展は異なり，平均7.7年で肝硬変へ進展すると言われているレシピエントは高齢者の場合，さらに早く2.2年の進行度であったとされている[18]．すなわち，移植後，HCV再感染を生じたレシピエントは肝硬変への進展が極めて早いことが認識され出した．このことは1990年以降，HCVレシピエントの再移植例が増加している事実[11]と合わせると，その事態の深刻さが理解されるであろう（Figure 1）．このように一旦，HCVに再感染し，慢性肝炎に陥ったレシピエントは通常の慢性肝炎と異なり，肝硬変への進展が極めて早いことは驚くべき事実である．この事実が，最近の脳死肝移植を主体とした欧米のHCV陽性レシピエントの現状である．

III わが国における生体肝移植のHCVレシピエントの成績

信州大学外科の中澤が日本肝臓学会Single Topic Conferenceでまとめたわが国の生体肝移植HCVレシピエントの成績からみると，200例のレシピエントの生存率は1年78.8%，2年71.8%，4年68.2%であった[19]．

一方，最新の日本肝移植研究会の報告では，HCVレシピエント167例の生存率は1年生存75.1%，3年生存70.1%，5年生存66.8%であり，18歳以上成人1,790例の生存率，1年生存78.0%，3年生存72.8%，5年生存69.8%，10年生存64.0%に比べると，その生存率が約3%劣っていることが判明した（Figure 2）[20]．統計学的にはなんら有意差はないとの判断である．

統計学的には有意の差はないものの，HCV陽性レシピエントの生存率低下の要因として肝細胞癌

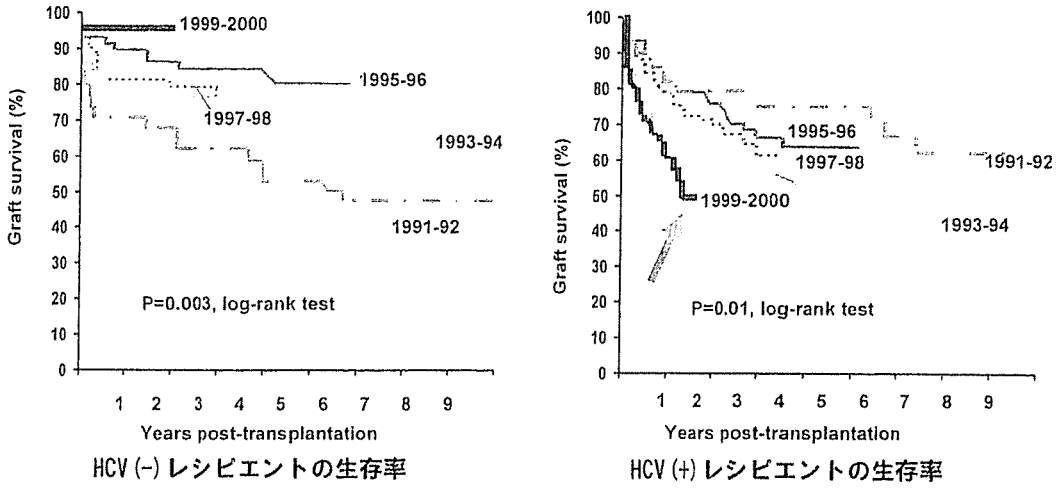

Figure 1. 欧米における HCV 陽性，陰性別肝移植レシピエントの生存率.

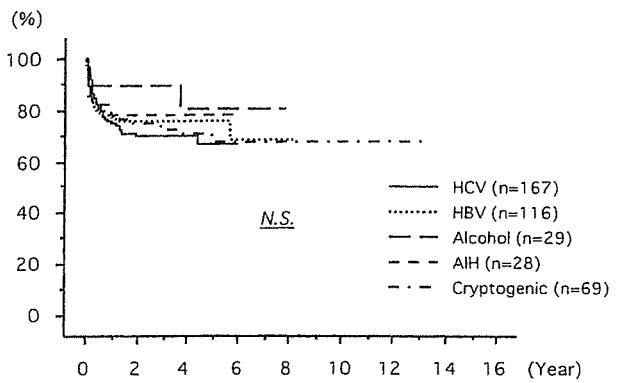

Figure 2. 生体肝移植における肝細胞性疾患の累積生存率（日本肝移植研究会登録症例　文献 20 参照）.
HCV；C 型肝炎ウイルス陽性肝硬変，HBV；B 型肝炎ウイルス陽性肝硬変，Alcohol；アルコール性肝硬変，AIH；自己免疫性肝硬変，Cryptogenic；原因不明肝硬変.

の関与が考えられる．しかし，日本肝移植研究会の肝細胞癌全症例 479 例とその中の HCV 陽性肝細胞癌 277 例のそれぞれ 1 年生存率 80.9% と 81.3%，3 年生存率 69.3% と 70.0%，5 年生存率 65.7% と 66.3% の成績を検討しても，たとえ HCV 陽性肝細胞癌例でも，明らかな生存率の低下は認められない．さらに，藤堂らのわが国の肝細胞癌 221 例（うち 59%）の 1 年生存 80%，3 年生存 77%，4 年生存 77% の成績との比較検討を行っても，肝細胞癌が HCV レシピエントの生存率に影響を及ぼしているとは考えられなかった.

すなわち，この 3 つの報告をまとめると，わが国における HCV 陽性レシピエントの状況を以下のようにまとめることができる．すなわち，HCV 陽性レシピエント 167 例の 5 年生存率は 66.8% と 18 歳以上のレシピエント 1,790 例の 5 年生存率 69.8% より劣っているが，欧米の違いほどではなかった．一方，肝細胞癌 479 例中，HCV 陽性 227 例の 5 年生存率は 66.3% で肝細胞癌全体の 5 年生存率 64.3% とほぼ同じ成績であり，さらに中澤らの HCV 陽性レシピエント 4 年生存率 68.2% でその 60% が HCV 陽性を考慮しても，影響は少ないと考えられた．よしんば HCV 陽性レシピエントの予後を肝細胞癌が影響を与えているとしても，わが国における HCV 陽性レシピエントの生存率は約 5 年間で約 5% 程度劣る程度であると思われた．しかし，これらの事実は 10 年生存率での欧米との比較ができない現状で，早急な結論を下すことはできない[21].

IV　重症化，線維化進展，硬変化の要因（欧米とわが国との比較検討）

1. ドナーとレシピエントの年齢

これらの原因の 1 つとして，ドナーの年齢の高齢化が挙げられている．Berenguer らの報告[11]から，明らかに，ここ数年間のドナーの高齢化が示唆されている．このことは ELTR（ヨーロッパ肝移植登録）の脳死肝移植やアメリカの生体肝移植からの報告でも明らかである.

生体肝移植が中心のわが国ではドナーの年齢は

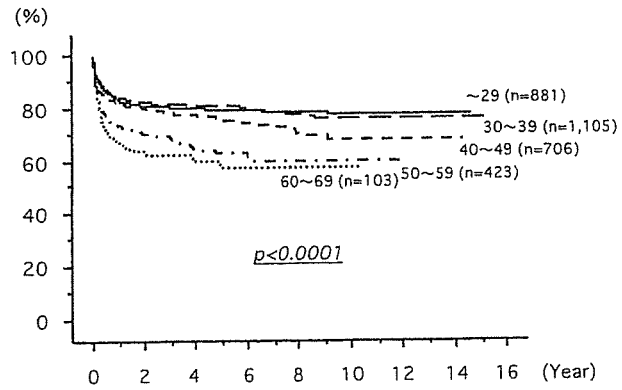

Figure 3. 生体肝移植におけるドナー年齢別の累積生存率（日本肝移植研究会登録症例 文献20参照）.

如何なる関与があるのであろうか．一般的には，ドナーの年齢が高齢化すると，その肝移植成績，生存率は低下する．このことは日本肝移植研究会の報告でも症例別の検討はないが，有意な差を持って高齢者ドナーの生存率の低下をみることができる．たとえば，ドナー年齢29歳以下，39歳以下，49歳以下，59歳以下，60歳以上の5年生存率はそれぞれ77.1%，75.6%，67.6%，59.7%，57.1%である（Figure 3）．ただし，このことは肝移植全般の成績で，HCV陽性例に限った統計ではないことに注意を払わなければならない．

欧米の脳死，もしくは生体肝移植におけるドナー高齢化による肝移植後の成績の悪化の1つの可能性として，以下のことが考えられる．通常のHCV感染では，若年者の罹患後の状況と，高齢者の罹患後の状況では，明らかに高齢者のほうが線維化や肝硬変への進展は急速で，また肝細胞癌の移行も早急であるとされている．この事実を鑑みると，高齢のドナー肝臓への大量のHCV感染が，線維化の進展に大いに関連があることが推測される．

しかしながら，現時点で，この生体肝移植ドナーの高年齢との関連性はわが国における生体肝移植では当てはまらないようである．何故ならば，わが国のHCV陽性レシピエントは比較的高齢で，そのドナーは兄弟，子供などで，むしろドナーの年齢は若年者が多いものと推定される（現時点でそのデーターはまとめられていない．）[22]．

筆者らは，それよりも，レシピエントの高齢化の方がHCV陽性レシピエントの成績の悪化に関連していると推測している．事実，ELTRの脳死例，アメリカの生体肝移植例では高齢者レシピエントの成績が統計学的に有意に低下している[22]．さらに，中澤の報告でも，55歳以上のHCV陽性レシピエントと55歳以下のレシピエントの4年生存率はそれぞれ56%と81%と統計学的に有意に高齢者の方が生存率は低下している．

したがって，筆者らはこのHCV陽性レシピエントの生存率の低下は，必ずしもドナーの高齢化ではなく，レシピエントの高齢化を考慮しなければならないと考える．

2. 免疫抑制剤

免疫抑制剤の相違による，グラフト肝でのHCVの増殖機構が異なることが示唆されている．レプリコン実験などの基礎的研究から，タクロリムスよりサイクロスポリンの方が *in vitro* の系でHCVの増殖抑制が顕著で，その抑制率はインターフェロンとほぼ同等であるとされた[23][24]．これらを総合すると，*in vitro* のレプリコンを主体とする実験系では，どうもサイクロスポリンの方がHCVの増殖抑制を導き出していると考えた方が妥当である．

問題は，臨床の場でサイクロスポリンが肝移植後，HCV感染に関して有効であるかの検証が必要である．実際に，サイクロスポリンを肝移植後使用することで肝炎進展リスクが低くなったとの報告[25]がある一方で，肝移植後の生存率やグラフト生着率に関しては賛否両論あり[26]，その臨床的評価は一定していない．

一方，これら再発したHCV肝炎に対する治療の介入として免疫抑制剤という環境は如何なる影響を与えるのであろうか．わが国のInoueらはサイクロスポリンとインターフェロンの併用療法でSVR 76.3%としている[27]．勿論，この両者の投与は副作用も多く，さらにわが国に多いIb，高ウイルス量のHCV感染レシピエントに対して，使用可能かどうか，検証することも必要となる．

わが国の臨床の場における免疫抑制剤の使用状況をみると，おおよそ80%以上はタクロリムスで

ある．すなわち，シクロスポリンの使用は現時点でそれほど多くはない．そのような状況で，HCV陽性レシピエントと非HCVレシピエントの生存率の差が多く見積もっても5%以内ということは，果たして今の使用状況の免疫抑制剤の種類が関与しているのかどうか，慎重に成らざるを得ないと考える．

3. ステロイドパルス

肝移植後，急性拒絶反応はもとより，カルシニューリン抑制剤とともに併用する施設が多い．この副腎皮質ホルモンとHCVに関しては，いくつかの考えが報告されている．HBVとは異なりHCVにはglucocorticoid response elementが証明されていないことより，実験系ではこのステロイドはHCVの増殖系を明確に促進するという証明はないが，臨床的には多くの報告から，ステロイドはHCV RNAを増加させるとされている[28]．

そして，肝移植医療で，拒絶時に用いられるステロイドパルス療法がHCV再感染にもっとも関与し，これがリスクファクターであるとしている報告が幾多もある[29]．

さらに，ステロイドの総投与量とHCVの再発との関連性も示唆され，再発群が非再発群に比して有意にステロイドの総投与量が多いとされている[30]．そのステロイドの投与期間との関連性についてはまだまだ一定の見解は得られていないが，ステロイドは少なければ少ないほどHCVの再燃を抑制するが，逆に拒絶反応を誘発し，生存率を低下させては元も子もなくなるので，最低限度のステロイドパルスは必要である．基本的には維持投与はなくす方向が最適な環境の1つになるように思えるが，これもまだまだエビデンスを得る努力が必要となる因子である．

4. 生体ドナーとsmall for sized graft

生体肝移植の方がHCV感染後の病態悪化や病状の進展が顕著であると報告された[31)~34)]．HCV再感染やその時期が早まること，さらには重症型肝炎が多いことが示唆された．その要因としてはIRES (Internal Ribosomal Entry Site) の活性化，再生肝細胞内でのHCVの濃縮，再生増殖肝細胞がLDLレセプターのup-regulationを介してHCVの進入を促進する，いわゆるendocytosisの活性化が関与するなどの理由が考えられている．

したがって，アメリカでは急性拒絶反応が少なく，若年者で，肝移植前の病態が比較的軽症で，非アフリカ系アメリカ人，さらに，肝移植前にHCVを除去あるいは軽減させるなどの条件が生体肝移植後のHCVの再感染を少なくする因子としている．一方で，生体肝移植ではHLAの合致率が高く，さらに再生肝細胞というこの2点が生体肝移植後のHCV再燃に不利に働くとの認識を有しているようである．

しかしながら，必ずしも再生肝臓とHCVの増殖の関連性に関して臨床的な事実はないように思える．たとえば，わが国に多いHCV陽性肝細胞癌に対する，肝切除後にHCVの急速な増殖によるFCHやウイルスのflare，重症型肝炎は，ほとんど経験がないであろう．

さらに，生体肝移植におけるsmall for sized graftの存在もHCV陽性レシピエントの成績不良の要因と考えられた．しかし，中澤の報告では必ずしもsmall for sized graftが生存率に関与しないことが判明している．

したがって，現時点のわが国の成績から生体肝移植がHCV陽性レシピエントの生存率の低下に深く関与しているとは考えられないとの結論が得られている．

V HCV再感染に対する治療 (post transplant treatment)

肝移植後の抗ウイルス療法として，ウイルス排除が第1の目的である．しかし，一般に考えられているBichemical Responderが肝移植後の臨床に意味があるのか否か，難しいところである．すなわち，壊死，炎症反応を抑制する抗炎症療法に臨床的意義がもたらされるのか．そして，一般的な慢性肝炎にとられるような肝細胞癌抑止を目標にすべき対象なのかも明確ではない．現時点では，ウイルス排除に固執した方が，臨床的意義が深いと考える．なぜならば，免疫抑制剤，さらには肝細胞の再生という基盤での抗炎症作用が，はたして抗線維化に繋がるか，甚だ疑問点が多いからで

Table 1. 2000年以降のpost transplant treatmentの成績

報告者（文献）	症例	IFN量（回数）	リバビリン期間		ETVR	SVR	脱落/減量
Samuel et al[35]	28	2b/3M/(3x/w)	1000	12M	21%		16/28
Bizollon et al[36]	54	?/3M/(3x/w)	?	6M		26%	
Shakil et al[37]	38	?/3M(3x/w)	800	12M		18%	16/38
Lavezzo et al[38]	57	2b/3M/(3x/w)	800	6M	23%	17%	29/57
Kornberg et al[39]	15	2b/3M/(3x/w)	600	12M	64%	88%	2/15
Narayanan et al[40]	26	2b/3M/(3x/w)	1000	12M	35%	23%	13/26
Wiesner et al[41]	9	2b/3M(3x/w)	600	12M	11%	?	8/9
Alberti et al[42]	18	?3M(3x/w)	600	12M	44%	27%	?
Ahmad et al[43]	20	2b/3-5(3x/w)	600	12M	20%		5/20
De Vera et al[44]	32	?/1.5-3M(3x/w)	400	12M	9%		13/32
Coltler et al[45]	12	2a/3M(3x/w)	−	12M	50%	?	7/8

Table 2. ペグインターフェロンとリバビリン併用療法の成績

報告者（文献）	報告年	症例数	年齢	BR率	中止率	減量率	移植後投与開始時期	拒絶反応
Babatin[51]	2005	13	49.4	9/13	4/13	6 (ribavirin)/13	26.4カ月後	3/13
Planas[52]	2005	30	56		11/30	12/30	52カ月後	0
Toniutto[53]	2005	12	56.5	3/12	7/12	11/12		0
Rodriguez-Luna[49]	2004	19	53		7/12		128週後	1/19
Mukherjee[48]	2003	39	50.4	12/39	17/39		22カ月後 (2～166)	0
Dumortier[50]	2004	20	53.8	15/20	4/20	6(IFN), 13(RIB)/20	28カ月後	5/20
Samuel[47]	2003	22	58	11/22	14/22		95.5カ月後	
Castells[54]	2005	24	61.4	8/23			3.8カ月後	1/23

ある．2000年以前は，インターフェロンの単独投与が行われたが，期待された効果は得られず，むしろ拒絶反応を誘発するとして多くの施設では施行されなかった．しかし，2000年以降，HCVレシピエントの急速な病状悪化から，盛んに抗ウイルス療法の臨床試験が試みられてきた（Table 1）[35)～45)]．すべて欧米の報告であるため，感染時期の相違，ウイルスのサブタイプの違い，人種間の相違など一概にわが国での慢性肝炎や肝移植後の慢性肝炎に対する治療結果と比較検討することは困難である．そこで得られつつある結論は，インターフェロン単独療法よりインターフェロンとリバビリン併用療法の方がウイルス排除やトランスアミナーゼ値の正常化率は高率である．しかし，半数以上のレシピエントで併用療法の中止か薬剤投与量の減量などで，当初の目的を達せられずに治療を断念する症例が圧倒的に多いということである．

欧米のインターフェロンとリバビリン併用療法の成績を単純にまとめると，年齢，人種その他の条件を無視して，報告例を総数として計算すると307例にインターフェロンとリバビリン併用療法が使用され，その治療効果としてSVR率は208例中55例（26%）であった．最も問題となる中止率や脱落率，減量率を大まかに計算すると233例中109例（47%）に認められている．

これらは移植後，肝炎の再燃を観察した後，post transplant treatmentとして治療が開始されているが，肝炎の発症の如何にかかわらず，移植後早期にインターフェロン治療を行うpreemptive treatmentも数施設で行われ，わが国のSugawaraらは移植後早期にインターフェロン治療を行い，

39% のSVRを得られたと報告している．これらの大半はGenotype Iの高ウイルス量であることから，この治療効果は注目に値する[46]．

2003年のSamuelら[47]の報告から始まったペグインターフェロンとリバビリン併用療法は，集計するとおおよそ179例に投与されている（Table 2）[47)~54)]．それぞれの条件や人種が異なるが，これらをまとめてみると，HCV陽性レシピエントに肝移植後，3カ月から96カ月の間にペグインターフェロンとリバビリンが投与開始されている．男性128例，女性51例で平均年齢54.4歳であった．今まで報告されているペグインターフェロンはすべてα2bで1.0～1.5μg/kg/週で，リバビリンは400 mgから1000mgであった．投与期間はI型とIV型は48週間，II型とIII型は24週間投与であった．

成績全体をまとめると，SVRは179例中46例（26%）であり，いわゆるBiochemical Responderは129例中58例（45%）であった．投与中止例は148例中48例（32%）にみられ，インターフェロンもしくはリバビリンの減量例は75例中46例（61%）に及んでいた（Table 2）．

以前から，言及されていたインターフェロンによる拒絶反応の誘発は記載のある報告だけでみると75例中16例（13%）に認めたとされている（Table 2）．

以前のインターフェロンの週3回投与とリバビリン併用療法と比較してみると，なんと大雑把な計算であるが，ペグインターフェロンを用いた最新の報告とペグ化していないインターフェロンと，リバビリン併用療法でそのSVR率は26%と全く変わりはなかったことが判明した．さらに，驚いたことに中止率や脱落率もほとんど変わりのないことが明らかになった．すなわち，インターフェロンでもペグインターフェロン投与でも，リバビリン併用療法による成績は全く変わりのないことがわかった[55]．従来のインターフェロンよりもペグインターフェロンの方が，血中濃度，AUCさらにはコンプライアンスから通常の慢性肝炎に対してはより普遍化されているが，肝移植医療の領域では必ずしもそうではないようである．すなわち，副作用の発現が認められた際の対処に困難を要する可能性を示すからである．従来型インターフェロンで副作用が出現しても，血中濃度から考慮すると，即座に投与中止で，その濃度は下降し，副作用は改善するだろう．しかし，ペグインターフェロンの場合，その効果を血中濃度とするならば，副作用の継続が，例え投与中止しても改善されない可能性がある．勿論，中和抗体がない現状では，危険があるといわざるを得ない．したがって，肝移植後のインターフェロン投与に関しては，通常のインターフェロンで導入するのが副作用の面からも推奨されるかもしれないが，全くエビデンスのない話で，これらは今後の症例数の増加から結論が得られるのかもしれない．

HCV陽性レシピエントに対して，今，考えられているのは，以下の点である．①肝移植後は3～6カ月以内にインターフェロンとリバビリン併用療法を速やかに開始することである．②可能な限りステロイドは離脱状況が望ましい．③そして，副作用の点からインターフェロン用量，投与間隔，リバビリン用量は適宜漸減して，少なくとも半年，可能であれば48週間継続投与が望ましい．④脱落例に対しては，通常の慢性肝炎治療に即してトランスアミナーゼ値を正常化させる目的の抗炎症療法の継続を選択せざるを得ないと思われる．適切な薬剤として強力ネオミノファーゲンCとUDCA辺りが妥当であろうか．その場合，線維化の進展抑制が目標となるであろうが，臨床的事実は1つもないのが現状である．

特に，肝移植後，いつ抗ウイルス療法を開始するかが，1つの問題点である．肝移植後のプロトコール肝生検の妥当性は別として，術後3～6カ月，1年，1.5年後に肝生検を施行して，F1/A1以上の変化がみられた段階で抗ウイルス療法（ペグインターフェロンとリバビリン）を開始するのが世界の趨勢になりつつあるようであるが，preemptive treatmentの成績も良好なので，今後の症例の積み重ねが必要となってくるであろう[56]．

VI Prophylaxis

肝移植後のインターフェロンとリバビリン併用療法のコンプライアンスが極めて悪いとなると，

やはり肝移植前に抗ウイルス療法を試みようと考えるのは自然の流れである．勿論，肝移植の適応疾患であるから非代償性肝硬変がほとんどである．これら肝硬変に対する併用療法のコンプライアンスも肝硬変に合併する血小板減少などと合わせて困難であることも事実である．しかし，投与方法，投与量を考慮することにより，全く抗ウイルス療法を施行しない例に比して，確かにHCVの再感染が抑制されることも当然と考える．例えば，インターフェロンα2-bを100万単位と低用量にして週に3回投与し，さらに低用量のリバビリン400mgにて33%にHCV RNAの陰性化をみたとしている[57]．その他にも2，3の臨床的試みもある[58]．勿論，肝硬変に対するPEGインターフェロンとリバビリン併用療法は一部で標準治療よりSVR率が低値である[59]とされているが，肝硬変に対する併用療法の医学的エビデンス[60)~62)]としては，通常の慢性肝炎と同等のSVRを得るとされている．これらを考えるならば，何も非代償性肝硬変を対象にするのではなく，代償性肝硬変を対象に術前抗ウイルス療法を行えば効果を得ることが容易に予想される．しからば，代償性肝硬変を肝移植の適応として抵抗はないのかということになる．解決方法として，代償性肝硬変を有する肝細胞癌が最適な対象となるのではないかと筆者たちは考えている[63]．

われわれはすでに肝移植前に血中HCVRNAを短期間に陰性化する目的で速効性のインターフェロンβを用い，血小板減少に備えながら約2週間投与し，血中HCVRNAを4.2Meq/mlから陰性化を確認してから生体肝移植を行い，術後3年間HCVRNA陰性，肝機能検査値の正常化をもたらした症例を報告している[64)~66)]．

しかし，その後の症例ではあまりにも肝予備力低下のために予定の投与が完遂できず，再感染に甘んじているのも事実である．

筆者らは，HCV陽性の肝移植候補者のなかで，比較的肝硬変でもCTPスコアーの低い症例を対象にこの術前インターフェロンβの投与を考えている．そうすると，必然的にCTP分類Cの非代償性肝硬変はこの抗ウイルス療法の適応から外され，むしろ代償性肝硬変もしくは慢性肝炎を背景に有する（再発を繰り返す）肝細胞癌が最も適した術前治療群になるものと想定していることを，再度強調しておきたい．

さいごに

肝移植医療は医学的エビデンスがない状況で発展したという経緯がある．しかし，少なくともこのHCV感染と肝移植に関しては臨床的エビデンスを得る努力をしながら，慎重にその疑問を解いていきたいと考える[67)68)]．現時点ではHCVの肝移植後の再感染機構の解明がなされていないこと，欧米とわが国ではどうもその成績が異なるようであるが，いずれにせよHCVの再感染は長期観察すると移植成績に何らかの影響を及ぼすと思われるので，その適応，実践に関しては慎重でなければならないものと考える．

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Original Paper

Outcome and Pattern of Recurrence after Curative Resection for Hepatocellular Carcinoma in Patients with a Normal Liver Compared to Patients with a Diseased Liver

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KEY WORDS:
Hepatocellular carcinoma; Normal liver; Diseased liver; Recurrence

ABBREVIATIONS:
Hepatocellular Carcinoma (HCC); Alpha-Fetoprotein (AFP); Alanine Aminotransferase (ALT); Prothrombin Time (PT)

ABSTRACT

Background/Aims: The purpose of this study was to investigate whether differences existed in demography and outcome after resection for hepatocellular carcinoma (HCC) in patients with a normal liver compared to patients with a diseased liver.

Methodology: Twenty-seven Caucasian patients with HCC in a histologically proven normal liver (NL group) in the Netherlands and 141 Asian patients with HCC in a diseased liver (DL group) in Japan underwent a curative liver resection. Patient and tumor characteristics, post-resectional disease-free, overall survival rates and pattern of recurrence were investigated.

Results: HCC's in the NL group were found to be larger, in a more advanced stage and needed more extended resections compared to HCC's in the DL group. Microvascular invasion was similar in both groups, while capsule formation was observed less in the NL group. Overall survival and disease-free survival after curative resection were not statistically different between both groups. Also even after stratification for T-stage, there was no difference in survival. Although the rate of recurrence was similar in both groups, a significantly higher number of extrahepatic metastases was observed in the NL group.

Conclusions: Distinct demographic differences existed between patients with HCC in the NL group compared to patients in the DL group. Extrahepatic recurrences were more frequent after curative resection for HCC in a normal liver. No difference in survival was demonstrated between both groups.

INTRODUCTION

Hepatocellular carcinoma (HCC) developing in a normal liver is still a rare occurrence. However a rising incidence is reported especially in elderly males in the Netherlands (1,2). So far the results of resection are rarely reported and its biological behavior has not been fully elucidated (2-5). A confusing matter is that, in some reports, patients with a liver with clear signs of inflammation were included in study cohorts of non-cirrhotic livers (6-8). This is debatable because livers with active inflammation need to be considered abnormal because this has been shown to have impact on survival after liver resection (9,10). The aim of this study is to analyze the outcome after curative liver resection for HCC in two predefined distinct patient populations. The first is a Caucasian Dutch patient group with HCC in a histological normal liver, such as is prevalent in Europe and the USA. The second group is an Asian Japanese group with HCC in a diseased liver, which is common in the Eastern part of the world. By comparing these two distinct populations we hoped to gain insight in the Demography and biological behavior of HCC's occurring in histological normal livers.

METHODOLOGY

The medical records from 41 consecutive Dutch patients who had undergone a curative liver resection for HCC treated in the division of Hepato-Pancreato-Biliary surgery and Liver Transplantation, University Medical Center Groningen between 1980 and 2003 and consecutive 150 Japanese patients treated in the department of Transplantation and Digestive Surgery, Nagasaki University Graduate School of Biomedical Sciences between 1992 and 2003 were reviewed. Patients were included if they were Cau-

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casian (Dutch group) or Asian (Japanese group), they had undergone a curative liver resection and on the basis of the histology of the liver. A curative liver resection is defined as a partial hepatectomy with histologically clear margins (R0 resections). Normal livers were defined as livers without any histological sign of fibrosis, cirrhosis or inflammation. Diseased livers were defined as livers with histological presence of fibrosis or cirrhosis or signs of inflammation. In the Groningen unit, 27 patients out of 41 (66%) had HCC in a histologically proven normal liver (Normal Liver group: NL group). The median follow-up in these patients was 35 months (range 0.1-262). In contrast, in the Nagasaki unit 141 patients out of 150 (94%) had a HCC in a histologically proven diseased liver (Diseased Liver group: DL group). The median follow-up of these patients was 35 months (range 0.1-135). For the purpose of this analysis, these selected groups of patients with distinct differences in liver histology were included for further analysis. For the sake of homogeneity of the study population patients with fibrolamellar HCC were excluded from the analysis.

Serological presence of any hepatitis B antigen was considered as positive evidence of hepatitis B infection. Serologic presence of hepatitis C antibody was considered as positive evidence of hepatitis C infection. Before the establishment of the serological test for hepatitis C in 1988, status of hepatitis C infection was unknown in the six cases. The type of hepatic resection performed was classified according to the terminology of the International Hepato-Pancreato-Biliary Association (11). In both facilities, surgical treatment was considered only when a liver resection with curative intent could be performed and the projected liver remnant was large enough to provide adequate postoperative liver function. In the Dutch center this was done on the basis of estimated remnant volume with a minimum remnant volume of 25%. In the Japanese unit this was mainly done by measuring indocyanine green test (15 minutes retention) combined with other liver function tests.

The tumor size was defined as the largest diameter of the tumor specimen. Microscopic vascular invasion was defined as the presence of tumor emboli within the central vein, the portal vein, or large capsular vessels. To control for potential differences in clinicopathologic variables among centers, patients were also stratified according to the new American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) primary tumor (T) classification system (12). Tumor grade was assessed using the scheme outlined by Edmondson and Steiner and was based on the area showing the highest grade (13). Follow-up of the patients was done, in principle, every 3 months with serum alpha-fetoprotein (AFP) level and ultrasonography. When recurrence of HCC was suspected, computed tomography scanning was performed. In principal, (neo)adjuvant chemotherapy was not used in the both facilities.

Age, AFP level, biochemical parameters, tumor size and number were treated as continuous variables.

TABLE 1 Patient Characteristics

	Normal Liver group (n=27)	Diseased Liver group (n=141)	*p*-value
Age (years)	59 (26-76)	63 (20-80)	NS
Male gender	16 (59%)	116 (82%)	<0.01
Positive HepB serology	0 (0 %)	36 (26%)	<0.001
Positive HepC serology	0 (0 %)	80 (57 %)	
Positive Hep B&C serology	0 (0 %)	6 (4%)	
	6 data in the NL group were unknown		
ALT (U/L)	28 (10-150)	45 (9-222)	<0.01
Total Bilirubin (mg/dL)	0.6 (0.3-8.8)	0.7 (0.3-7.1)	NS
Albumin (g/L)	4.2 (2.0-5.2)	3.9 (3.0-4.8)	<0.05
Prothrombin time (%)	97 (81-111)	91 (54-122)	<0.05
Platelets (x10^3)	260 (138-513)	139 (40- 870)	<0.0001
AFP (ng/mL)	9 (3-13600)	20 (1.2-75610)	NS
Normal liver	27/27 (100%)		<0.01
Chronic hepatitis		77/141 (55%)	
Liver fibrosis/cirrhosis		64/141 (45%)	

ALT: alanine aminotransferase; AFP: alpha-fetoprotein; NS: not significant.

TABLE 2 Tumor Characteristics and Operative Methods

		Normal Liver group (n=27)	Diseased Liver group (n=141)	*p*-value
Tumor size (cm)		9.0 (1.7-25.0)	3.3 (0.8-17.0)	<0.0001
Tumor number		1 (1-3)	1 (1-6)	NS
Vascular invasion		12/27 (44%)	56/141 (40%)	NS
Capsule formation		20/27 (74%)	126/141 (89%)	<0.05
Tumor grade	well - mod differentiated	19/21 (90%)	129/138 (93%)	NS
	poorly differentiated	2/21 (10%)	9/138 (7%)	
		6 data in the NL group, 3 data in the DL group were unknown		
Tumor stage	T1	10 (37%)	73 (52%)	<0.05
	T2	8 (30%)	52 (37%)	
	T3	5 (18%)	10 (7%)	
	T4	4 (15%)	6 (4%)	
Operative methods	Wedge resection or Segmentectomy	6 (22%)	100 (71%)	<0.05
	Hemihepatectomy	16 (59%)	34 (24%)	
	Extended hemihepatectomy	5 (19%)	7 (5%)	
Postoperative mortality (<1M)		1 (3.7%)	4 (2.8%)	NS

NS: not significant.

All data were expressed as median value with ranges. Statistical analysis was done with Mann-Whitney u-test for continuous values and Chi-square test for categorical values. Survival was measured from the time of resection until death or last follow-up. Survival curves were constructed using the Kaplan-Meier product limit method and compared using log-rank test. Statistical difference was defined as a p value of less than 0.05. The StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA) was used for the all statistical analysis.

RESULTS

Table 1 shows the patients' characteristics in each group. Patients in the DL group were significantly more frequently male compared to patients in the NL

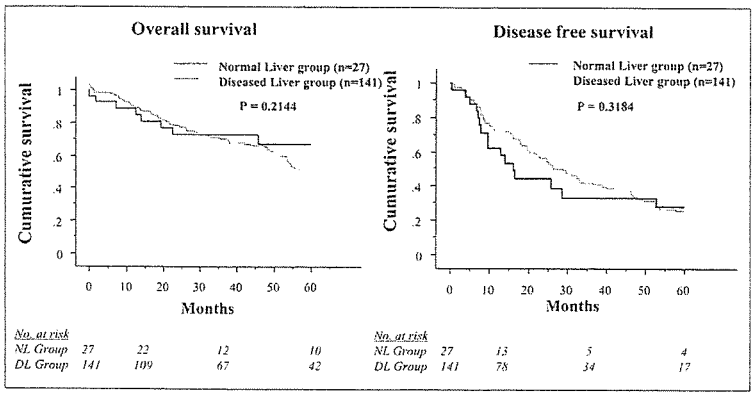

FIGURE 1 The overall and disease-free survival after curative liver resection for HCC in the normal liver and in the diseased liver. NL group: normal liver group; DL group: diseased liver group.

			Normal Liver group (n=27)	Diseased Liver group (n=141)
Intrahepatic only		8 (44.4%)	67 (80.0%)	
Intra- and extrahepatic	liver	+ lung	3 (16.6%)	3 (3.5%)
		+ lymph node		2 (2.3%)
		+ bone	1 (5.5%)	
		+ brain		1 (1.2%)
		+ peritoneum		2 (2.3%)
		+ bone + lung		1 (1.2%)
		+ lymph node + lung		1 (1.2%)
		+ lung + bone + brain		1 (1.2%)
		+ lung + adrenal gland		1 (1.2%)
Extrahepatic	bone		3 (16.6%)	2 (2.3%)
	lung		1 (5.5%)	1 (1.2%)
	lung + bone		1 (5.5%)	
	lymph node		1 (5.5%)	
	adrenal gland			1 (1.2%)
	peritoneum			1 (1.2%)
Total			18	84

group. No patients in the NL group were sero-positive for Hepatitis B or C compared with 87% in the DL group ($p<0.001$). Inherent to the normal histology, serum levels of alanine aminotransferase (ALT), albumin, prothrombin time (PT) and platelet counts were significantly better in the NL group. Serum AFP levels were not statistically different between the groups. In the DL group, 55% of the resected livers were chronically inflamed and 45% were fibrotic or cirrhotic.

Table 2 shows the characteristics of the HCC's in each group and types of resections performed. The size of the tumor was larger in the NL group compared to the DL group ($p<0.0001$). There was no difference in the number of HCC nodules at the time of resection. No difference in the rate of microscopic vascular invasion and grade of differentiation of the tumors between the groups was observed. There was significantly less capsule formation observed in the NL group compared to the DL group ($p<0.05$). Consequent to the finding that the HCC's found in the NL group were larger and more frequently invasive to the adjacent organs, tumor staging according to AJCC/UICC classification was higher in the NL group compared to that in the DL group ($p<0.05$). Due to the quality of the parenchyma and the better liver function, major resections were possible in the NL group (78%), while only wedge resections or segmentectomies were possible in 71% in the DL group.

The overall five-year survival and disease-free survival were not significantly different between the groups **(Figure 1)**. Even when patients were stratified with the new AJCC/UICC primary tumor classification system, there was no statistical difference between the groups in both overall and disease-free survival in each stage (overall 5-year survival: T1 DL 62.3%, NL 87.5%; T2 DL 29.4%, NL 64.8%; T3 DL 34.3%, NL 100%; T4 DL 41.7%, NL 0%, disease-free 5-year survival: T1 DL 33.7%, NL 41.7%; T2 DL 17.7%, NL 29.2%; T3 DL 0%, NL 20.0%; T4 DL 0%, NL 0%). In the DL group, 78 (55%) patients died; 58 (41%) due to tumor recurrence, eight (6%) due to postoperative liver failure or sepsis (four within one month), four (3%) due to chronic liver failure and eight (6%) due to miscellaneous diseases. In the NL group, one patient died within one month postoperatively due to a too large liver resection. Another died later due to sepsis. All other deceased patients (n=6, 22%) died due to tumor recurrence at the end of follow-up.

Table 3 summarizes the recurrence pattern of HCC in both groups. Recurrence of HCC occurred in 18 patients (67%) in the NL group and in 84 patients (60%) in the DL group (not significant). In the NL group, six patients (33%) had exclusively extrahepatic recurrence compared to only five (6%) in the DL group ($p<0.0005$). In those six patients who had exclusively extrahepatic recurrence in the NL group, HCC's in four patients (66.7%) were within AJCC/UICC tumor stage 1 or 2. In the NL group, a liver re-resection was performed for recurrent disease in two patients and in another patient a lumpectomy was done because of a recurrence in a lymph node. In the DL group, liver re-resection was performed in nine patients with liver-limited recurrence and in two patients a liver re-re-resection needed to be done. One patient underwent a bone resection of the spine, while the other one underwent lung surgery for solitary extrahepatic metastasis.

DISCUSSION

This study concerned a comparison of patients with HCC in two distinct homogeneous groups of patients. A Dutch (Caucasian) group of patients with a histologically proven normal liver (NL group) and a Japanese (Asian) group of patients with abnormal liver histology (DL group). In both groups only curative liver resections were performed. Although institutional differences in operative and postoperative management are present between both groups the long-term follow-up in both populations equalizes such differences to a great extent. Patients in the DL group

were significantly more frequently male compared to patients in the NL group. Patients in the NL group had significantly larger HCC's with less capsule formation compared to patients in the DL group. Also tumor stage was more advanced in the NL group compared to the DL group. This difference in size and consequently in tumor stage, might be explained by two reasons. Symptoms in patients with normal livers may appear later due to the greater functional reserve of the healthy remnant. Another reason might be the fact that those patients with normal liver are not screened for HCC while in Japan patients with a diseased liver are regularly screened for the development of HCC.

Despite the above-mentioned differences, the overall patient and disease-free survival was not different between both groups even after stratification for tumor stage. This indicates that Caucasian patients with a HCC in a normal liver have no survival benefit after a curative liver resection over Asian patients with a diseased liver. These findings correspond with a recent report from Esnaola *et al.* concerning a comparison of clinicopathological characteristics and outcome after liver resections for HCC in Japan, United States and France (14). However other reports showed different results (3,7,8,15). Shimada *et al.* reported better patient and disease-free survival after curative resection in patients with a non-fibrotic liver compared to those in patients with a fibrotic liver (7). Also, Grazi *et al.* reported a 5-year patient survival of 51% in patients without liver cirrhosis and 42.2% in patients with cirrhosis ($p<0.05$) (15). These differences might be explained by the heterogeneity of the patient groups. Especially, their non-fibrotic or non-cirrhotic group included patients with an inflamed liver (7,8,15). Additionally, fibrolamellar carcinomas were included, which has a distinctly different clinical behavior from normal HCC's (3).

Our analysis revealed an important difference in biological behavior of the HCC's between both groups. HCC's in Caucasian patients with normal livers become silently larger and show less capsule formation, a well-known poor prognostic sign (16). From this study it became apparent that also the recurrence pattern is different. Although overall recurrence rate (intra- and extrahepatic) was not different between both groups, exclusively extrahepatic recurrence was significantly ($p<0.0005$) more frequently observed in the patients with a normal liver (6/18; 33%) compared to patients with a diseased liver (5/84; 6%). This finding can be the explanation of the observation reported by Schlitt *et al.* about more frequent extrahepatic recurrences of HCC after liver transplantation for HCC in patients with a non-cirrhotic liver compared to HCC in patients with cirrhotic liver (17). Also in the European Liver Transplant Registry (ELTR) 2004, the 5-year survival after liver transplantation for HCC in a non-cirrhotic liver was worse compared to that in a cirrhotic liver (18). Our observation has implications for the follow-up of Caucasian patients with a HCC in a normal liver. During follow-up of patients resected for HCC in a normal liver we have to look specifically for these extrahepatic recurrences. Because chemotherapy has poor results for this type of tumor early recurrences outside the liver might be considered for surgery in selected patients with solitary extrahepatic metastasis (19-21). Also when recurrences do occur in the remnant liver this different biological behavior has consequences in Caucasian patients with HCC in the normal liver. A thorough survey for dissemination outside the liver should be done if the patient is considered for re-resection or transplantation (22,23).

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Biliary complications in recipients of living-donor liver transplantation

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Abstract
The key points of the management of biliary complications in recipients of living-donor liver transplantation are described. The characteristics of these complications are somewhat different from those in deceased-donor liver transplantation, mainly due to the technical difficulties. Appropriate prevention, diagnosis, and treatment are essential for successful transplants, to avoid the development of secondary biliary cirrhosis when complication occurs.

Key words Liver transplantation · Living donor · Biliary complication

Introduction

Although living-donor liver transplantation (LDLT) has been established as a therapeutic modality for endstage liver disease in both children and adults, biliary complication still remains the "Achilles' heel", as the major cause of graft loss. Thus, adequate diagnosis and treatment are required to avoid the development of secondary biliary cirrhosis when complication occurs. There are several advantages of LDLT over deceased-donor liver transplantation (DDLT), including good graft viability with short ischemia time under conditions of elective surgery, but there are technical difficulties because of the anatomical limitations with tiny (and frequently, multiple) bile ducts when compared to DDLT.[1,2] Regarding the procedure for LDLT, duct-to-duct reconstruction has taken the place of conventional hepaticojejunostomy, with several possible advantage. Treatment of complications should be considered according to their clinical manifestations, also taking into consideration the type of reconstruction. Herein, we describe key points in the prevention and management of biliary complications after LDLT.

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Incidence of and risk factors for biliary complications in recipients of LDLT

The reported incidences of biliary complications in children with hepaticojejunostomy and adults with duct-to-duct anastomosis are shown in Tables 1[4–7] and 2.[8–15] The etiology of biliary complications in LDLT is multifactorial, and several risk factors have been proposed, including the age and sex of the recipient, the severity of the original disease, the number and size of reconstructed bile ducts, the type and methods of reconstruction, and ABO blood type incompatibility. The Kyoto group[5] reported that, in their 400 patients, including 55 adults, the risk factors for bile leakage were biliary stent placement, intrapulmonary shunting, and female recipients. The risk factors they proposed for biliary stricture were anastomotic leakage, cytomegalovirus infection, hepatic artery complication, and female recipients.[5] Most of these complications are not specific for LDLT. Preoperative status, immunologic factors, infections, and hepatic artery complications are all risk factors in DDLT also. Different from DDLT, complications that could be related to preservation injury, such as diffuse biliary casts, are rare in LDLT, because of good graft viability with shorter ischemic time, but possible technical difficulties with tiny bile ducts in the graft liver finally contribute to the higher incidence of biliary complications in LDLT (of up to 60%) than in DDLT. Initially, LDLTs were performed for children with biliary atresia, so the procedure of biliary reconstruction was hepaticojejunostomy.[16,17] In many centers this has currently been replaced by duct-to-duct reconstruction, which has several theoretical advantages over hepaticojejunostomy, such as shorter operation time, no contamination by bowel contents, and a physiological

Table 1. Biliary complications in pediatric recipients of LDLT

Center	Year	No. of patients	Bile leakage (%)	Biliary stricture (%)	Overall biliary complication rate (%)	Reference number
Brussels, Belgium	1999	42	3 (7)	10 (24)	34	4
Kyoto, Japan	2001	400[a]	45 (12)	35 (9)	18	5
Hamburg, Germany	2004	44	NA	NA	5	6
Johns Hopkins, USA	2004	48	10 (21)	2 (4)	33	7

NA, not available
[a] Includes 55 adult patients

Table 2. Biliary complications in adult recipients of LDLT with duct-to-duct reconstruction

Center	Year	No. of patients	Bile leakage (%)	Biliary stricture (%)	Overall biliary complication rate (%)	Reference number
Tennessee, USA	2001	6	4 (67)	0	67	8
Paul-Brousse, France	2001	7	0	0	14	9
Nagasaki, Japan	2002	5	0	1 (20)	20	10
Keio, Japan	2002	10	4 (40)	4 (40)	0	11
Kyoto, Japan	2002	52	5 (10)	12 (23)	31	12
Hong Kong, China	2004	41	3 (7)	10 (24)	24	13
Tokyo, Japan	2004	81	12 (15)	10 (12)	32	14
Mt Sinai, USA	2004	96	13 (14)	20 (21)	34	15

result with preservation of the function of the sphincter of Oddi. However, possibly due to its technical problems, including preservation of the blood supply for the recipient bile ducts, the incidence of complications was generally reported to be higher in duct-to-duct reconstructions, so that some investigators now advocate routine hepaticojejunostomy.[11,18]

Prevention of biliary complications in recipients of LDLT

Donor surgery

Preoperative evaluation of the biliary anatomy in the donor is essential to rule out complicated anatomy of the graft bile duct. Several noninvasive modalities with three-dimensional analyses have been introduced, including magnetic resonance imaging and computed tomographic cholangiography.[19,20] However, these imaging studies are still not sufficiently reliable;[21,22] thus, intraoperative cholangiography should be performed to decide on the appropriate point of transection of the bile duct. In right-liver grafts, in particular, the incidence of multiple ducts is high, reported to be up to 80% in previous studies,[10,23] due to the anatomical characteristics of the right liver.[1] Although the relationship between the presence of multiple ducts and the incidence/severity of biliary complications is still controversial,[9,10] several studies have indicated that the presence of multiple bile ducts in the graft is a risk factor for biliary complications;[15,24] thus, the number of bile ducts should be as low as possible. There is a technical dilemma in considering the balance between donor safety and graft quality. The stump of the graft bile duct should be apart from the confluence to avoid stricture of the remnant bile duct in the donor liver; however, this contributes to a higher incidence of multiple ducts in the graft. Intraoperative cholangiography, using C-arm fluoroscopy, might be useful in confirming the bile duct anatomy and an appropriate transection point. To maintain sufficient blood supply for the graft bile duct, the connective tissue around the bile duct should be left in place, with minimal dissection. The use of electric cautery around the hilar plate should be strictly avoided.

Recipient surgery

The procedure of conventional hepaticojejunostomy is well established, but technical problems still remain in duct-to-duct reconstruction. When a duct-to-duct reconstruction is planned, there are two major technical considerations: (1) to maintain a viable blood supply to the biliary tract, and (2) to leave sufficient length of the bile duct for a tension-free anastomosis. To achieve these criteria, the connective tissue around the bile duct should be kept intact with the hepatic artery, as high as possible in the hepatic hilum. However, sufficient length

of the hepatic artery is also required for tension-free arterial anastomosis; thus, it should be isolated from the bile duct. Theoretically, the blood supply to the recipient extrahepatic bile duct should be maintained, even though the hepatic arteries are dissected away from the bile duct, because the supraduodenal segment of the bile duct receives the majority of its blood supply via axial 3 o'clock and 9 o'clock arteries from the posterior-superior pancreatico-duodenal artery and gastroduodenal artery.[10,25] However, the confluence and hepatic ducts are reported to be nourished via the hilar plexus at the inferior aspect of the hilar plate, which mainly receives its blood supply by the right and left hepatic arteries;[26,27] thus, the hepatic arteries should not be dissected away from the bile ducts so that the whole arterial circulation is maintained at the pericholedochal plexus. To overcome this possible dilemma, Lee et al.[28] recently introduced a new intrahepatic Glissonian approach for recipient hepatectomy, which allowed tension-free anastomosis with sufficient length of bile duct; results showed no leakage and a 10% incidence of biliary stricture, during a mean follow-up of 11 months. Further follow-up is required to determine the feasibility of this new technique. With regard to the suture technique (continuous or interrupted) and suture material (size, absorbable or nonabsorbable, monofilament or braided), no consensus has been reached. The Kyoto group recommended continuous sutures with absorbable monofilament material, 6-0 in size,[12] while the Tokyo group adopted interrupted sutures with absorbable braided material, 4-0 in size.[14] The Hong Kong group prefers interrupted sutures with nonabsorbable monofilaments.[13] The incidence of biliary complications at these centers is similar, at around 30%.

The efficacy and feasibility of stent placement is also under debates. The Hong Kong group have argued for the safety and feasibility of biliary anastomosis without a stent.[13] In DDLT, Scatton et al.[29] reported, in a multicenter prospective randomized trial, that a significantly higher incidence of biliary complications was shown in the T-tube group. However, in LDLT, many centers prefer to adopt stent placement, because of its possible advantages for patient management after transplantation, with easy access to the bile duct and ability to perform cholangiography. Also, in LDLT, a prospective randomized study with sufficient follow-up is required to finally determine the efficacy/feasibility of stent placement.

Diagnosis of biliary complications in recipients of LDLT

The clinical manifestations of biliary complications after liver transplantation vary considerably. Some patients may have mild biliary enzyme elevation without any symptoms, while others may have fulminant cholangitis with sepsis. Accordingly, an appropriate diagnosis should be made based on all the clinical findings, including liver function test results, inflammatory changes, imaging studies, and liver biopsy, when applicable. Computed tomography and ultrasound sonography are both useful to detect intrahepatic bile duct dilatation related to an anastomotic stricture, and abscess formation due to bile leakage. When patients have a biliary stent or T-tube, cholangiography can be performed. For duct-to-duct anastomosis, endoscopic cholangiography is valuable not only for diagnosis but for use in treatment, with stent placement for anastomotic strictures, as outlined below.

Treatment of biliary complications in recipients of LDLT

Depending on the timing, severity, and clinical manifestations of biliary complications, appropriate treatment should be adopted to avoid the development of secondary biliary cirrhosis. Bile leakage at the cut surface of the liver is usually managed successfully by percutaneous drainage without laparotomy. If the bile leakage from the anastomosis is severe and refractory, even after adequate biliary drainage, for both hepaticojejunostomy and duct-to-duct reconstruction, surgical revision of the anastomosis should be performed.[14] A duct-to-duct reconstruction, with anastomotic leakage/stricture is usually converted to a hepaticojejunostomy when surgical intervention is done.[30] Even if an anastomotic leakage is minor, it will always contribute to subsequent stricture;[5] therefore, treatment of the leakage is required. For an anastomotic stricture in a hepaticojejunostomy, conventional radiologic intervention, with stent placement or balloon dilatation after percutaneous biliary drainage, is usually successful.[5,31] For a duct-to-duct anastomosis, the additional option of endoscopic management is available. As mentioned elsewhere in this single-topic supplement of the *Journal of Hepato-Biliary-Pancreatic Surgery*, the Kyoto group has introduced the endoscopic insertion of stents, with promising results (see article by Yazumi et al., page 502). Also, the unique approach of endoscopic magnet compression anastomosis has been reported.[32] With any of these treatments, transplant physicians should carefully follow their patients after the treatment has been initiated, and if the condition is refractory and the patient develops secondary biliary cirrhosis, replacement of the liver graft is often warranted to avoid a fatal outcome.

Biliary complications in the living donor

According to a survey of outcomes in 1508 living donors from five Asian centers, 15.8% had various complications, including 6.8% with bile leakage and 1.1% with biliary stricture.[33] In another survey, from the Japanese Liver Transplantation Society,[34] 11% of 1852 donors had biliary leaks and strictures; the majority of these complications occurred after right hepatectomy. Ten donors underwent surgical revision for biliary complications.

Conclusion

LDLT has gained a role even in western society to solve the problem of donor shortages. However, technical dilemmas still do exist, especially in regard to biliary reconstruction, as mentioned in this article. Further clinical trials are required to standardize the reconstruction procedure, and this should minimize the biliary complications after LDLT.

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