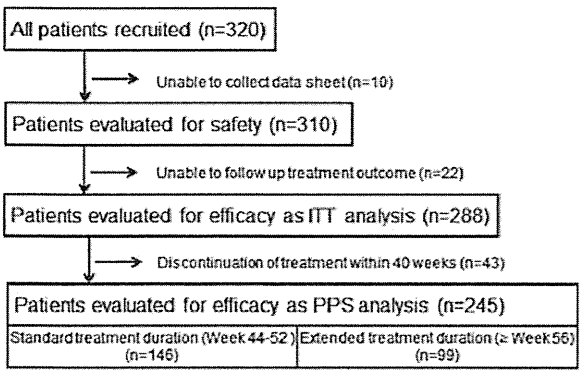

Fig. 1　Flow diagram of the patient's enrollment.

7）主要評価項目

主要評価項目は，治療終了後24週時のHCV-RNA陰性化（SVR）とし，Intention-to-treat（ITT，1回以上治療薬の投与を受け，1回以上有効性の観察がある集団）解析およびPer Protocol Set（PPS，44週間以上治療継続できた集団）解析をおこなった．本来ITT解析は登録された症例を全て対象とすべきであるが，調査票回収不能や有効性評価欠落などのプロトコール違反を除外するため上記のような定義で解析した．

8）副次的評価項目

投与開始4週，8週，12週，16週，20週，24週，48週，治療終了時のHCV-RNA陰性化率，HCV-RNA陰性化時期とSVR率との関係，背景因子別（年齢，性，IFN治療歴，前治療効果，BMI，臨床検査値，HCV-RNA量，組織学的所見（A因子，F因子），PEG-IFNα-2aおよびRBVのadherence）のSVR率とした．なおadherenceは，プロトコールに規定された48週間の予定総投与量に対する実際の総投与量のパーセンテージとした．

9）安全性判定

有害事象，臨床検査値（好中球数・血小板数・ヘモグロビン量の推移）および投与継続率，減量率，中止率について検討した．

また血球減少については，治療期間中の最小値を以下の基準に基づきgrade分類を行なった．好中球数grade 1：1,500 /μL以上，grade 2：1,000 /μL以上1,500 /μL未満，grade 3：500 /μL以上1,000 /μL未満，grade 4：500 /μL未満，血小板数grade 1：7.5万/μL以上，grade 2：5万/μL以上7.5万/μL未満，grade 3：2.5万/μL以上5万/μL未満，grade 4：2.5万/μL未満，ヘモグロビンgrade 1：10 g/dL以上，grade 2：8 g/dL以上10 g/dL未満，grade 3：6.5 g/dL以上8 g/dL未満，grade 4：6.5 g/dL未満．

10）統計学的解析

背景因子別のSVR率の有意差検定にはχ^2検定を行なった．SVRとnon-SVRの背景因子の比較には，χ^2検定およびunpaired t-testを行い，有意な因子についてロジスティック回帰による多変量解析を行なった．なお，有意水準を5%未満とした．

なお本研究は鹿児島大学医学部・歯学部附属病院臨床研究倫理委員会の承認を受けている．

結　果

1. 登録状況（Fig. 1）

2008年1月～12月で73施設から320例が登録された．そのうち2011年2月28日の時点で調査項目記入用紙の回収が可能であった310例を解析対象とした．安全性評価は310例全例で，効果判定は判定不能の22例を除く288例で解析を行った．

2. 患者背景

全例（310例）および効果判定可能例（288例）の患者背景をTable 1に示す．効果判定可能例のうち44週以上投与された完遂例（PPS）は245例（85.1%）で，そのうち標準投与は146例，延長投与は99例であった．プロトコールでは投与開始後12週目にHCV-RNAが陽性であれば延長投与可能としていたが，実際には延長投与例の中に12週目までにHCV-RNAが陰性化（early virological response：EVR）しているにもかかわらず延長投与が行われた症例が30例含まれていた．EVRにおいて延長投与が行われた例は標準投与例と比較して，高齢，再治療例が多い，BMIが高い，血小板が少ない，陰性化時期が遅いなどの背景の特徴があった（Table 2）．

3. ウイルス学的効果

①効果判定可能例（288例）におけるSVR率

ITT解析ではSVR率53.1%（153/288）であり，44週間以上投与できた治療完遂例のPPS解析では59.6%（146/245）であった．

②PPS（245例）における4週毎のウイルス陰性化率（Fig. 2）

治療期間中にTaqMan PCRで「検出せず」を示したのは，4週目（RVR）17.2%，12週目（EVR）58.0%，48週目88.3%，終了時84.1%であった．

③標準投与例，延長投与例におけるウイルス陰性化時期別SVR率（Fig. 3）

12週間以内のHCV-RNA陰性化例においては，標準

Table 1 Baseline characteristics of the patients.

	Patients for safety assessment (n＝310)	Patients for efficacy assessment (n＝288)
Age (years)	58.8±9.3	58.9±9.1
Gender (male/female)	133/177	119/169
History of IFN treatment (no/yes)	181/129	169/119
Response of prior treatment (relapse/non-response)	41/52	41/44
BMI (kg/m^2)	23.3±3.4	23.3±3.3
White blood cell count (/μL)	4999±1554	4979±1503
Neutrophil count (/μL)	2609±1084	2599±1073
Hemoglobin (g/dL)	13.7±1.5	13.7±1.5
Platelet count (×10^4/μL)	16.2±4.9	16.1±4.7
ALT (IU/L)	68.5±75.5	68.6±75.7
γ-GTP (IU/L)	61.0±71.3	60.4±71.2
Total cholesterol (mg/dL)	172.2±32.9	172.4±32.9
LDL cholesterol (mg/dL)	99.5±25.9	100.9±25.1
Triglyceride (mg/dL)	106.1±51.2	105.9±51.2
AFP (ng/mL)	9.3±13.9	9.3±13.9
HCV-RNA (Log IU/mL)	6.4±0.8	6.3±0.8
Histological grading (A0/A1/A2/A3)	3/84/95/19	3/79/90/19
Histological staging (F0/F1/F2/F3/F4)	7/85/62/40/11	7/80/61/37/10

投与，延長投与ともに70％以上のSVR率が得られ，両者に差は認められない．一方，13週目以降にHCV-RNA陰性化が得られた例においては，延長投与の方が標準投与よりも高いSVR率が得られ，特に25週以降の陰性化例においては，標準投与では1例のSVRも得られなかった．しかし，37週目以降に陰性化した例では，延長投与してもSVRとなった例は1例もなかった．

④標準投与例における年齢別，性別SVR率（Fig. 4）

男女別ではSVR率に有意な差はなかったが，60歳以上では60歳未満よりも有意にSVR率が低かった（45.9％ vs. 63.7％）．年齢と性で区分すると，60歳以上の女性のSVR率が42.6％と最も低値であった．

⑤標準投与例におけるSVR例とnon-SVR例の比較（単変量解析）（Table 3）

治療前の因子では，年齢，BMI，血小板数，総コレステロールおよび治療前HCV-RNA量に有意な相違が見られ，治療開始後の因子においては，HCV-RNA陰性化時期，治療期間とPEG-IFNα-2aおよびRBVのadherenceに有意な差を認めた．

⑥標準投与例においてSVRに寄与する因子の解析（多変量解析）（Table 4）

単変量解析にて有意であった項目について多変量解析を行った結果，治療前の因子においては，年齢が若いこと，BMIが低いこと，総コレステロールが高いこと，HCV-RNA量が少ないこと，が独立してSVRに寄与していた．これらに治療開始後の因子を加えると，EVRであることが唯一のSVRに関連する因子となった．

4. 有害事象発現率および治療中止率

①有害事象（血球減少以外）の発現率（Table 5）

有害事象は213例（68.7％）に認め，総発現件数は658件であった．有害事象の中では皮膚および皮下組織障害が29.7％と最も多かった．

②血球減少発現率（grade分類）（Table 6）

ほぼ全例で血球成分すべてにgrade 1以上の減少が見られ，grade 3以上の血球減少は，好中球で58.7％，血小板で5.5％，ヘモグロビンで5.1％であった．

③中止率とその原因

44週未満での中止例は43例（13.9％）であったが，そのうち有害事象による中止は14例（4.5％）であった．それ以外の中止理由は，無効中止15例，偶発的合併症3例，経過観察不能（通院せず，など）11例であった．

考　察

九州地区は本邦の中ではHCVキャリア率および肝癌

Table 2 Comparison of patient characteristics between standard and extended treatment duration in cases with early virological response.

	Standard treatment duration (n＝111)	Extended treatment duration (n＝30)	P-value
Age (years)	57.0±9.5	61.7±7.2	0.0139*
＜60/≧60	59/52	9/21	0.0243**
Gender male/female	52/59	11/19	0.3197**
History of IFN treatment initial treatment/retreatment	71/40	11/19	0.0072**
Response of prior treatment relapse/non-response	21/6	10/4	0.0502**
BMI (kg/m^2)	22.4±2.7	24.3±3.7	0.0028*
Neutrophil count (/μL)	2739.9±1087.4	2602.6±1275.2	0.5764*
Hemoglobin (g/dL)	13.9±1.4	13.7±1.4	0.5269*
Platelet count (×10^4/μL)	17.2±4.7	14.6±4.2	0.0058*
ALT (IU/L)	71.7±105.6	50.4±36.6	0.2800*
γ-GTP (IU/L)	53.3±69.5	54.0±99.6	0.9669*
Total cholesterol (mg/dL)	177.7±28.4	176.2±34.2	0.8309*
LDL cholesterol (mg/dL)	122.1±144.8	93.7±30.9	0.5623*
Triglyceride (mg/dL)	97.6±50.4	119.6±72.0	0.0890*
HCV-RNA (Log IU/mL)	6.3±0.7	6.1±1.3	0.4188*
5.0-5.9/6.0-6.9≧7.0	29/62/16	5/18/3	0.2645**
Histological grading A0-A1/A2-A3	31/45	9/9	0.7267**
Histological staging F0-2/F3-4	64/12	14/5	0.5188**
Timing of HCV-RNA undetectable ≦Week 4/Week 5-8/Week 9-12	36/40/35	4/8/18	0.0127**

Mean±SD *t-test, **Chi-square test

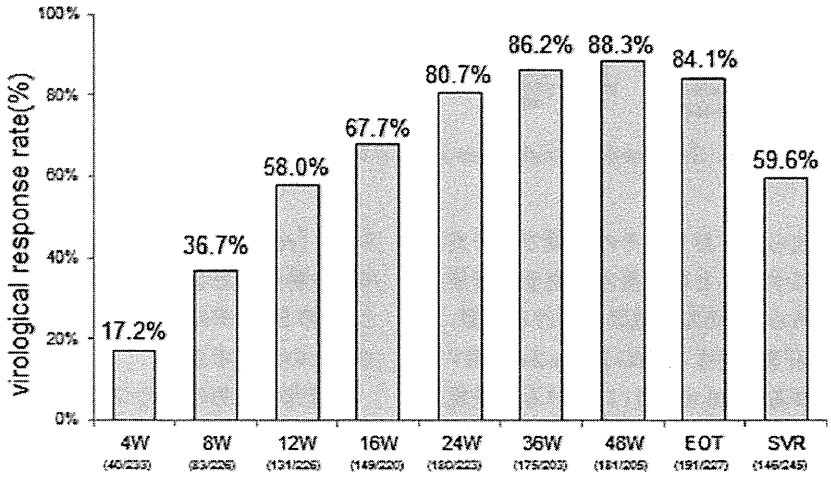

Fig. 2 Virological response rates at each point during PEG-IFNα-2a+RBV treatment in per protocol set population.

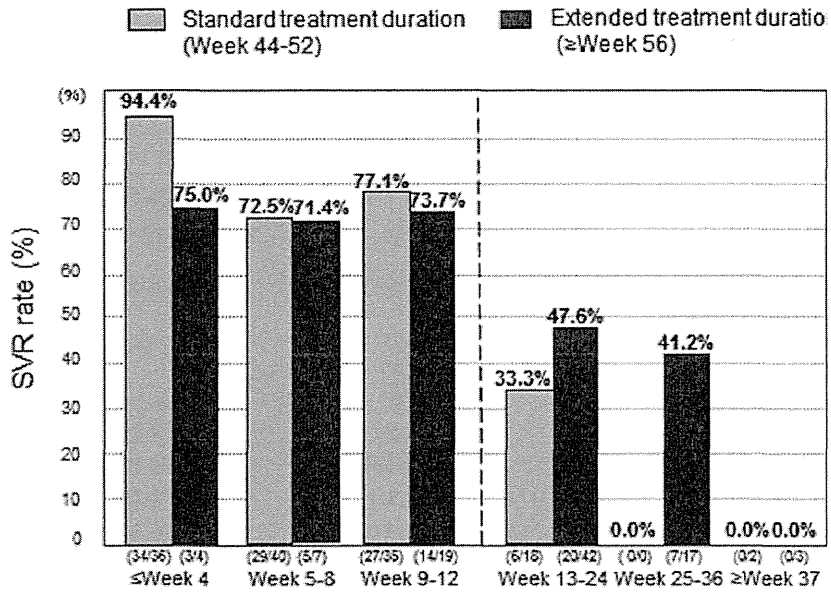

Fig. 3 Sustained virological response rates in patients with standard and extended treatment duration stratified by the time at which serum HCV-RNA became undetectable.

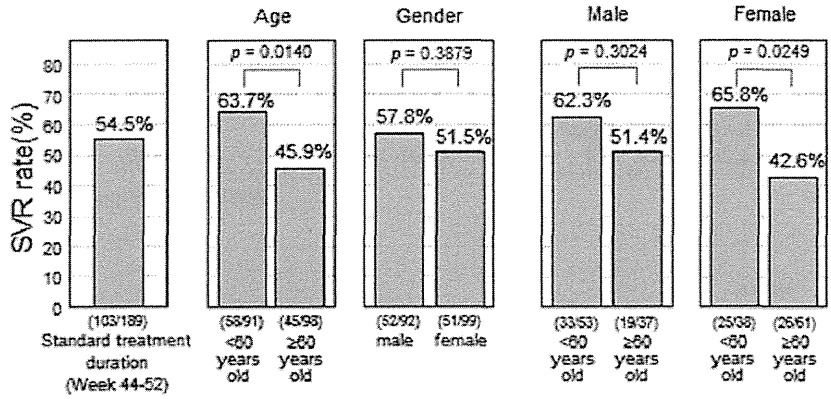

Fig. 4 Sustained virological response rates according to age and gender.

死亡率が高いことが知られており，その地域での肝炎治療の実態を明らかにすることは今後の肝癌予防対策を講じる上で重要である．今回九州地区における1型，高ウイルスのC型慢性肝炎に対するPEG-IFNα-2a＋RBV療法の市販後のいわゆる「real world」における治療成績を明らかにするため，九州全域の主な専門医療機関における多数例での前向き多施設共同研究を行った．

まずSVR率に関しては，治療完遂例で59.6%，ITT解析でも53.1%と海外および国内で行われた治験の成績[1)~3)]とほぼ同等の成績が得られた．この成績は，2009年から72週間までの長期投与が可能となった影響もあるが，「real world」での対象は治験の対象とは異なり，年齢や併発疾患など様々な条件が悪いことを考慮すると，このSVR率はかなり良好な成績であると言えるのではないかと考える．

本研究の目的のひとつは，それまでアンプリコア法により行われていたIFN治療中の効果予測を，2007年12月に臨床で使用可能となった高感度のHCV-RNA測定系であるTaqMan PCRを用いて検討することであった．結果として12週目までにHCV-RNAが「検出せず」まで減少した例においては標準投与と延長投与との間に差が見られず，13週から36週までに陰性化した例に

Table 3 Comparison of patients characteristics between SVR and Non-SVR groups.

	Non-SVR (n=86)	SVR (n=103)	P-value
Age (years)	60.0±10.0	56.8±9.4	0.0254*
<60/≥60	33/53	58/45	0.0140**
Gender male/female	38/48	52/51	0.3879**
History of IFN treatment initial treatment/retreatment	50/25	67/23	0.3301**
Response of prior treatment relapse/non-response	10/15	15/8	0.0806**
BMI (kg/m^2)	23.4±3.7	22.4±2.8	0.0297*
<25/≥25	61/23	84/19	0.1453**
White blood cell count (/μL)	4920±161	5093±147	0.4283*
Neutrophil count (/μL)	2492±990	2696±1104	0.2062*
Hemoglobin (g/dL)	13.7±1.5	14.0±1.5	0.1391*
Platelet count (×10^4/μL)	15.2±4.6	17.1±4.7	0.0066*
ALT (IU/L)	68.1±54.3	75.8±109.7	0.5505*
γ-GTP (IU/L)	67.3±71.2	58.0±70.9	0.3920*
Total cholesterol (mg/dL)	168.5±34.5	178.8±28.8	0.0469*
LDL cholesterol (mg/dL)	99.7±24.9	104.8±24.6	0.3108*
Triglyceride (mg/dL)	111.0±53.3	98.2±46.7	0.1277*
HCV-RNA (Log IU/mL)	6.5±0.6	6.2±0.8	0.0209*
5.0-5.9/6.0-6.9/≥7.0	13/53/18	30/53/16	0.0854**
Histological grading A0-A1/A2-A3	24/35	28/42	0.9377**
Histological staging F0-2/F3-4	44/16	59/11	0.1249**
Timing of HCV-RNA undetectable ≤Week 4/Week 8-12/≥Week 13	16/11/23	69/27/7	<0.0001**
Treatment duration (weeks) <Week 44/≥Week 44-52	36/50	7/96	<0.0001**
PEG-IFNα-2a Adherence <60%/60-80%/≥80%	30/16/33	12/9/82	<0.0001**
Ribavirin Adherence <60%/60-80%/≥80%	27/24/27	17/18/66	<0.0001**

Mean±SD *t-test, **Chi-square test

おいて延長投与の優位性があり，従来のアンプリコア法で得られていた結果と同様であった．よって現在の厚生労働省がガイドラインで示されている延長投与の基準は，TaqMan PCR 法を用いた場合においても妥当なものであることが検証された．

次に治療効果に影響する因子に関しては，これまでにウイルス側因子として HCV-RNA 量，コア領域の 70 番，91 番アミノ酸変異[8]，NS5A 領域の ISDR 変異[9]，IRRDR 変異[10]，宿主側因子として年齢，性，IL28B 領域の遺伝子多型[11][12]，線維化，インスリン抵抗性[13]，治療因子として PEG-IFN または RBV の adherence，延長投与などが報告されている[14]．本研究では延長投与を行う基準を規定していなかったため，標準投与例のみで治療効果に寄与する因子を解析してみると，治療前の因子としては年齢，BMI，総コレステロール，HCV-RNA 量が有意な因子であった．IL28B やウイルス変異の検査は現時点では保険適応となっていないため，一般臨床においては 48 週間の標準治療の効果予測としてこれらの因子が指標になるものと考えられる．BMI やコレステロールなど治療前に介入可能な因子に関しては，今後介入法の検討が必要であろう．また本研究でも明らかになったように，高齢女性における治療効果不良の問題も残されている．我が国の高齢女性にはウイルス変異やメタボリック因子などの IFN 抵抗性要

Table 4 Multivariate analysis for the factors associated with sustained virological response (in cases with standard treatment duration).

Factors		Before start of therapy			All		
		Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	every 10 years of age	0.600	0.386-0.896	0.0168	0.580	0.270-1.178	0.1473
BMI	every 5 kg/m^2	0.487	0.252-0.915	0.0280	0.637	0.213-1.848	0.4069
Total cholesterol	every 20 mg/dL	1.279	1.011-1.635	0.0435	1.349	0.940-1.987	0.1123
Platelet count	every 20000/μL	1.105	0.949-1.296	0.2038	0.918	0.716-1.178	0.4946
HCV-RNA	every 1 log IU/mL	0.535	0.305-0.887	0.0205	0.555	0.236-1.195	0.1521
EVR		—	—	—	24.651	6.709-125.889	<0.0001
Treatment duration	every 4 weeks	—	—	—	1.189	0.819-1.772	0.3738
PEG-IFNα-2a Adherence	every 20%	—	—	—	1.803	0.817-4.047	0.1433
Ribavirin Adherence	every 20%	—	—	—	0.991	0.524-1.851	0.9762

EVR: early virological response

Table 5 Adverse events (except for cytopenia)

System Organ Class†	n (%)
General disorders and administration site conditions	50 (16.1%)
Skin and subcutaneous tissue disorders	92 (29.7%)
Psychiatric disorders	27 (8.7%)
Gastrointestinal disorders	30 (9.7%)
Musculoskeletal and connective tissue disorders	9 (2.9%)
Respiratory, thoracic and mediastinal disorders	8 (2.6%)
Metabolism and nutrition disorders	14 (4.5%)
Eye disorders	6 (1.9%)
Renal and urinary disorders	6 (1.9%)
Vascular disorders	2 (0.6%)
Hepatobiliary disorders	8 (2.6%)

Number of patients for safety assessment: 310
Number of patients with at least one adverse event: 213
Number of adverse events: 658
†It is reference about MedDRA.

因が集積しているとの報告があり[15]，これらの症例に対してテラプレビルなどの新規抗ウイルス薬をどのように使用していくかも今後の重要な課題である．

治療開始後の因子を加えて解析すると，SVRに寄与する因子として治療前因子はすべて有意ではなくなり，EVRのみに集約されることから，治療前にPEG-IFNα-2a＋RBV療法の効果予測をあまり綿密に行うより，現実的には治療のresponseをみてから方針を判断するresponse-guided therapyがよいのではないかと考える．

しかし，すでに現在の「real world」ではEVRが得られなかったり，EVRであっても8週目HCV-RNAが陽性の高齢女性や線維化進展例においては72週間の延長投与が一般的に行われるようになっており，本研究で抽出された治療効果規定因子はあくまで48週間治療に限定した因子と捉えなければならない．さらに，EVRでありながら延長投与された例の中に高齢者や線維化進展例が多く含まれており（Table 2），本研究の標準治療における解析にはこれらの症例を除外していることから，結果的に条件の比較的良い群が解析対象となったバイアスが存在することも念頭に置く必要がある．

有害事象に関しては，開発治験時のものと発生率に大差なく，副作用による中止率も低く，本治療は一般

Table 6 Incidence of cytopenia: grade classification

Factor	Grade classification	Number of events (%)
Neutropenia	Grade 1	29 (9.4%)
	Grade 2	87 (28.1%)
	Grade 3	161 (51.9%)
	Grade 4	21 (6.8%)
	Total	298 (96.1%)
Thrombocytopenia	Grade 1	203 (65.5%)
	Grade 2	88 (28.4%)
	Grade 3	17 (5.5%)
	Grade 4	0 (0.0%)
	Total	308 (99.4%)
Anemia	Grade 1	131 (42.3%)
	Grade 2	162 (52.3%)
	Grade 3	15 (4.8%)
	Grade 4	1 (0.3%)
	Total	309 (99.7%)

Number of patients for safety assessment: 310

臨床においても専門医の下できちんと管理して行えば，安全に行える治療であることが証明できた．

近年，C型肝炎の治療は直接ウイルスに作用するDAA製剤の開発が進み，今後DAAによる治療が中心となると予想されている．すでに本邦でもプロテアーゼ阻害薬であるテラプレビル[16)17)]が使用可能となり，1型，高ウイルスの難治性C型慢性肝炎に対しては，PEG-IFN＋RBVにテラプレビルを併用する3剤療法が第一選択とされている[18)]．しかし我が国のC型肝炎患者は高齢化している実態があり，現在のDAAでは使用できない，または次世代のDAA製剤が使用できるまで待てない，という患者が現実的にはたくさん存在する．このような背景を考慮すると，難治性C型慢性肝炎であってもPEG-IFNα-2a＋RBV療法で安全に50%以上のSVR率が得られることを「real world」の多数例で証明できた今回の試験の意義は大きいと考えられる．

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Efficacy and safety of pegylated interferonα-2a plus ribavirin treatment in refractory chronic hepatitis C patients —a multi-center study in Kyushu—

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We examined the efficacy and safety of peginterferon (PEG-IFN) alfa-2a plus ribavirin (RBV) therapy for chronic hepatitis C (CHC) patients with genotype 1 and high viral load by multi-center (73 institutions) study in Kyushu and totally 320 patients were enrolled. The sustained virological response (SVR) rates were 53.1% and 59.6% in intention-to-treat and per protocol set analysis, respectively. Treatment prolongation over 48 weeks was more effective in cases which serum HCV-RNA became negative between 13 and 36 weeks after start of therapy. Multivariate analysis for baseline characteristics revealed that age, BMI, total cholesterol and viral load were significantly associated with SVR. However, when added on-treatment factors, early virological response was the only factor associated with SVR. Discontinuation of treatment due to adverse events was no more than 4.5%. In conclusion, PEG-IFN alfa-2a plus RBV treatment to refractory CHC patients is a well tolerated and can achieve over 50% of SVR.

Key words: refractory chronic hepatitis C　pegylated interferon α-2a plus ribavirin treatment　anti-viral effect　multi-center study　Kyushu region

Kanzo 2013; 54: 266—276

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＜短　報＞

腎機能からみたC型慢性肝炎に対するペグインターフェロンα-2b/リバビリン/テラプレビル三剤併用療法における貧血の予測

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はじめに：Peginterferon α-2b（Peg-IFN）/Ribavirin（RBV）/Telaprevir（TVR）三剤併用療法により難治性のC型慢性肝炎（CHC）においても高い治癒率が得られる一方で，貧血や皮膚症状などの程度が強いことが問題となっている[1)2)]．副作用対策として，高齢者や女性，貧血の程度を指標にTVR初期投与量の減量を考慮することが推奨されているが[3)]，三剤併用療法での貧血の機序としては，TVRの腎障害によるRBV誘起性貧血の増強が示されている[4)]．そこで，三剤併用療法における腎機能の変化と貧血の推移の関連を検討し，TVR初期投与量について考察した．

対象と方法：当院において三剤併用療法を導入し12週が経過したgenotype 1bかつ高ウイルス量（≥5.0 LogIU/mL）のCHC患者37例を対象とした．治療は，PEG-IFN規定用量/20μg減量＝36/1例，TVR2250/1500 mg＝32/5例，RBV規定用量/200 mg減量＝32/5例で開始し，このうちPEG-IFNとRBVの二剤減量開始が1例，RBVとTVRの二剤減量開始が1例あった．まず薬剤中止例の要因とその抗ウイルス効果への影響を検討した．次に治療継続できた31例においてヘモグロビン（Hb）値およびestimated glomerular filtration rate（eGFR, mL/min/1.73 m^2）の推移を検討し，貧血の進行に影響する因子を解析した．eGFRは，男性：$194\times Cr^{-1.094}\times age^{-0.287}$，女性：eGFR（男性）×0.739を用い，線維化の指標としてaspartate aminotransferase-to-platelet ratio index（APRI）＝[（AST/正常上限値）×100]/血小板数（10^9/L）を使用した[5)]．データは中央値（範囲）で示し，2群間比較はMann-Whitney U検定，χ二乗検定もしくはFisherの直接法を用いて解析した．Cut-off値の設定にはROC解析を用いた．

結果：Intention-to-treat解析での抗ウイルス効果は，rapid viral response（RVR）は73.0%（27/37），SVR 12は84.2%（16/19）であった．経過中，各薬剤を減量もしくは中止した症例数はPEG-IFN10例，RBV32例，TVR27例であった．一方でRBVとTVRともに減量しなかった症例は4例のみであり，これらはPEG-IFNの減量も要しなかった．薬剤中止に関しては10例でTVRを中止し［時期：7（1-11）週］，そのうち6例は三剤とも中止した［時期：4（1-10）週］．三剤中止の理由は，3例が消化器症状，2例が貧血，1例が細菌性心外膜炎であった．RVR27例とnon-RVR10例の比較では，IL 28B genotype（TT：89% vs. 50%，p＝0.021）と三剤中止（有：7% vs. 40%，p＝0.035）に有意差を認めた．三剤中止6例と治療継続できた31例の比較では，高血圧の有無（有：83% vs. 23%，p＝0.009），Hb値（＜13.5 g/dL：67% vs. 16%，p＝0.022）およびIV型コラーゲン7S［8.3（4.9-11.0）vs. 5.2（3.4-7.3）ng/mL，p＝0.023］に有意差を認めたが，腎機能は関連がなかった．

治療継続31例におけるHb値の推移は治療前13.9（11.7-16.8）g/dLで，3日目に一時的に上昇後，徐々に低下し12週目に最低値9.6（7.2-14.8）g/dLを示した（Fig. 1a）．eGFRは治療前75.1（51.9-102.8）mL/min/1.73 m^{2}で，3日目に最低値55.7（22.3-87.2）mL/min/1.73 m^{2}を示し，その後はやや回復するも低値で推移し，12週以降に回復を認めた（Fig. 1b）．Fig. 1aのHb値の推移にはRBVやTVRの減量・中止が影響を与えているが，三剤併用療法の実臨床においては本研究と同様に両剤の減量やTVRの単独中止が多くの例で必要になることを考慮して，本研究においては減量・中止例も含めてHb最低値を示した12週時点を貧血の評価ポイントに設定した．12週時点でのHb値（Hb-12W）≥10 g/dLの11例と＜10 g/dLの20例の比較では，治療前アルブミン値［3.9（3.8-4.2）vs. 3.7（2.6-4.5）g/dL，p＝0.008］，

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＜受付日2013年4月5日＞＜採択日2013年5月20日＞

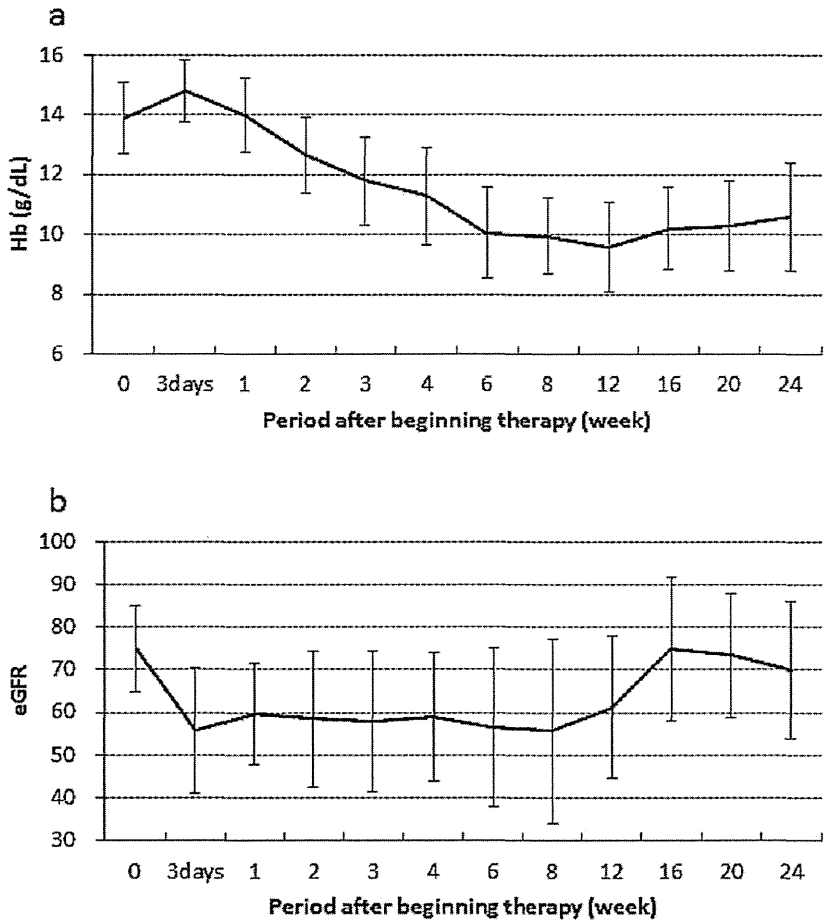

Fig. 1 Changes in a) Hb and b) eGFR in the patients who received peginterferon, ribavirin, and telaprevir triple therapy.

APRI［0.54（0.26-2.45）vs. 1.17（0.36-3.59），$p=0.032$］および3日目のeGFR（eGFR-3D）［64.6（48.5-87.2）vs. 54.3（36.2-60.8）mL/min/1.73 m^2，$p=0.005$］に有意差を認めた（Table）．Hb-12W≥10 g/dLに影響するeGFR-3Dのcut-off値は60 mL/min/1.73 m^{2}であった（AUC＝0.78，sensitivity＝92.3%，specificity＝70.0%，PPV＝80.0%，NPV＝87.5%，accuracy＝82.6%）．eGFR-3D≥60 mL/min/1.73 m^{2}の10例と＜60 mL/min/1.73 m^{2}の19例の比較では，治療前eGFR［83.3（68.2-102.8）vs. 69.7（51.9-78.5）mL/min/1.73 m^2，$p<0.001$］のみ有意差を認めた．eGFR-3D≥60 mL/min/1.73 m^{2}に影響する治療前eGFRのcut-off値は80 mL/min/1.73 m^{2}であった（AUC＝0.74，sensitivity＝100%，specificity＝58.3%，PPV＝81.5%，NPV＝100%，accuracy＝85.3%）．このcut-off値を用いると，治療前eGFRもHb-12Wに有意な影響を示した（$p=0.013$）（Table）．

考察：治療効果には三剤を中止しないことが重要であるが，中止における腎機能の影響は明らかではなかった．これには中止理由の多くが貧血以外であったことが影響しているかもしれない．治療中のeGFRとHbの変動に関しては，治療開始後3日でeGFRは最低値を示しHbは僅かに上昇するが，これはTVRによる腎前性腎障害の影響と考えられる[4]．尚，eGFRのその後の回復は，補液や薬剤減量の効果と推測される．腎機能と貧血の関連については，治療早期のeGFR低下がその後の貧血の進行に影響していることが明らかとなり，治療早期のeGFR低下は開始前のeGFRで予測できる可能性が示唆された．また，貧血の進行には肝線維化の進展も関与しており，線維化進展例ではさらに

Table Patients' characteristics according to hemoglobin levels at 12 weeks after beginning peginterferon, ribavirin, and telaprevir triple therapy (n=31)

	Hb-12W≥10 g/dL n=11	Hb-12W<10 g/dL n=20	*P*-value
Age (years)	62 (26-70)	60 (49-65)	0.984
<60/≥60 (years)	5/6	9/11	1.000
Sex: male/female	8/3	12/8	0.698
Body weight (kg)	63 (42-82)	63 (42-82)	0.421
ITPA genotype: CC/CA/AA	8/2/1	16/4/0	0.391
Diabetes mellitus: +/−	3/8	3/17	0.638
Hypertension: +/−	1/10	6/14	0.372
Hemoglobin (g/dL)	14.5 (13.4-16.8)	13.9 (11.7-16.4)	0.131
Platelet counts (/μL)	18.5 (11.9-23.0)	16.2 (7.9-25.1)	0.069
AST (IU/L)	31 (21-164)	65 (19-142)	0.107
ALT (IU/L)	36 (22-155)	64 (16-176)	0.282
Albumin (g/dL)	3.9 (3.8-4.2)	3.7 (2.6-4.5)	0.008
Creatinine (mg/dL)	0.76 (0.59-0.93)	0.80 (0.58-1.13)	0.869
Uric acid (mg/dL)	5.9 (3.4-9.4)	5.8 (3.3-9.8)	0.901
eGFR (mL/min/1.73 m^2)	75.7 (60.7-102.8)	73.6 (51.9-94.8)	0.167
eGFR: <80/≥80	6/5	19/1	0.013
eGFR-3D (mL/min/1.73 m^2)	64.6 (48.5-87.2)[a]	54.3 (36.2-60.8)[b]	0.005
eGFR-3D: <60/≥60	3/7	14/1	0.002
IV collagen 7S (ng/mL)	4.7 (3.4-5.6)[c]	5.7 (3.9-7.3)[d]	0.059
APRI	0.54 (0.26-2.45)	1.17 (0.36-3.59)	0.032
Peg-IFN dose during 12 weeks (μg/kg/week)	1.42 (1.29-1.59)	1.44 (1.07-1.71)	0.984
RBV dose during 12 weeks (mg/kg/day)	10.2 (6.5-14.3)	8.4 (5.0-12.6)	0.186
RBV dose reduction	8	18	0.317
TVR dose during 12 weeks (mg/kg/day)	29.1 (17.1-39.1)	28.5 (13.9-44.0)	0.837
TVR dose reduction/discontinuation	7/1	10/3	0.754

Values are median (range) or number of patients. [a]n=10, [b]n=15, [c]n=8, [d]n=13.
Hb-12W, hemoglobin levels 12 weeks after beginning therapy; ITPA, inosine triphosphate pyrophosphatase; eGFR-3D, eGFR 3 days after beginning therapy; APRI, aspartate aminotransferase-to-platelet ratio index.

十分な注意が必要である.

CHC 患者は高齢化しており，三剤併用療法の安全性を高めるためには，投与初期の腎機能に配慮して薬剤投与量を決定することが重要であると考えられた.

索引用語：テラプレビル，貧血，eGFR

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本論文内容に関連する著者の利益相反：なし

英文要旨

Prediction of anemia in triple therapy with peginterferon α-2b, ribavirin, and telaprevir for patients with chronic hepatitis C from the viewpoint of renal function

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Anemia is one of the most important side effects in triple therapy, and it is known that ribavirin-induced anemia is enhanced by telaprevir-induced renal dysfunction. Therefore, we investigated the relationship between hemoglobin (Hb) levels and the estimated glomerular filtration rate (eGFR). Hb levels showed a transient increase at 3 days, then gradually decreased until achieving nadir at 12 weeks. Conversely, eGFR achieved nadir at 3 days. A Hb level of <10 g/dL at 12 weeks was significantly associated with eGFR at 3 days, and the cut-off value was 60 mL/min/1.73 m^2. An eGFR of <60 mL/min/1.73 m^2 at 3 days was significantly associated with eGFR at baseline, and the cut-off value was 80 mL/min/1.73 m^2. eGFR may be a useful clinical parameter for protecting against severe anemia.

Key words: telaprevir, anemia, eGFR

Kanzo 2013; 54: 509—512

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A prospective randomized controlled trial of hemostasis with a bipolar sealer during hepatic transection for liver resection

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Background. *Excessive intraoperative blood loss and the possible requirement for blood transfusion are major problems in hepatic resection for liver tumors. The decrease of blood loss is a goal in liver surgery, and several technical developments have been introduced for this purpose. The aim of this prospective randomized study was to compare the use of the Cavitron Ultrasonic Surgical Aspirator (CUSA) with a radiofrequency-based bipolar hemostatic sealer versus CUSA with standard bipolar cautery (BC) in patients undergoing hepatic resection.*

Methods. *One hundred nine patients with liver tumors were randomized to undergo hepatic transection via CUSA with a bipolar sealer (Aquamantys 2.3 Bipolar Sealer;* n = *55) or BC (*n = *54). Blood loss during parenchymal transection and speed of transection were the primary end points, whereas the degree of postoperative liver injury and morbidity were secondary end points.*

Results. *Compared with the BC group, the bipolar sealer showed lesser blood loss during transection and blood loss divided by resection area (*P = *.0079 and .0008, respectively), shorter transection time (*P = *.0025), faster speed of transection (*P < *.0001), and fewer ties and ties divided by resection area required during transection (*P < *.0001).*

Conclusion. *CUSA with a bipolar sealer is superior to CUSA with standard BC for various hepatectomy in terms of less blood loss and faster speed of transection, with no increase in morbidity. (Surgery 2013;154:1046-52.)*

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SEVERAL DIFFERENT OPERATIVE DEVICES for hepatic transection and coagulation have been proposed with the aim to minimize intraoperative blood loss, which is associated with an increased rate of postoperative morbidity and mortality, as well as with decreased long-term survival.[1,2] Most blood loss occurs during parenchymal transection.[3] Several techniques have been developed for safe and careful parenchymal dissection. The popular devices facilitating bloodless transection include standard bipolar cautery (BC; B. Braun Aesculap Japan, Bunkyo-ku, Tokyo),[4] the Cavitron Ultrasonic Surgical Aspirator (CUSA; Tyco Healthcare, Mansfield, MA), which uses ultrasonic energy,[5] and the radiofrequency (RF) coagulator (TissueLink; TissueLink Medical, Inc, Dover, NH), which uses RF energy.[6] In Several previous studies, researchers investigated the role of these different operative devices in hepatic transection compared with the traditional clamp-crushing technique or CUSA.[7-9]

Indeed, hepatic transection by the clamp-crushing technique or CUSA is safe and simple and can be performed with different coagulators. The bipolar sealer used in the current study is a relatively new device that delivers RF energy coupled with saline solution irrigation for hemostatic sealing at lower temperatures (<100°C) than conventional electrocautery devices. This device functions to shrink the collagen in the walls of the tissue vessels without causing charring or burning, in contrast to standard electrocautery.[10] Several clinical applications of this bipolar sealer have

This RCT study was registered with the UMIN Clinical Trials Registry (UMIN-CTR) on April 1, 2011 (Registration number UMIN000005325).

Accepted for publication April 25, 2013.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2013.04.053

been reported in the literature, including its use in orthopedic oncology procedures,[11] total hip,[10] and total knee arthroplasty,[12,13] spinal procedures,[14] and pulmonary resection.[15]

The bipolar seems less efficient in sealing the vascular structures encountered during dissection, and it may produce necrosis on the cut surface, which may be a source of morbidity. In contrast, BC seems to be one of the most widely used procedures and a more economic coagulation device in liver procedures. The aim of this prospective randomized study was to compare the use of CUSA with a bipolar sealer versus CUSA with BC in patients undergoing hepatic resection.

METHODS

Patients. All patients scheduled for liver resection at Hirakata Hospital of Kansai Medical University (Osaka, Japan) between August 2010 and January 2012 were screened for this study. The inclusion criteria were elective hepatectomy, age of >18 and <80 years, adequate cardiopulmonary and renal function, and ability to provide written informed consent. Patients with portal vein tumor thrombus or previous portal vein embolization and those in whom portal vein resection was anticipated were excluded. Patients with ruptured hepatocellular carcinoma (HCC), those undergoing repeat hepatectomy, and those in whom concomitant bowel or bile duct resection was anticipated also were excluded.

Before the operation, each patient underwent conventional liver function tests and measurement of the indocyanine green retention rate at 15 minutes. Hepatitis screening was performed by measurement of hepatitis B surface antigen and hepatitis C antibody. The levels of α-fetoprotein and protein induced by vitamin K absence or antagonist-II were also measured. Preoperative radiologic assessment always included computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis.

Operative techniques. Operations were classified according to the Brisbane terminology proposed by Strasberg et al.[16] Anatomic resection was defined as resection of the tumor together with the related portal vein branches and the corresponding hepatic territory. Anatomic resection procedures were classified as hemihepatectomy (right hemihepatectomy was defined as resection of Couinaud subsegments[17] V–VIII, and left hemihepatectomy was defined as resection of subsegments II–IV), extended hemihepatectomy (hemihepatectomy plus removal of additional contiguous segments), sectionectomy (resection of 2 Couinaud subsegments), or segmentectomy (resection of one Couinaud subsegment).

All nonanatomic procedures performed for both peripheral and central tumors were classified as limited resection. Peripheral tumors and tumors with extrahepatic growth were treated by partial hepatectomy because in using this method we were able to achieve a resection margin wider than 1 cm. Conversely, central tumors located near the hepatic hilum or major vessels were treated by enucleation because it was too difficult or dangerous to remove enough of the liver to obtain an adequate margin. A Pringle's maneuver usually was not performed during hepatic resection. In cases of blood loss of >500 mL during transection, we performed Pringle's maneuver with an ischemic time of 15 minutes and reflow time of 5 minutes.

The transection was performed with the CUSA, and the vessel coagulation was performed by the bipolar sealer (Aquamantys 2.3 Bipolar Sealer; Salient Surgical Technologies, Portsmouth, NH; Fig 1) or BC (Fig 2) according to the randomization process, to which the surgeon was not blinded. This device delivers RF energy to bleeding tissues via the use of a conductive saline fluid that increases the affected surface area during hemostasis and maintains a relatively cool surface temperature of approximately 100°C.[10] The thermal effect of the RF energy shrinks type I and III collagen fibers in the walls of arteries and veins, which serves as the mechanism to minimize perioperative bleeding.[10]

The surgeon maintained full control of saline flow by an electronic switch. Vessels thicker than 2 mm were ligated with thin (3/4–0) sutures in both groups. A closed-suction silicon drain was inserted into the subphrenic or subhepatic space close to the cut surface of the liver before abdominal wound closure. The drain was brought through a separate stab wound on the anterior abdominal wall and connected to a closed system with low suction pressure. The abdominal drain was removed on postoperative day 3, unless there was excessive leakage of ascites or bile. The study protocol was explained to all patients, and they understood that they would be selected randomly to undergo hepatic resection via CUSA with a bipolar sealer or with BC. All patients provided written informed consent to participate in the trial and were randomized by the envelope method. All operations were performed by the same surgeon, who had experience with more than 700 hepatic resections. The protocol for this study was approved by the institutional ethics committee.

Outcome measures. The primary end points were blood loss during parenchymal transection

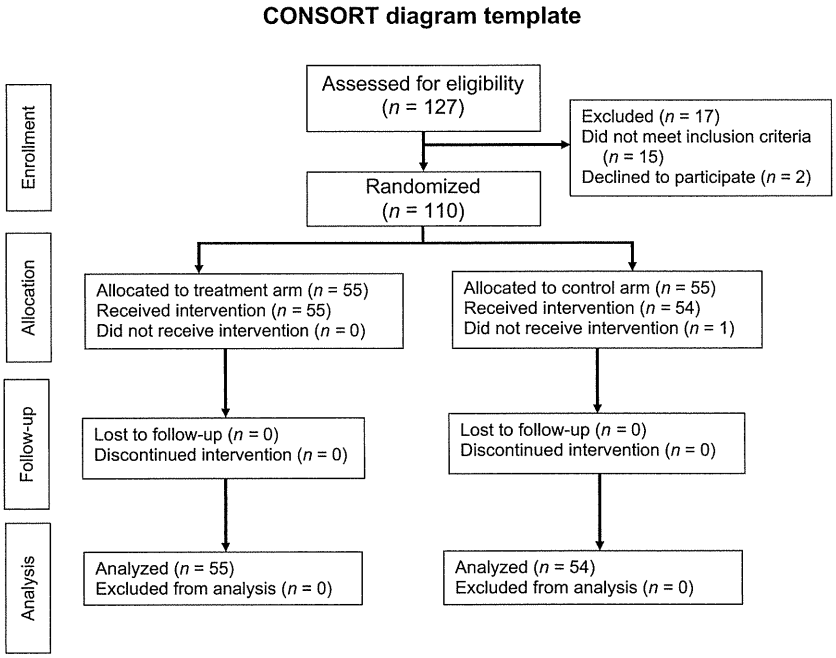

Fig 1. CONSORT diagram for this study.

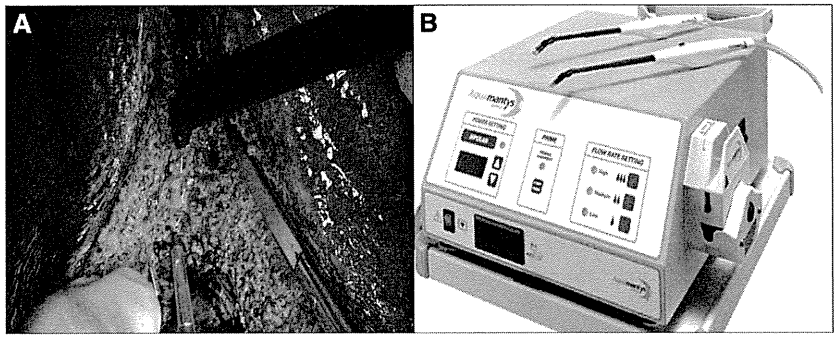

Fig 2. (*A*) Photograph showing transection of the liver using the CUSA and bipolar sealer. (*B*) Aquamantys RF bipolar sealer device.

Fig 3. Photograph showing transection of the liver using the CUSA and BC.

and speed of resection. Blood loss was carefully monitored before, during, and after liver transection. The amount of blood loss was estimated by inclusion of the suction volume after subtraction of rinsed fluids and weighing of the swabs that were used during transection. As soon as liver resection was completed, sterile paper was applied to the remaining liver surface, and the outline of the cut surface was drawn onto this paper to measure the surface area.

The secondary end point was the incidence of postoperative morbidity. Postoperative complications were defined and classified by the modified Clavien system.[18] To summarize, Grade I was any deviation from the normal postoperative course

Table I. Demographic, clinical, and pathologic characteristics of the 2 groups

	Bipolar cautery (n = *54*)	*Aquamantys bipolar sealer* (n = *55*)	P *value*
Age, y	71 ± 9	71 ± 10	.8700
Sex (male/female)	37/17	34/21	.4630
HBV/HCV/NBC/HBV + HCV	4/27/23/0	7/25/22/1	.5917
Diagnosis			.9176
Hepatocellular carcinoma	34 (63)	33 (60)	
Metastatic liver tumor	14 (26)	14 (25)	
Intrahepatic cholangiocarcinoma	3 (5)	5 (9)	
Benign disease	3 (5)	3 (5)	
Child-Pugh class (A/B)	46/8	46/9	.8237
ICGR15, %	11.8 ± 5.5	13.5 ± 4.8	.1192
Albumin, g/dL	3.9 ± 0.5	3.9 ± 0.4	.4226
Total bilirubin, mg/dL	0.7 ± 0.4	0.8 ± 0.3	.7391
Prothrombin time, %	93 ± 14	89 ± 13	.1936
Platelet count, $\times 10^4/\mu L$	20.8 ± 10.7	19.1 ± 9.4	.5987
AST, U/L	33 ± 23	41 ± 24	.1127
ALT, U/L	30 ± 32	39 ± 29	.1471
Operative procedure			.4358
Extended hemihepatectomy	4 (7)	5 (9)	
Hemihepatectomy	9 (17)	16 (29)	
Sectionectomy	27 (50)	22 (40)	
Segmentectomy	4 (7)	4 (7)	
Limited resection	10 (19)	8 (15)	
Tumor size, cm	3.2 ± 2.1	3.9 ± 2.7	.1911
Tumor number	1.4 ± 0.8	1.4 ± 0.7	.9915
Associated liver disease			.9785
Normal	18 (33)	18 (33)	
Fibrosis or hepatitis	27 (50)	27 (49)	
Cirrhosis	9 (17)	10 (18)	

Values in parentheses are percentages. Data represent the mean ± SD or the number of patients. Continuous data are mean ± SD.
ALT, Alanine aminotransferase; *AST*, aspartate aminotransferase; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *ICGR15*, indocyanine green retention rate at 15 min; *NBC*, nonhepatitis B or C virus.

that did not require special treatment, Grade II was a deviation that required pharmacologic treatment, Grade III required operative or radiologic intervention without (IIIa) or with (IIIb) general anesthesia, Grade IV was any life-threatening complication involving dysfunction of one (IVa) or multiple (IVb) major organs, and Grade V was death. Postoperative bile leakage was diagnosed by the following findings: detection of bile from the wound or the drain (total bilirubin level in the drain fluid >3 times that in the serum), intra-abdominal accumulation of bile confirmed by drainage, or demonstration of bile leakage on postoperative cholangiography.

Statistical analysis. In our recent experience, a mean blood loss of 990 mL with an SD of 510 mL was expected. To validate the hypothesis that the bipolar sealer could reduce blood loss by 300 mL with an α error of 0.05 and a β error of 0.20, a required sample size of 47 patients per group was calculated. Allowing for a dropout rate of 10% after randomization, we concluded that at least 52 patients were needed in each group. Results are expressed as mean ± SD. Demographic, physiologic, and clinical data for the 2 groups were compared by the *t*-test or the Mann-Whitney *U* test for continuous variables, whereas the χ^2 test or Fisher exact test was used for categorical data.

RESULTS

A total of 119 patients were assessed for eligibility for this study (Fig 3). Fifteen patients did not meet the inclusion criteria for the following reasons: bowel/bile duct resection,[3] repeat hepatectomy,[6] portal vein thrombus or previous portal vein embolization,[3] ruptured HCC,[2] and anticipated vascular resection.[1] Two patients declined to participate. Fifty-five patients were randomized to undergo treatment with the CUSA with the bipolar sealer, and 54 were randomized to undergo treatment with the CUSA with BC. Table I summarizes the baseline and operative characteristics. The 2 groups were well matched for all studied parameters that may represent risk factors for adverse outcomes.

Table II. Operative outcomes of the 2 groups

	Bipolar cautery (n = *54*)	*Aquamantys bipolar sealer* (n = *55*)	P *value*
Operation time, min	409 ± 148	382 ± 115	.3098
Total blood loss, mL	1076 ± 762	677 ± 433	.0486
Blood transfusion, ±	10/44	3/52	.0354
Resection area, cm^2	71 ± 42	75 ±52	.5501
Transection time, min	115 ± 65	81 ± 42	.0025
Blood loss during transection, mL	697 ±837	271 ± 233	.0079
Speed of transection, cm^2/min	0.52 ± 0.34	0.88 ± 0.46	<.0001
Blood loss/resection area, mL/cm^2	10.6 ± 9.1	4.9 ± 5.8	.0008
Number of ties	22.8 ± 11.1	13.1 ± 7.8	<.0001
Number of ties/resection area, /cm^2	0.54 ± 0.31	0.23 ± 0.15	<.0001
Number of patients who underwent Pringle's maneuver	14	11	.4619
Morbidity, ±	5/49	3/52	.4463
Bile leakage	3	0	
Intra-abdominal abscess	1	0	
Liver failure	0	0	
Pleural effusion and/or ascites	1	2	
Pneumonia	0	1	
Grade of operative complications			
I	0	0	.4105
II	0	1 (33%)	
IIIa	3 (60%)	2 (66%)	
IIIb	1 (20%)	0	
IVa	1 (20%)	0	
IVb	0	0	
V	0	0	
Postoperative hospital stay, d	17.1 ± 13.1	12.1 ± 6.5	.2492

Data represent the mean ± SD or the number of patients.

Operative outcomes for both groups are listed in Table II. There were no statistically significant differences between the 2 groups in the operation time, resection area, or number of patients who underwent Pringle's maneuver. Total blood loss, blood loss during transection, and blood loss divided by resection area were lesser in the bipolar sealer than in the BC group (P = .0486, .0079, and .0008, respectively). The requirement for blood transfusion was lesser in the bipolar sealer group (P = .0354). The transection time was lesser in the bipolar sealer group (P = .0025), and the speed of transection was faster (P < .0001). Moreover, fewer ties and ties divided by resection area were required during transection in the bipolar sealer than in the BC group (P < .0001). Postoperative morbidity and hospital stay were similar between groups, as were local recurrences at a mean follow-up of 14 months (median, 14; range, 7–24) and 13 months (median, 14; range, 7–24).

Postoperative peak values of serum aspartate aminotransferase were 355 ± 209 IU/L and 349 ± 220 IU/L in the BC and bipolar sealer groups, respectively, and those of serum alanine aminotransferase were 297 ± 206 IU/L and 283 ± 192 IU/L in the BC and bipolar sealer groups, respectively. Peak transaminase levels occurred on the first or second postoperative day in most cases, but there was no difference between the 2 groups. Similarly, there was no difference between the 2 groups in the postoperative peak levels of total serum bilirubin (2.2 ± 1.0 mg/dL vs 2.1 ± 1.0 mg/dL), lactate dehydrogenase (575 ± 207 IU/L vs 549 ± 262 IU/L), C-reactive protein (14.2 ± 8.4 mg/dL vs 11.7 ± 6.4 mg/dL), white blood cells (11,600 ± 4,300/mm^3 vs 11,700 ± 3,300/mm^3), nor minimum hemoglobin level (10.2 ± 1.7 g/dL vs 10.8 ± 1.5 g/dL). The minimum albumin level (2.5 ± 0.4 g/dL vs 2.7 ± 0.3 g/dL), prothrombin time (61 ± 14% vs 62 ± 10%), and platelet level (10.6 ± 5.0 × 10^4/mm^3 vs 11.3 ± 8.5 × 10^4/mm^3) were also similar between the 2 groups. The cost of the BC and bipolar sealer devices was 650 and 310 USD. Although repeated use of BC is possible, the bipolar sealer is disposable.

DISCUSSION

Excessive intraoperative blood loss and the possible requirement for blood transfusion are

major problems in hepatic resection for HCC or colorectal liver metastases.[19-21] Reduction of blood loss is one of the goals in liver operations, and several technical developments have been introduced for this purpose, including the Pringle maneuver[22] and selective vascular occlusion,[23] among other techniques. Regarding operative devices, CUSA has contributed to safe hepatectomy by making it easy to identify the vessels during parenchymal transection,[4] but it has no function in tissue sealing, and meticulous ligation is required to avoid bleeding or bile leakage from the cut surface of the liver. Thus, establishment of rapid hemostasis is critical. The current findings suggest that treatment with a bipolar sealer can decrease effectively total blood loss, intraoperative blood loss during hepatic parenchymal dissection, and the need for transfusion. These results corroborate and extend those of previous studies reporting the successful use of this technology during adolescent idiopathic scoliosis, primary total hip arthroplasty, or orthopedic joint reconstruction.[10,12-14,24,25]

The bipolar sealer reportedly seals blood vessels in soft tissue and cut bone while keeping the surface temperature at <100°C.[10] This device works by coupling RF energy from a standard electrosurgical generator with saline irrigation to conduct thermal energy. The thermal effect shrinks the collagen in the walls of veins and arteries, effectively stopping bleeding and oozing from the vessels without producing smoke or charring or burning tissue. The saline coupling of the bipolar sealer technology provides an advantage over conventional electrocautery for sealing cancellous tissue. This coupling provides a direct conduit between the electrodes and the embedded vessels, resulting in a rapid energy transfer. Furthermore, the depth of necrosis is minimal (<0.3 mm at 6 weeks and none at 12 weeks), allowing native blood vessels to assist with bone healing.[10] Collagen types I and III are known to shrink when heated and are abundant in the walls of blood vessels; the dry weight of veins and arteries is 58% and 28% collagen, respectively.[26] Connective tissue rich in type I collagen, such as that found in bone and articular cartilage, can shrink to about 60% its original size when heated to at least 60°C.[27,28] Hemostasis via vessel shrinking occurs without the tissue desiccation, smoking, and charring of conventional electrocautery.

In previous studies authors reported that the use of the RF coagulator TissueLink is associated with deep tissue coagulation and considerable liver necrosis in both human[29] and animal[30] studies. However, the present study demonstrated that the degree of liver injury was similar in the 2 groups.

Bile leakage is a particular concern in liver transection and can prolong the patient's hospital stay. Lupo et al[31] reported an increased incidence of biliary fistula after using RF, but all bile leakage occurred in the BC group. The bipolar sealer, with its sealing effect, also seemed effective in preventing bile leakage from the cut surface of the liver. The bipolar sealer is easy to handle and can seal tissues broadly, including relatively large vessels and bile ducts. According to our study, the bipolar sealer seemed to prevent bile leakage without ligation in ducts up to 4 mm in size.

In conclusion, the introduction of a bipolar sealer with CUSA resulted in decreases in excessive blood loss overall and increased speed in transection time with no increase in morbidity compared with standard bipolar cautery with CUSA during hepatectomy.

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