HBV carrier state[19]. Also, in Europe, most HBV infections are genotypes A and D, and significantly more genotype A carriers developed chronic liver disease when compared with genotype D carriers[20]. The reason for the increased prevalence rate of genotype A in Iwate Prefecture among the young generation is unclear, and it is therefore necessary to follow these carriers over the long term.

HBV is one of the major causative agents of HCC in Japan. In particular, HBV genotypes B and C are frequently seen in patients with HCC. Previous reports in Japan showed that the mean age is higher in HCC patients with genotype B than in those with genotype C, although results in Taiwan and another Asian countries are controversial [5, 11-13]. In general, genotype B is less prevalent than genotype C among patients with liver cirrhosis, because HBV genotype B is associated with earlier seroconversion from HBeAg to the corresponding anti-HBe and with lower histological activity scores. In the present study, we also demonstrated that HBV carriers with genotype B and HCC were significantly older than cases with genotype C. In addition, genotype B carriers showed lower serum ALT levels during follow-up than genotype C carriers. Therefore, these results suggest that genotype C carriers might have a tendency for persistent fluctuation of abnormal serum ALT levels over the long-term, accelerating the development of HCC.

Recently, lamivudine, an oral cytosine nucleoside analogue, which potently inhibits HBV replication by interfering with HBV reverse transcriptase activity, has been used clinically for the treatment of chronic HBV infection[21-23]. This therapy for chronic HBV infection induced a marked decrease in HBV-DNA and ALT levels, resulting in histological improvement, although lamivudine-resistant HBV strains have appeared in long-term lamivudine therapy[24, 25]. Therefore, this therapy is expected to change the natural course of HBV carriers with persistent abnormal liver function.

In conclusion, the prevalence of genotypes B and C were equal in HBV carriers residing in Iwate Prefecture. Differences between HBV genotypes, in particular genotypes B and C, were closely associated with positive rate of HBeAg, fluctuating serum ALT levels, and clinical outcomes of these carriers.

The authors would like to thank Prof. S. Horiuchi (Department of Biochemistry, Iwate Medical University, School of Medicine) for her helpful advice and comments.

内容自抄

B型肝炎ウイルス（HBV）には８つの遺伝子型（A～H）が存在しているが，HBVキャリア住民の遺伝子型頻度や自然歴は十分に検討されていない．そこで，検診受診者を対象にHBVキャリアの遺伝子型とその臨床的特徴を検討した．岩手県予防医学協会でHBVキャリアと診断された661例と岩手県癌登録事業より肝細胞癌で死亡が確認された30例を対象とした．遺伝子型の測定はELISA法を用いた．岩手県のHBVキャリア住民の遺伝子型の頻度は，各遺伝子型と年齢との関係をみると，Aは20～30歳代でのみ認められ，Bは70歳以上で高く，Cは40～60歳代では半数以上を占めた．各遺伝子型のHBe抗原陽性率の頻度は，CがA，Bより高率であった．経過観察期間中の血清ALT値は，Cが，A，Bに比較して有意に高値であった．肝癌例ではBでの発癌年齢はCに比較して有意に高齢であり，経過観察期間中の血清ALT値も低値であった．

References

1) **Okamoto H, Tsuda F, Sakugawa H, et al.** : Typing hepatitis B virus by homology in nucleotide sequence: comparison of surface antigen subtypes. J Gen Viol **69**, 2575-2583, 1988.
2) **Stuyver L, De Gendt S, Van Geyt C, et al.** : A new genotype of hepatitis B virus: complete genome and phylogenetic relatedness. J Gen Virol **81**, 67-74, 2000.
3) **Courouce AM, Plancon A and Soulier JP** : Distribution of HBsAg subtypes in the world. Vox Sang **44**, 197-211, 1983.
4) **Ding X, Mizokami M, Yao GB, et al.** : Hepatitis b virus genotype distribution among chronic hepatitis B virus carriers in Shanghai, China. Intervirology **44**, 43-47, 2001.
5) **Kao JH, Chen PJ, Lai MY, et al.** : Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology **118**, 554-559, 2000.
6) **Orito E, Ichida T, Sakuragawa H, et al.** : Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. Hepatology **34**, 590-594, 2001.
7) **Lindh M, Andersson AS, Gusdal A, et al.** : Genotype, nt 1858 variants, and geographic origin of hepatitis B virus-large-scale analysis using a new genotyping method. J Infect Dis **175**, 1285-1293, 1997.
8) **Mayerat C, Mantegani A, Frei PC, et al.** : Does hepatitis B virus (HBV) genotype influence the clinical outcome of HBV infection? J Viral Hepat **6**, 299-304, 1999.
9) **Joh R, Hasegawa K, Ogawa M, et al.** : Genotype analysis of hepatitis B virus from patients with fulminant hepatitis: comparison with acute self-limited hepatitis. Hepatol Res **26**, 119-124, 2003.
10) **Orito E, Mizokami M, Sakuragawa H, et al.** : A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotype B and C. Japan HBV Genotype Research Group. Hepatology **33**, 218-223, 2001.
11) **Orito E and Mizokami M** : Hepatitis B virus genotype and hepatocellular carcinoma in Japan. Intervirology **46**, 408-412, 2003.
12) **Sugauchi F, Orito E, Ichida T, et al.** : Epidemiologic and virologic characteristics of hepatitis b virus genotype B having the recombination with genotype C. Gastroenterology **124**, 925-932, 2003.
13) **Sugauchi F, Kumada H, Sakuragawa H, et al.** : Two subtypes of genotype B (Ba and Bj) of hepatitis B virus in Japan. Clin Infect Dis **38**, 1222-1228, 2004.
14) **Fattovich G, Brollo L, Giustina G, et al.** : Natural history and prognostic factors for chronic hepatitis type B. Gut **32**, 294-298, 2001.
15) **Brunetto MR, Giarin NM, Oliveri F, et al.** : Wild-type and e antigen-minus hepatitis B viruses and course of chronic hepatitis. Proc Natl Acod Sci **88**, 4186-4190, 1991.
16) **Ishikawa K, Koyama T and Masuda T** : Prevalence of HBV genotypes in asymptomatic carrier residents and their clinical characteristics during long-term follow-up: the relevance to changes in the HBeAg/anti-HBe system. Hepatol Res **24**, 1-7, 2002.
17) **Usuda S, Okamoto H, Iwanari H, et al.** : Serological detection of hepatitis B virus genotypes by ELISA with monoclonal antibodies to type-specific epitopes in the preS2-region product. J Viol Methods **80**, 97-112, 1999.
18) **Koyama T, Matsuda I, Sato S, et al.** : Prevention of perinatal hepatitis B virus transmission by combined passive-active immunoprophylaxis in Iwate, Japan (1981-1992) and epidemiological evidence for its efficacy. Hepatol Res **26**, 287-292, 2003.
19) **Niitsuma H, Ishii M, Ojima T, et al.** : An adult patient with acute hepatitis B (genotype A) infection who became a chronic carrier. Acta Hepatol Jpn **40**, 346-349, 1999.
20) **Mayerat C, Mantegani A and Frei PC** : Does hepatitis B virus (HBV) genotype influence the clinical outcome of HBV infection. J Viral Hepatol **6**, 299-304, 1999.
21) **Dienstag JL, Perrillo RP, Schiff ER, et al.** : A preliminary trial of lamivudine for chronic hepatitis B infection. N Engl J Med **333**, 1657-1661, 1995.
22) **Lai CL, Chien RN, Leung NWY, et al.** : A one-year trial of lamivudine for chronic hepatitis B. N Engl J Med **339**, 61-68, 1998.
23) **Suzuki Y, Kumada H, Ikeda K, et al.** : Histological changes in liver biopsies after one yeaqr of lamivudine treatment in patients with chronic hepatitis B infection. J Hepatol **30**, 743-748, 1999.
24) **Leung NWY, Lai CL, Chang TT, et al.** : Extended lamivudine therapy in patients with chronic hepatitis B enhances hepatitis e antigen seroconversion rates: results after 3 years of therapy. Hepatology **33**, 1527-1532, 2001.
25) **Akuta N, Suzuki F, Kobayashi M, et al.** : The influence of hepatitis B virus genotype on the development of lamivudine resistance during long-term treatment. J Hepoatol **38**, 315-321, 2003.

41：358

消化器科，41(4)：358-363，2005

特集II 非代償性肝硬変症治療の工夫

B型非代償性肝硬変に対するラミブジンの治療効果と限界*

宮坂昭生**
熊谷一郎**
阿部弘一**
滝川康裕**
加藤章信**
鈴木一幸**

Key Words : hepatitis B virus-related decompensated cirrhosis, lamivudine

はじめに

B型非代償性肝硬変においては各種肝庇護療法，分岐鎖アミノ酸栄養療法が効果なく肝不全への進行が予測される例ではラミブジン投与により肝機能の改善を計ることが期待されている．しかし，非代償性肝硬変に対するラミブジンの評価はいまだ定まっていない．そこで，非代償性肝硬変に対するラミブジンの有効性と限界を明らかにすることを目的として検討した．

対象と方法

対象は2000年以降に当科にて経過観察中のB型肝硬変例の中で，各種治療にも関わらず黄疸あるいは腹水が出現し肝不全への進行が懸念され，ラミブジン投与を行った非代償性肝硬変15例〔男性10例，女性5例，平均年齢51.5歳(36～69歳)〕を対象とした．

対象の背景を表1に示す．

ラミブジン100～150mg/日経口投与し，平均22か月(1.5～55か月)観察し，肝機能とHBV-DNA量の推移，予後，YMDD変異の出現の有無とその対応などについて検討した．

表1 対象の背景

年齢	51.5歳(36～69歳)
男女比	男性10例，女性5例
黄疸	9例
平均総ビリルビン値	3.5±3.3mg/dl
平均血清アルブミン値	2.9±0.6g/dl
平均プロトロンビン時間	42±17%
腹水	8例
脳症	0例
平均Child-Pugh score	9.5±2.6
平均血清ALT値	117±79IU/L
HBe抗原陽性：HBe抗原陰性	12例：3例
平均HBV-DNA量	3.4×10^8copies/ml (3.1×10^6～1.0×10^9copies/ml)
Genotype(A/B/C/D)	0/1/14/0

結　果

1．ラミブジン投与後の経過

ラミブジン投与後の経過と転帰を図1および表2に示す．全対象のうち3例が死亡し，2例(症例4，6)が肝不全死，1例(症例3)が胸水穿刺後の急性循環不全による他病死であった．また，1例(症例11)がラミブジン投与後も黄疸が増強し内科的治療は困難と判断し米国にて脳死全肝移植を受けた．また，1例(症例14)が経過中に直腸癌が発見され肝予備能低下により手術困難と判断されたが，ラミブジン投与5か月後に改善し手術を受けている．肝不全死した2例と肝移植

* Efficacy and limitation of lamivudine treatment in patients with hepatitis B virus-related decompensated cirrhosis.

** Akio MIYASAKA, M.D., Ichirou KUMAGAI, M.D., Kouichi ABE, M.D., Yasuyuki TAKIKAWA, M.D., Akinobu KATO, M.D. & Kazuyuki SUZUKI, M.D.: 岩手医科大学医学部第一内科〔〒020-8505 盛岡市内丸19-1〕; First Department of Internal Medicine, School of Medicine, Iwate Medical University, Morioka 020-8505, JAPAN

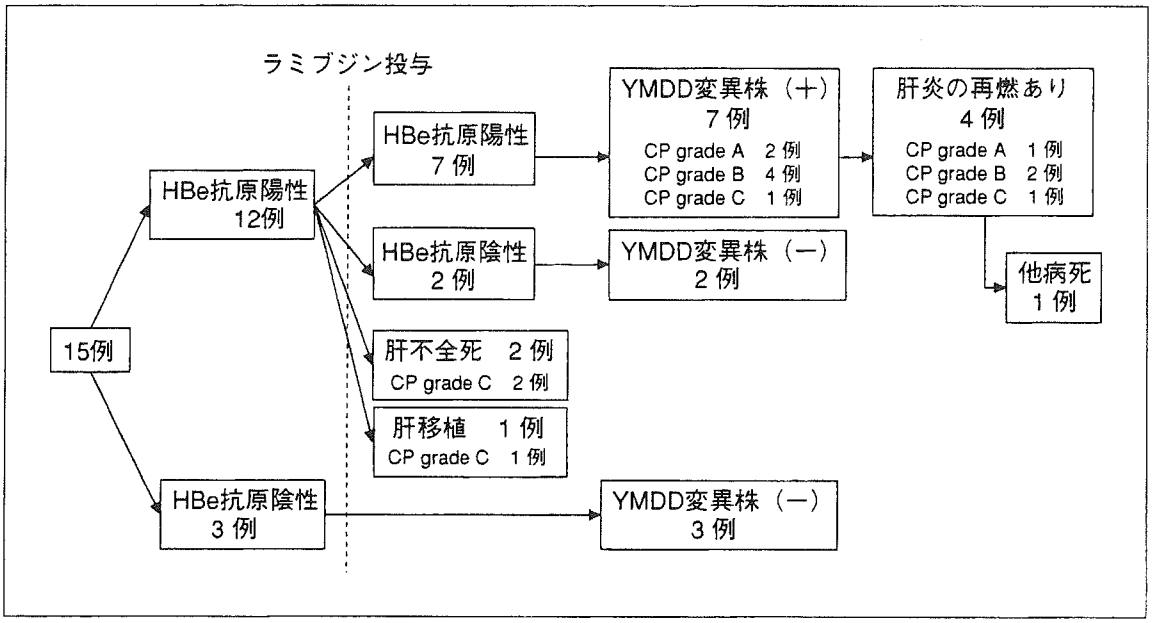

図1 ラミブジン投与後の経過

表2 ラミブジン投与期間と転帰

症例	投薬期間（月）	CP分類 投与前 投与後	YMDD変異 投与前 投与後	YMDD変異出現時期（月）	転帰
1.	55	B(8) → A(5)	(－)	(－)	生
2.	26	B(9) → B(9)	YMDD → YIDD	15	生
3.	26	B(8) → C(12)	YMDD → YIDD	9	死（他病死）
4.	1.5	C(13) → C(15)	nt. → nt.	(－)	死（肝不全死）
5.	37	A(5) → B(8)	nt. → YIDD	36	生
6.	2	C(13) → C(15)	nt. → nt.	(－)	死（肝不全死）
7.	37	A(6) → A(5)	nt. → YIDD	28	生
8.	33	C(12) → A(5)	(－)	(－)	生
9.	31	B(9) → A(5)	(－)	(－)	生
10.	19.5	C(12) → B(7)	YMDD → YVDD	13	生
11.	2	C(13) → C(11)	(－)	(－)	生（肝移植）
12.	22	B(9) → B(8)	YMDD → YIDD	20.5	生
13.	16.5	B(7) → A(6)	YMDD → YVDD	16.5	生
14.	14	B(9) → A(6)	(－)	(－)	生（直腸癌）
15.	8	C(10) → B(7)	(－)	(－)	生

を受けた1例はChild-Pugh grade Cであった．

ラミブジン投与前HBe抗原陽性12例，陰性3例であったが，ラミブジン投与後HBe抗原陽性12例中，肝不全死した2例と肝移植を受けた1例を除いていたHBe抗原陽性9例中2例（22％）にseroconversionを認めた．HBe抗原陽性が持続した7例は全例ラミブジン投与後1年前後にYMDD変異株が出現し，1年で8％（12例中1例），2年で42％（12例中5例），3年で55％（11例中6例）であった．YMDD変異株が出現した7例中4例に肝炎の再燃を認めたため，アデフォビルを投与し肝炎の沈静化をみた．ラミブジン投与前にHBe抗原陰性であった3例とseroconversionを認めた2例からは現在のところYMDD変異株の出現を認めていない．

Child-Pugh scoreはラミブジン投与前9.5±2.6点であったラミブジン投与後最終観察時点では8.3±3.5点となり，改善10例，不変1例，増悪4例であった．Grade Cからgrade Bへの改善は2例，grade Aへの改善は1例，grade Bからgrade Aへの改善は4例であったが，肝不全死例ではscoreの改善がみられず，むしろ増加を示し

表3 ラミブジン投与前後の比較

症例	T-Bil 前	T-Bil 後	ALT 前	ALT 後	Alb 前	Alb 後	PT 前	PT 後	腹水 前	腹水 後	脳症 前	脳症 後	CP分類 前	CP分類 後	HBV-DNA量 前	HBV-DNA量 後
1.	1.8	1.9	75	18	3.3	4.3	47	72	(+)	(−)	(−)	(−)	B(8)	A(5)	8.1(LEG)	<3.7(LEG)
2.	2.1	2.5	78	115	2.2	3.0	48	31	(−)	(−)	(−)	(−)	B(9)	B(9)	3.6×10^{8}	2.8×10^{8}
3.	2.5	3.5	329	61	2.8	2.7	58	29	(−)	(+)	(−)	(−)	B(8)	C(12)	$>1.0\times10^{9}$	2.0×10^{8}
4.	8.2	16.3	32	20	2.4	2.1	29	22	(++)	(++)	(−)	(++)	C(13)	C(15)	1.0×10^{8}	1.4×10^{5}
5.	1.0	2.0	188	235	4.0	3.8	75	34	(−)	(−)	(−)	(−)	A(5)	B(7)	6.5(LEG)	$>1.0\times10^{9}$
6.	7.3	21.7	32	50	2.3	2.0	25	6	(++)	(++)	(−)	(++)	C(13)	C(15)	7.0×10^{7}	3.0×10^{5}
7.	1.1	0.8	167	46	4.2	4.5	53	79	(−)	(−)	(−)	(−)	A(6)	A(5)	7.7×10^{8}	8.5(LEG)
8.	4.9	0.7	53	10	3.5	5.0	22	83	(++)	(−)	(−)	(−)	C(12)	A(5)	$>1.0\times10^{9}$	$<2.0\times10^{2}$
9.	2.1	0.9	118	258	3.1	3.6	38	89	(−)	(−)	(−)	(−)	B(9)	A(5)	7.9×10^{7}	$>1.0\times10^{9}$
10.	2.9	1.6	97	72	2.5	2.9	34	40	(++)	(−)	(−)	(−)	C(12)	B(7)	4.8×10^{8}	$>1.0\times10^{9}$
11.	12.5	23.6	67	48	2.5	3.1	17	13	(++)	(+)	(−)	(−)	C(13)	C(11)	3.1×10^{6}	2.8×10^{4}
12.	1.5	1.1	62	45	2.6	2.4	71	100	(++)	(+)	(−)	(−)	B(9)	B(8)	7.8×10^{7}	5.6×10^{3}
13.	1.3	1.3	141	21	3.4	3.9	47	69	(−)	(−)	(−)	(−)	B(7)	A(6)	7.2(LEG)	3.2×10^{8}
14.	1.2	0.6	206	14	2.3	4.0	42	100	(+)	(+)	(−)	(−)	B(9)	A(6)	$>1.0\times10^{9}$	$<2.0\times10^{2}$
15.	2.8	1.3	108	20	2.5	3.4	32	57	(−)	(−)	(−)	(−)	C(10)	B(7)	2.7×10^{7}	$<2.0\times10^{2}$

た．肝移植例は内科的治療により2点の改善をみたがgrade C内での変動であった．また，YMDD変異株出現後肝炎が再燃した4例中2例ではscoreは増加した．

2．肝予備能の推移

対象の血液検査値の推移を表3に示す．

ラミブジン投与後の血清総ビリルビン値は，肝不全死例，肝移植例ではいずれも上昇傾向を示したが，他の例では最終的に低下を示した．しかし，YMDD変異株が出現し肝炎の再燃した例では経過中に軽度の再上昇を認めた．

血清アルブミン値は，アルブミン投与などの影響を受けるが，肝不全死例，肝移植例を除いた例では徐々に上昇している．しかし，YMDD変異株が出現し肝炎が再燃した例では一過性に低下傾向を示した．

プロトロンビン時間はラミブジン投与後，肝不全死例，肝移植例では改善は明らかではなかった．他の例ではラミブジン投与後上昇しているが，YMDD変異株が出現し肝炎が再燃した例では同様に一過性に低下を示した．

血清ALT値の推移を図2に示す．全例，ラミブジン投与1か月後には低下し，投与後6～9か月は低値のまま推移した．しかし，YMDD変異株が出現し肝炎が再燃した例ではYMDD変異株出現後，血清ALT値の上昇と変動を認めた．

HBV-DNA量の推移を図3に示す．血清ALT値と同様に全例ラミブジン投与後低下したが，YMDD変異株が出現後した症例では上昇していた．

3．投与開始時の血液検査値と転帰との関連

図4に投与開始時の血液検査値と転帰との関連を示した．肝不全死例，肝移植例と生存例の判別は血清総ビリルビン値7 mg/dl以上，Child-Pugh score 13点以上で可能であった．

考　案

肝硬変に対するラミブジン治療はいまだ保険適応はない．しかし，肝炎の沈静化のみならず肝予備能を向上させ，肝不全への移行を遅らせることを目的としたラミブジン治療は有効であると考えられる．これまでに，B型非代償性肝硬変に対するラミブジン治療の有効性を示すい

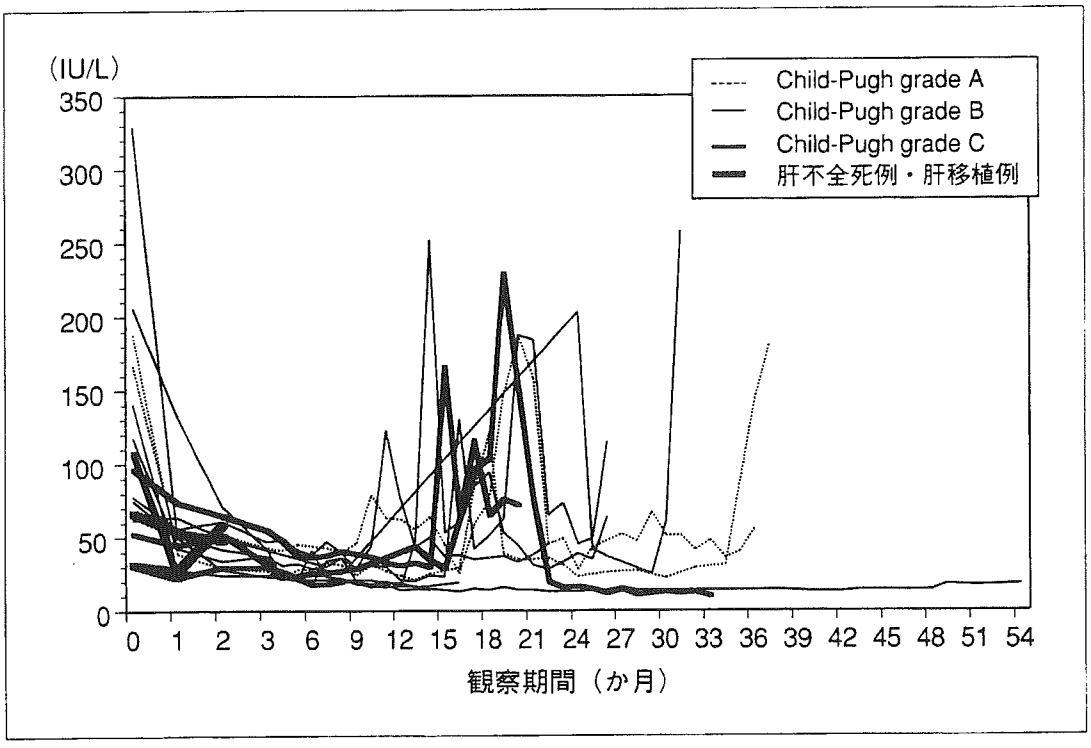

図2　血清ALT値の推移

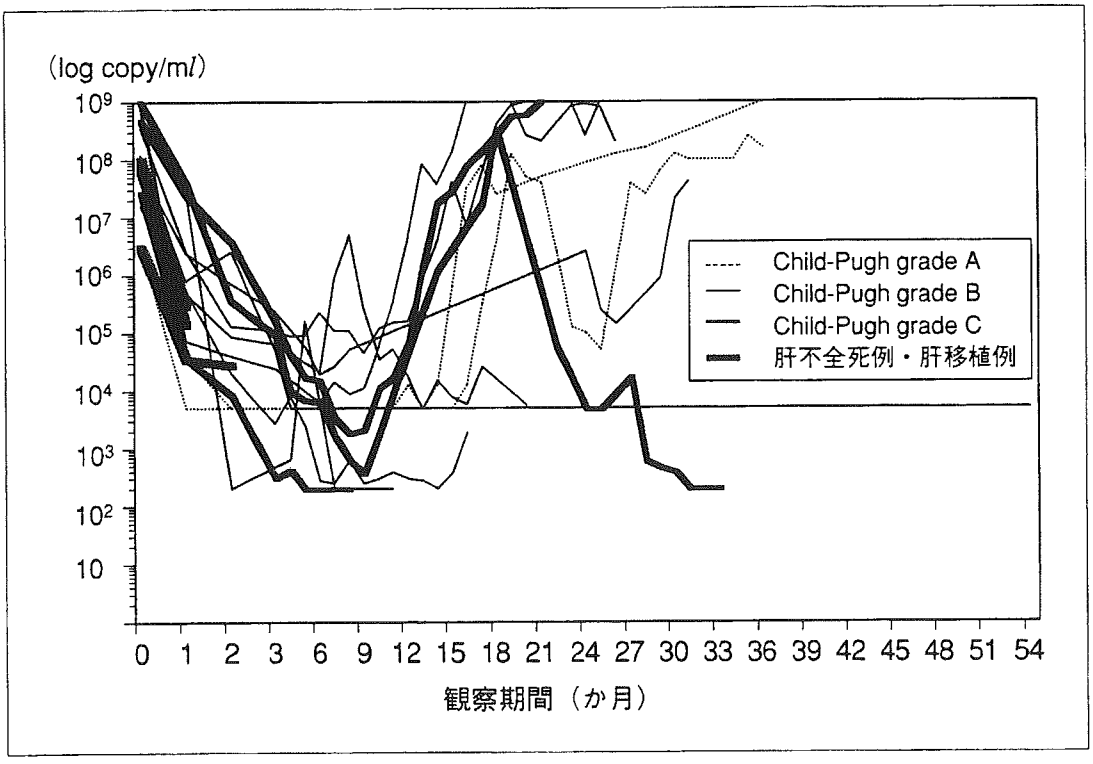

図3　HBV-DNA量の推移

くつかの報告がある．Yaoら[1]は非代償性肝硬変23例にラミブジンを投与し，Child-Pugh score 3点以上の改善を認めた症例が14例(60.9%)存在したと報告し，Velleneuveら[2]も肝機能検査値が改善し，23例中22例に2点以上のChild-Pugh scoreの改善が認められたと報告している．また，Kapoorら[3]もラミブジン投与により，Child-Pugh scoreが平均8.3から6.7へ有意に改善したと報告している．当科における検討でも，ラミブジン投与開始後，ほとんどの例でHBV-DNA量および血

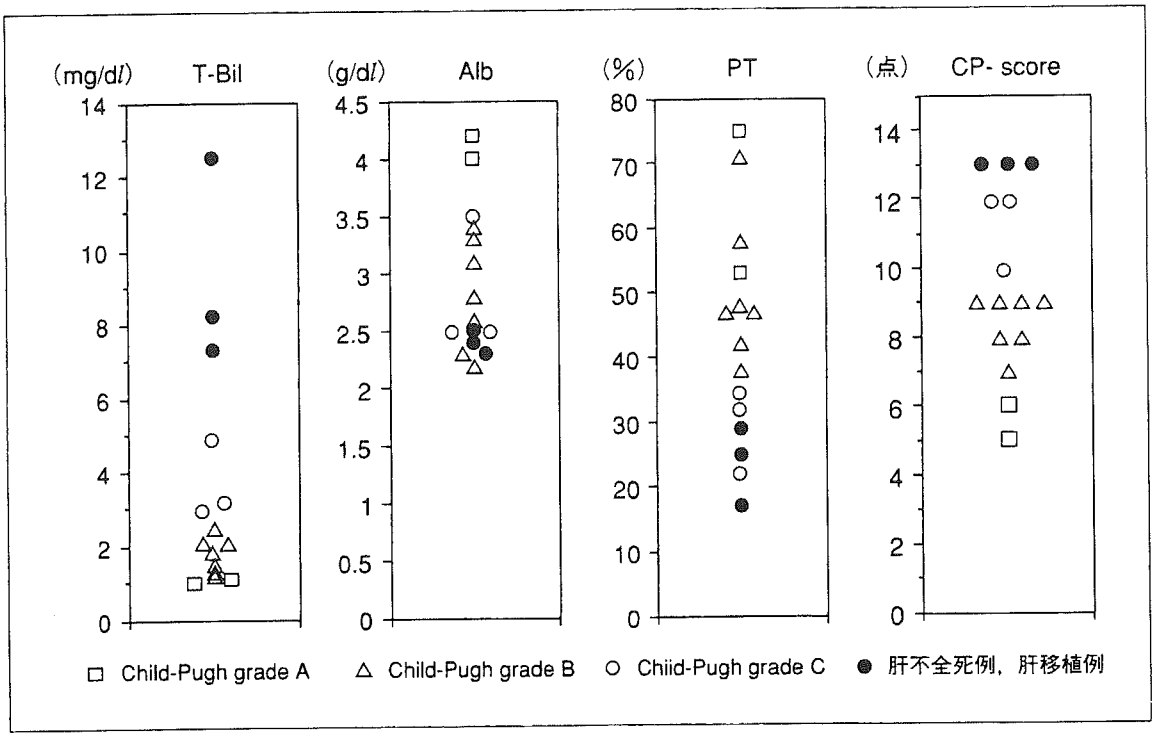

図4　投与開始時の検査値と転帰

清ALT値の低下，血清総ビリルビン値，血清アルブミン値などの肝予備能の改善を認め，Child-Pugh scoreも平均9.5から8.3へと低下し，B型非代償性肝硬変に対するラミブジン治療は有効であると考えられた．

しかし，Fontanaら[4]は非代償性肝硬変では治療開始前の血清総ビリルビン値とクレアチニンの高値，HBV-DNA陽性例では予後不良で，ラミブジン投与後の死亡率は投与後6か月以内とそれ以降の二峰性のピークがあると報告している．当科でもラミブジンを投与しても，肝予備能が改善せず2か月以内に肝不全にて死亡する症例が2例，ラミブジン投与後も黄疸が増強し内科的治療は困難と判断し肝移植を受けた症例が1例認められた．これらの予後不良例の特徴は，治療開始前の血清総ビリルビン値が7 mg/dl以上で，Child-Pugh score 13点以上であった．したがって，今後，B型非代償性肝硬変に対するラミブジン投与は少なくともこれらの値以下で開始すべきと考えられた．

一方，ラミブジンの投与が長期になると，YMDD変異株出現後のBreakthrough hepatitisが問題となり，肝予備能の少ない肝硬変では時に致死的となる．YMDD変異株はラミブジン投与後1年で約20%，2年で約40%，3年で約50%出現するとされ，YMDD変異株出現に関与する因子として，投与前のHBV-DNA量，HBe抗原の有無などが考えられている．当科における早期に肝不全死した2例と肝移植を受けた1例を除く12例の検討では，1年前後以降にYMDD変異株が出現し，1年で8%(12例中1例)，2年で42%(12例中5例)，3年で55%(11例中6例)であり，投与前のHBV-DNA量は高値であった．また，YMDD変異株の出現した7例は全例HBe抗原陽性が持続した症例であったが，投与前にHBe抗原陰性であった症例やseroconversionを認めた症例からのYMDD変異株の出現についてはさらなる観察期間が必要であると考えられる．

YMDD変異株が出現した例では，血清ALT値が正常な時期からHBV-DNA量の増加が確認できた時点から血清アルブミン値は低下しはじめ，血清ALT値の上昇とともに急激に肝予備能は低下し肝不全状態に逆戻りするとされる[5]．そのようの症例に対しては現在，インターフェロン，アデフォビルが使用可能であるが，インターフェロンは肝予備能の低下した非代償性肝硬変に対して使用困難であるため，副作用の少ないアデフォビルが有効であると考えられ，肝硬変例へ

のラミブジンとアデフォビルの併用療法の安全性と抗ウイルス効果も確認されている[6].

おわりに

B型非代償性肝硬変に対してラミブジンは有効であり，肝硬変への進展を阻止することが期待されるが，高度黄疸を呈し肝予備能が著しく低下している例では限界がある．また，ラミブジンの効果発現までには数日かかることより適切な投与時期を見誤らないことが重要である．さらに，長期投与によりYMDD変異株出現後のBreakthrough hepatitisに注意する必要がある．

文　献

1) Yao FY, Terrault NA, Freise C, et al. Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating a comparative study using a matched, untreated cohort. Hepatology 2001 ; 34 : 411.
2) Velleneuve JP, Condreay LD, Willems B, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. Hepatology 2000 ; 31 : 207.
3) Kapoor D, Guptan RC, Wakil SM, et al. Beneficial effects of lamivudine in hepatitis B virus-related decompensated cirrhosis. J Hepatol 2000 ; 33 : 308.
4) Fontana RJ, Hann HL, Perrillo RP, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. Gastroenterology 2002 ; 123 : 719.
5) 長岡進矢，八橋　弘．非代償性B型肝硬変の実態と予後．肝胆膵 2005 ; 50 : 695.
6) Perrillo RP, Hann H-W, Mutimer D, et al. Adefovir dipivoxil added to ongoing lamivudine in chronic hepatitis B with YMDD mutant hepatitis B virus. Gastroenterology 2004 ; 126 : 81.

*　　*　　*

3. HBV遺伝子型別にみた肝癌例の臨床像

鈴木　一幸*　阿部　弘一*　葛西　幸穂*　黒田　英克*
葛西　和博*　三浦　義明*　小山　富子**

はじめに

B型肝炎ウイルス（HBV）のgenotypeと肝病態との関連が注目されている[1-7]．わが国の肝細胞癌（以下，肝癌）の大部分はgenotype Bとgenotype Cであるが，genotypeの違いにより発癌年齢，肝病態（肝機能，HBe抗原陽性率など）に差を認めることが明らかにされ[5-7]，さらにgenotype Bの肝癌ではそのsubtype（Ba, Bj）による差[8]が発癌年齢に関連していることが報告されている．しかしながら，HBVのgenotypeの分布には地域差がみられること[6,9]，医療機関を受診するHBVキャリアの多くは肝機能異常が持続し肝病態の進行した例が多いことなどのバイアスがかかっていることから，genotype別の肝癌発生率やその臨床像の違いを明らかにするためにはさらに検討が必要と考えられる．そこで，当科で経験した肝癌例と検診受診者の追跡調査で死亡が確認された肝癌例についてgenotypeを測定し，genotype別の臨床像を比較検討した．

Ⅰ．対　象

1．検診受診者から肝癌死亡が確認された例についての検討

1977～2004年までに岩手県予防医学協会で検診を受けHBVキャリアと診断された6,711例を岩手県がん登録「個人同定資料」と照合し肝癌で死亡が確認された60例を抽出し，この中から岩手県予防医学協会において血清保存が良好でHBV遺伝子の測定が可能であった30例（男21，女9）を対象とした．なお，対象者のデータ入手については岩手医科大学医学部倫理委員会および岩手県医師会がん登録運営委員会の承認を得て行った．

2．当科受診の肝癌例の検討

1991～2004年までに当科で入院加療を受けたHBV肝癌（HCVとの重感染例，アルコール因子が加重した例は除外）のうち，HBV genotypeの測定が可能であった55例（男44，女11）を対象とした．

Ⅱ．方　法

検診受診者から肝癌死亡が確認された30名については，死亡確認から初回検診までの期間（観察期間）中に複数回測定されていた検診時の血清ALT値を確認し，その最高値よりL群（血清ALT値が30 IU/L以下），M群（血清ALT値が30～60 IU/L），H群（血清ALT値が60 IU/L以上）に分類した．HBVのgenotype（Usudaらの方法[10]），HBe抗原（EIA法）を測定し，genotype別の臨床像を比較検討した．また，genotype Bのsubtypeは Sugauchiらの方法[11]にて決定した．一方，当科で入院加療を受けた肝癌例については，初回入院時の肝機能，HBe抗原陽性率，HBV-DNA量，

*岩手医科大学第1内科
**岩手県予防医学協会

表1　肝癌と診断された検診受診者のgenotype別検討

		Genotype B*		Genotype C
発症年齢（歳）		64±13	P<0.05	52.7±9
ALT値群	L群	1例（12.5％）		2例（9.1％）
	M群	1例（12.5％）		9例（40.9％）
	H群	6例（75.0％）		11例（50.0％）
初診時	陽性	0（0％）		6（27.3％）
HBe抗原	陰性	8（100％）		16（72.7％）

*9例がBj，1例がBa

背景肝病変，臨床病期，腫瘍マーカー（AFP，PIVKA-Ⅱ）などについてgenotype別に比較検討した．

Ⅲ．結　果

1．検診受診者からの肝癌死亡例

肝癌例の初診時の平均年齢は男性46.9歳，女性48.6歳であり，平均観察期間はそれぞれ7.1年，8.3年であった．GenotypeはBが9例（男6，女3），Cが21例（男，女）であり，genotype Bのsubtypeは1例がBa，8例がBjであった．Genotype別の臨床像を表1に示す．Genotype Bの肝癌例はgenotype Cの肝癌例に比較して肝癌発症年齢が有意に高齢であった．また，genotype Bでは全例HBe抗原は陰性を示したが，genotype Cでは27.3％がHBe抗原陽性を示し，これらは40～50歳代の例であった．経過観察中の血清ALT値はgenotype B，CともM群，H群を示す例が多く認められた．

2．当科受診者の肝癌例

肝癌例の平均年齢は52.9±10.1歳，背景肝病変は慢性肝炎16例，肝硬変39例であった．GenotypeはA 3例（5.4％），B 9例（16.4％），C 43例（78.2％）であり，genotype Bのsubtypeは全例Bjであった．Genotype別の臨床像を表2，3，4に示す．発癌年齢はgenotype Bで最も高齢であり，genotype Aが最も低年齢であった．HBe抗原陽性率もgenotype Bで低かったが，HBV-DNA量には差異はみられなかった．また，性差，背景肝病変，肝機能にも3群間に明らかな差異はみられなかった．一方，肝癌の臨床病期はいずれのgenotypeにおいてもstage Ⅲ～Ⅳの進行例が多く，腫瘍マーカーも高値例が多かった．

Ⅳ．考　案

今回，当科で経験した肝癌例と検診受診者から見出された肝癌例についてHBVのgenotypeを測定し，それぞれの臨床像を比較検討した．その結果，従来の報告[6-8]にみられるように，肝癌例はgenotype Cの割合が多く，発癌年齢はgenotype Bがgenotype Cに比べて有意に高齢であった．また，genotype Aは検診受診者からの発癌例ではみられなかったが，当科受診の肝癌例からは3例認められ，いずれも低年齢であった．その他，発癌年齢を除いた項目についてはgenotype間に明らかな差異はみられなかったが，検診受診者の肝癌例の検討より発癌例の多くはHBe抗原が陰性化しているのも関わらず血清ALT値が観察期間中に異常を示している頻度が高い傾向を示した．また，HBVによる肝癌例はgenotypeに関わらず進行した状態で発見されている例が多いことが認められた．

肝癌例を除く検診受診者のHBVキャリアのgenotypeを検討した岩手県の成績[9]では，genotype Aは20～30歳代のみにみられ，40～60歳代ではgenotype BとCが同程度，70歳以降がgenotype Bが優位となり，全体での割合はgenotype A 2.9％，B 44.9％，C 52.2％である．また，HBe抗原陽性率はgenotype Bでは20歳代を除いてほとんどの年代で低率であり，genotype Cでは20～30歳代で約20％が陽性，40～60歳代になると

表2　肝癌におけるGenotype別臨床像（1）

Genotype	A	B	C
Number	3	9*	43
Age	38.1 ± 12.1	59.7 ± 8.5	53.3 ± 10.1
Male：Female	2：1	8：1	35：8
CH：LC	1：2	5：4	10：33
HBeAg陽性率	66.7％	11.1％	41.9％
HBV-DNA	8.05×10^6	2.52×10^7	2.23×10^7
(kopy/ml)	$(5.6 \times 10^6 \sim 1.1 \times 10^7)$	$(8.9 \times 10^2 \sim 2.3 \times 10^8)$	$(2.1 \times 10^2 \sim 2.5 \times 10^8)$

*全例Bj

表3　肝癌におけるGenotype別臨床像（2）

Genotype	A	B	C
AFP	7891.3	8751.4	8573.2
(ng/ml)	(1000～17358)	(4.6～59100)	(4.1～88880)
PIVKA-Ⅱ	41669	8416	4002
(mAU/ml)	(10～124497)	(30～75300)	(10～55800)
Stage Ⅰ	0	1	2
Stage Ⅱ	0	2	5
Stage Ⅲ	1	2	12
Stage Ⅳa	1	0	10
Stage Ⅳb	1	1	1
不明	0	3	13

表4　肝癌におけるGenotype別血液生化学検査値

Genotype	A	B	C
T-Bil (mg/dl)	0.95 ± 0.07	0.95 ± 0.47	1.74 ± 3.38
AST (IU/l)	52 ± 27	50 ± 27	79 ± 78
ALT (IU/l)	51 ± 19	59 ± 43	58 ± 32
PLT ($\times 10^4/\mu l$)	16.7 ± 9.05	20.11 ± 10.20	12.16 ± 5.35

10％弱に低下する．さらに，血清ALT値をみると，genotype Bに比べてgenotype Cで異常を示す頻度が高く，これにはgenotype Cでは40歳以降にHBe抗原からHBe抗体へのseroconversionが起きにくいことが原因と考えられている[12]．したがって，発見される肝癌例は当然のことながらgenotype Cが多いことが予想されるが，検診受診者からの肝癌例におけるgenotype Bの頻度は当科受診者からの肝癌例のgenotype Bの頻度よりも若干高い傾向を示した．さらに今回の検討より，肝癌例ではHBe抗原陰性にも関わらず観察期間中の血清ALT値が軽度異常を持続していた例が多く認められた．通常，HBVキャリアの自然歴を考えると，大部分の例では10～30歳代にseroconversionが起こり血清トランスアミナーゼ値は正常化し，いわゆる無症候性HBVキャリアとなることが多い．そして，一部の例が慢性肝炎，肝硬変および肝癌へ進展するが，これらの進展例はHBe抗原が陽性を示す例が多い[13]．一方，HBe抗原が陰性にも関わらず血清トランスアミナーゼ

値が異常を持続する例も稀にみられるが，このような例ではウイルス因子のみならずアルコール，肥満，脂肪肝，薬剤などの影響も考慮しなければならない．今回検討した検診受診者からの発癌例については病歴（既往歴，薬剤歴，アルコール歴，肥満の有無など）の詳細が不明でありHBV-DNA量の測定も行われていないため，なぜ検診受診者からの肝癌例においてHBe抗原陰性にも関わらず観察期間中の血清ALT値が軽度異常を持続していた例が多いかの理由については明らかにすることができなかった．しかし，このことは今後のHBVキャリアのフォローアップ体制を見直すうえで重要な知見と考えられる．

肝癌例におけるgenotypeの頻度はその地域におけるgenotypeの頻度に影響を受け，さらに病院受診者というバイアスも受ける．実際，東北地域においては本州の他地域よりもgenotype BのHVBキャリアの頻度が高いことから，肝癌例でもgenotype Bの頻度が高いことが予想されるが，この点についても他施設との共同研究で明らかにする必要があると考えられる．次に，genotype Bの亜型（Bj，Ba）については台湾と日本におけるgenotype Bの肝癌例の発癌年齢が異なる（日本平均70歳，台湾平均50歳）ことから注目され検討された[5,7,8]．今回の検討では1例を除いてBjであったため，BjとBaの違いを明らかにすることはできなかったが，日本におけるGenotype B肝癌例の亜型別にみた臨床像を検討するためには多くの施設からBaの肝癌例を集積して検討する必要がある．

一方，genotype Aの肝癌例も少数例ながら存在し，われわれの経験した例はいずれも他のgenotypeに比較して発癌年齢は低かった．Genotype Aについては最近，大都市を中心に急性肝炎例が増加しており，一部の例は慢性に移行することより注目されている[14,15]．また，その亜型についても検討されほとんどがヨーロッパ型である．Genotype Aの肝癌例の発癌年齢あるいは臨床像が他のgenotypeと異なるか否かについては興味が持たれるが，1施設での症例数が少ないため検討が難しく全国的な症例の集積が必要と考えられる．

結　語

検診受診者からの肝癌例と病院受診者の肝癌例についてHBV genotypeを測定し，genotype別の臨床像を検討した．HBVキャリアの自然歴とHBVのgenotypeとの関連，genotypeと肝癌との関連などについてはさらに検討が必要である．また今回の検討より，HBVによる肝癌例の多くは進行した状態で発見されていることから，HBVキャリアについてもHCVキャリアと同様に定期的なフォローアップ体制の構築と治療方針の再検討が早急に必要と考えられる．

文　献

1) Mayerat C, Mantegani A, Frei PC : Does hepatitis B virus (HBV) genotype influence the clinical outcome of HBV infection? J Viol Hepatol 6 : 299–304, 1999
2) Mizokami M, Nakano T, Orito E et al : Hepatitis B virus genotype assignment using restriction fragment length polymorphism patterns. FEBS Lett 450 : 66–71, 1999
3) Stuyver L, De Gendt S, Van Geyt C et al : A new genotype of hepatitis B virus: complete genome and phylogenetic relatedness. J Gen Viol 81 : 67–74, 2000
4) Orito E, Mizokami M, Sakugawa H et al : A case control study for clinical and molecular biological differences between hepatitis B viruses of genotype B and C. Hepatology 33 : 218–223, 2001
5) Kao JH, Chen PJ, Lai MY et al : Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. Gastroenterology 118 : 554–559, 2000
6) Orito E, Ichida T, Sakugawa H et al : Geographic distribution of hepatitis B virus (HBV) genotype in patients with chronic HBV infection in Japan. Hepatology 34 : 590–594, 2001
7) Orito E, Mizokami M : Hepatitis B virus genotypes and hepatocellular carcinoma in Japan. Interviology 46 : 408–412, 2003
8) Sugauchi F, Orito E, Ichida T et al : Epidemiologic and virologic characteristics of hepatitis B virus genotype B having the recombination with geno-

type C. Gastroenterology 124 : 925–932, 2003
9) Kasai Y, Suzuki K, Abe K et al : Genotype of hepatitis B virus (HBV) and those clinical characterisitics in HBV carrier residents in Iwate, Japan: results from health-screening program. J Iwate Med Assoc 2005 (in press)
10) Usuda S, Okamoto H, Iwanari H et al : Serological detection of hepatitis B virus genotypes by ELISA with monoclonal antibodies to type-specific epitopes in the preS2-region product. J Viol Methods 80 : 97–112, 1999
11) Sugauchi F, Orito E, Ichida T et al : Hepatitis B virus of genotype B with or without recombination with genotype C over the precore region plus the core region. J Viol 76 : 5985–5992, 2002
12) Ishikawa K, Koyama T, Masuda T : Prevalence of HBV genotypes in asymptomatic carrier rersidents and their clinical characteristics during long-term follow-up: the relevance to changes in the HNeAg/anti-HBe system. Hepatol Res 24 : 1–7, 2002
13) 鈴木一幸，阿部弘一，熊谷一郎：HBV無症候性キャリアの自然経過，予後，死因．日本臨床増刊号 ウイルス性肝炎(下)，日本臨床社，2004, pp227–232
14) Kobayashi M, Suzuki F, Arase Y et al : Infection with hepatitis B virus genotype A in Tokyo, Japan during 1976 through 2001. J Gastroenterol 39 : 844–850, 2004
15) Joh R, Hasegawa K, Ogawa M et al : Genotypic analysis of hepatitis B virus from patients with fulminant hepatitis: comparison with acute self-limited hepatitis. Hepatol Res 26 : 119–124, 2003

* * *

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Hepatology Research 33 (2005) 241–249
HEPATOLOGY RESEARCH
http://www.elsevier.com/locate/hepres

Cost-effectiveness of radiofrequency ablation and surgical therapy for small hepatocellular carcinoma of 3 cm or less in diameter

Kenji Ikeda[a,*], Masahiro Kobayashi[a], Satoshi Saitoh[a], Takashi Someya[a], Tetsuya Hosaka[a], Hitomi Sezaki[a], Yoshiyuki Suzuki[a], Fumitaka Suzuki[a], Norio Akuta[a], Yasuji Arase[a], Hiromitsu Kumada[a], Masamichi Matsuda[b], Masaji Hashimoto[b], Goro Watanabe[b]

[a] *Department of Gastroenterology, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, Toranomon 2-2-2, Minato-ku 105-8470, Tokyo, Japan*
[b] *Department of Digestive Surgery, Toranomon Hospital, Tokyo, Japan*

Received 4 October 2004; received in revised form 11 April 2005; accepted 7 September 2005
Available online 2 November 2005

Abstract

Background: Cost-effectiveness of radiofrequency ablation (RFA) was assessed in treatment of hepatocellular carcinoma (HCC).
Patients and methods: During 5 years, 153 patients with HCC of 3 cm or less received RFA, and 60 underwent surgery. Judgment after RFA therapy was classified into three grades: residual tumor (grade 1), necrotic area with a less safety margin of 5 mm (grade 2), and necrosis with a safety margin of 5 mm in all directions (grade 3).
Results: Local recurrence rates after RFA and surgery were 7.9% and 0% at the third year. The rates in patients with grades 2 and 3 after RFA were 18.7% and 1.2% at the third year, respectively ($P = 0.0005$). Among 91 patients with grades 1 and 2 necrosis after initial therapy, 52 received additional ablation. Although local recurrence rate was 24.9% in 39 patients without additional therapy, the rates after therapy repetition were 10.9% in 21 patients with eventual grade 2 necrosis, and 0% in 31 patients with grade 3 ($P = 0.038$). Median costs of single RFA, repeated RFA, and surgery were ¥849,900, ¥1,086,000, and ¥1,745,100, respectively. Additional ablation reduced local recurrence by 20.7% at the cost of ¥236,100.
Conclusion: Cost-effectiveness of RFA in the treatment of small HCC was superior to that of surgery.

Keywords: Hepatocellular carcinoma; Radiofrequency ablation; Recurrence; Cost-effectiveness; Local recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common neoplasms in Africa and Asia including Japan [1]. Since it has recently became well known that more than 80% of the patients with HCC are associated with liver cirrhosis, a routine check-up for cirrhotic patients with ultrasonography (US) can usually detect small HCCs. However, because of the association of cirrhosis and tumor multiplicity, surgical resection is performed only in 20% or less of the cases [2–5]. Percutaneous loco-regional therapy is effective and feasible in the treatment of patients with a small-sized HCC of 3 cm or less in diameter. Percutaneous ethanol injection (PEI) [6,7], microwave coagulation therapy (MCT) and radiofrequency ablation (RFA) therefore, became prevalent recently in Japan, where viral liver disease due to hepatitis B and C was often found.

* Corresponding author. Tel.: +81 44 877 5111; fax: +81 44 860 1623.
E-mail address: ikedakenji@tora.email.ne.jp (K. Ikeda).

1386-6346/$ – see front matter © 2005 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.hepres.2005.09.002

In RFA therapy, radiofrequency waves are emitted from a percutaneously inserted electrode and they bring about tumor tissue necrosis by heating to a temperature of 60 °C or more [8–12]. It is now considered as one of the most effective ways of therapy for a small-sized HCC, among varied options of percutaneous tumor ablation [13,14]. Although this choice of treatment for a small HCC produces a round and good necrotic volume at the site of tumor tissue, local recurrence still occurs during a long-term observation for various conditions [12,14,15]. Possible reasons for the local recurrence include a limitation of proper judgment by current imaging diagnosis, shortage of necrotic rim around a tumor (so-called "safety margin"), and insufficient tissue necrosis adjacent to the major portal vein or hepatic vein. Because of the relatively high rate of local recurrence, RFA therapy seemed less radical than surgical resection even in the treatment of a small HCC. Treatment repetition is also associated with a decrease in quality of life of patients and increase in medical and social expense as a whole. Surgical therapy, on the other hand, is an invasive manner of treatment with a higher cost for the procedure, but is considered to show a lower recurrence rate.

The purposes of this study were [1] to examine the efficacy of RFA from the viewpoint of local recurrence, and [2] to elucidate cost-utility of RFA therapy for a small HCC compared with that of surgical treatment. Significance of repeated percutaneous ablation against HCC was also analyzed in the study.

2. Patients and methods

2.1. Patients

A total of 290 patients were diagnosed as having a small HCC of 3 cm or less in diameter, from March 1999 to April 2003, in the Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan. Of these 290 patients, 153 patients underwent percutaneous RFA therapy as a curative manner of treatment, 60 patients received surgical resection, 45 had transcatheter arterial embolization, and the remaining 32 patients were treated with ethanol injection, microwave coagulation therapy, or other palliative manners of treatment.

A total of 213 consecutive patients with a small HCC, who underwent either RFA or surgery, were analyzed in this study. These contemporary patients were analyzed for total recurrence rate, manners of recurrence, admission period, and medical cost.

The patients consisted of 144 men and 69 women, and the age ranged from 38 to 87 years old with a median age of 65 years. Before the treatment with RFA or surgical resection, all the patients underwent an evaluation consisting of a medical history inquiry, physical examination, tumor measurement, performance status, chest radiograph, liver imagings (computerized tomography, ultrasonography, and digital subtraction angiography), complete blood count, blood chemistry, alpha-fetoprotein (AFP) measurement, and urinalysis.

Demography and laboratory data were compared between the two therapy modalities (Table 1). The rate of decompensated cirrhosis was slightly higher in RFA treatment group, and indocyanine retention rate at 15 min were significantly higher and platelet count were lower in patients with RFA therapy.

2.2. Hepatocellular carcinoma

Patients were required to have HCC with a definitive diagnosis by either typical hypervascular radiological features or histology through needle biopsy. Although elevation of

Table 1
Demography and laboratory data of the patients with small liver cancer

	Radiofrequency ablation ($N = 153$)	Hepatic resection ($N = 60$)	P
Demography			
Men:women	101:52	43:17	0.52
Age (median, range)	66 (38–87)	64 (38–73)	0.25
Decompensated cirrhosis	17 (11.1%)	3 (5.0%)	0.20
HBs antigen	22 (14.4%)	15 (25.0%)	0.074
Anti-HCV antibody	119 (77.8%)	43 (71.7%)	0.37
History of alcohol intake > 500 kg	21 (13.7%)	12 (20.0%)	0.29
Observation period (years)	2.5 (0.7–5.0)	2.7 (0.7–5.0)	0.25
Laboratory data (median, range)			
ICG R15 (%)[a]	30 (8–100)	20 (3–68)	<0.001
Bilirubin (mg/dl)	1.0 (0.2–3.1)	1.0 (0.3–2.2)	0.057
Albumin (g/dl)	3.5 (2.2–4.2)	3.6 (2.6–4.4)	0.008
Aspartic transaminase (IU)	50 (17–281)	46 (20–202)	0.097
Platelet count ($\times 10^3$ mm^{-3})	88 (27–229)	140 (40–245)	<0.001
Prothrombin time (%)	84 (46–121)	91 (68–122)	0.002
Alpha-fetoprotein (ng/ml)	19 (2–4290)	12 (1–1460)	0.142
PIVKA-II (AU/l)[b]	16 (5–888)	20 (5–768)	0.152

[a] ICG R15: indocyanine green retention rate at 15 min.
[b] PIVKA-II: protein induced by Vitamin K antagonist-II.

Table 2
Characteristics of hepatocellular carcinoma in the both patient groups

	Radiofrequency ablation ($N = 153$)	Hepatic resection ($N = 60$)
Initial tumor:recurrent tumor	103:50	57:3
Median tumor size (range) (mm)	18 (6–30)	20 (7–30)
Tumor multiplicity		
Solitary	114 (74.5%)	50 (83.3%)
Multiple, localized to one segment	9 (5.9%)	0
Multiple, localized to one lobe	13 (8.5%)	7 (11.7%)
Multiple, extended to both lobes	17 (11.1%)	3 (5.0%)
Number of tumor nodules		
Solitary	114 (74.5%)	50 (83.3%)
Two	22 (14.4%)	8 (13.3%)
Three	12 (7.8%)	1 (1.7%)
Four or more	5 (3.4%)	1 (1.7%)
Portal vein invasion		
No	151	56
Yes	2	4

AFP without aminotransferase fluctuation was also taken into account in the diagnosis of HCC, imaging and pathology took precedence in the establishment of diagnosis. Disease had to be measurable by US, computerized tomography (CT), and digital subtraction angiography. In order to elucidate the detailed characteristic of the HCC, CT during arterial portography (CT-AP) and computerized tomographic hepatic arteriography (CT-HA) were performed in all the patients.

The median size of the largest tumor was 18 mm in diameter (range, 6–30 mm). The numbers of the tumor were one in 164 patients (74.5%), two in 30 patients, three in 13 patients, and four or more in 6. Details of HCC were compared between the RFA and surgery group in Table 2. Patients with a recurrent tumor tended to receive RFA therapy more frequently. Although tumor size was slightly larger in the surgery group, multiple tumors were more found in the RFA group.

2.3. Method of treatment

RFA was performed using three different apparatus: radiofrequency interstitial tumor ablation system (RITA, RITA Medical Systems Inc., Mountain View, USA), cool-tip system (Tyco Healthcare Group LP, Burlington, USA) and radiofrequency tumor coagulation system (RTC system, Boston-Scientific Japan Co., Tokyo, Japan). In all three systems, treatment procedures were performed according to their company's recommendation as to generator power and process time. In the treatment with the RTC system, we adopted a "stepwise hook extension technique" [16] instead of a standard method shown by the manufacturer.

Hepatic resection was performed under intra-operative ultrasonographic monitoring and guiding. In the case of small and superficial HCC, arterial, and portal vein clumping at hepatic hilum was not usually performed for maintenance of liver perfusion.

Physicians and surgeons usually held a conference about the choice of therapy in individual patients. The choice of treatment for the small HCCs principally depended on liver function and the site of the tumor in the liver: a tumor situated deeply in the liver was usually treated with RFA, and a superficial tumor was more often treated with surgical resection.

2.4. Evaluation of therapeutic effect and follow-up

Effect of RFA was evaluated with dynamic CT in a week after each RFA therapy. Judgment of necrotic area was classified into three categories: grade 1, necrotic area smaller than original tumor size; grade 2, necrotic area of the same size or larger than original tumor, but no safety margin of 5 mm around tumor; and grade 3, necrotic area larger than original tumor size with a safety margin of 5 mm or more in all directions. At least two physicians or radiologists confirmed the judgment of the treatment effect.

Physicians observed the patients every 4 weeks after the first treatment. Liver function test, hematology, and tumor markers were measured every month. After completion of eradication of HCC, recurrence was surveyed with CT imaging (helical CT or multi-detector CT) every 3 months.

During a median observation period of 2.6 years, two patients (0.9%) were lost to follow-up.

2.5. Evaluation of cost-effectiveness

The cost-utility of RFA was analyzed in comparison with that of surgery, from the viewpoint of society expense. Direct medical costs were only calculated in this study, excluding other social costs. Evaluation of cost-effectiveness balance was based on incidence of local recurrence as an intermediate endpoint. Discount rate was set at 0%. Sensitivity analysis was performed using [1] local recurrence rate after RFA therapy, and [2] net cost of surgical therapy.

2.6. Statistical analysis

Standard statistical measures and procedures were used. The chi-square test, Fisher's exact test, and Mann–Whitney's *U*-test were used to analyze the differences of demography, laboratory findings, and tumor characteristics between RFA group and surgery group. Recurrence and survival rate were analyzed using the Kaplan–Meier technique [17] with log-rank test. A *P*-value of less than 0.05 in two-tailed test was considered to be significant. Data analysis was performed using the computer program SPSS version 11 [18].

3. Results

3.1. Judgment of necrotic area after RFA therapy

Judgment of necrotic area as grades 1, 2, and 3 after first RFA therapy was 2 (1.3%), 89 (58.2%), and 62 (40.5%), respectively. Among 91 patients with grades 1 and 2, additional ablation therapy was performed in 52 patients (57.1%): 37 patients received therapy twice, 11 patients three times, and 4 patients four times or more as an initial session of loco-regional therapy. Although RFA was carried out in 36 patients as an additional loco-regional therapy, PEI or MCT was performed in the other 14 patients with the principal reason of tumor location in the liver.

Of the 52 patients with additional therapy, 31 patients (59.6%) accomplished grade 3 necrosis, and the other 21 (40.4%) showed grade 2 necrosis. At the end of the initial session of RFA, 60 (39.2%) attained grade 2 necrosis, 93 (60.8%) grade 3, and none remained at grade 1 (Fig. 1). The principal reason why therapy repetition did not bring about grade 3 necrosis in 21 patients was because tumor was adjacent to a large vessel of portal vein or hepatic vein. The other reasons included patient's disagreement, a problem in location of tumor, and transient aggravation of liver function.

3.2. Judgment of resected area and pathology after surgery

All the tumors in 60 patients with hepatic resection were completely removed on dynamic CT films after surgery. When the length between tumor margin and cut-surface of surgical resection was evaluated on resected pathology specimens, the "surgical margin" of HCC varied from 0 to 15 mm with a median of 6 mm.

3.3. Incidence and manners of recurrence

During the median follow-up period of 2.6 years, 70 patients showed tumor recurrence after therapy. Cumulative recurrence rates in patients with RFA and surgical resection were 16.6% and 14.9% at the end of the first year, 40.3% and 27.1% at the second year, and 50.2% and 30.3% at the third year, respectively (Fig. 2). The recurrence rate in patients with RFA therapy was higher than that of surgical resection (log-rank test, $P = 0.069$).

Recurrence rate was considered to be higher in patients with a "recurrent" tumor than in those with an "initial" tumor, recurrence rates were compared in a subgroup of patients with an initially developed HCC between the two groups. Cumulative recurrence rates in patients with RFA ($N = 103$) and surgical resection ($N = 57$) were 11.1% and 13.8% at the end of the first year, 31.6% and 26.5% at the second year, and 38.6% and 29.7% at the third year, respectively (Fig. 3). The recurrence rate in patients with RFA therapy was higher than that of surgical resection by 8.9% at the end of the third year (log-rank test, $P = 0.54$).

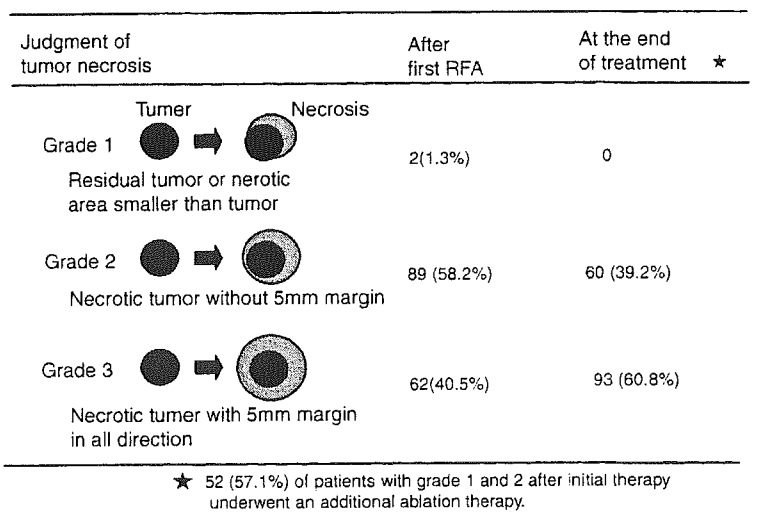

Fig. 1. Judgment of tumor necrosis after radiofrequency ablation therapy, according to three grades of treatment completeness.

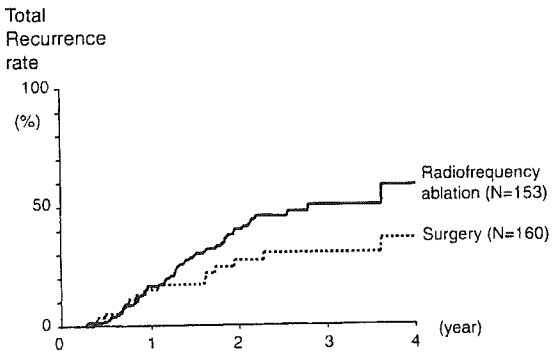

Fig. 2. Cumulative recurrence rates after therapy in all the patients with radiofrequency ablation therapy and in those with surgical resection.

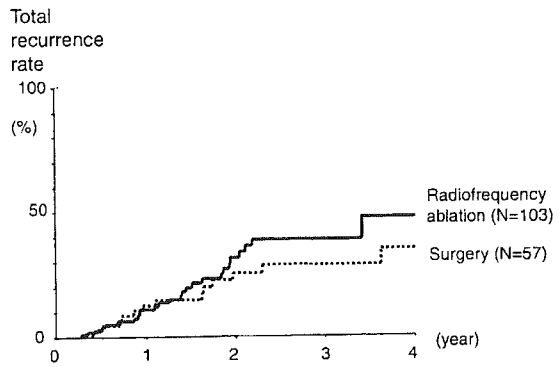

Fig. 3. Cumulative recurrence rates in subgroups of patients with "initially-developed liver cancer", excluding those patients with "recurrent liver tumor".

According to the site of recurrence, local recurrence was found in 9 patients (12.9%) and recurrence other than primary site in 61 (87.1%). When local recurrence rates were calculated in patients with RFA therapy and surgery, 1-year recurrence rates were 4.4% and 0%, second year rates were 7.9% and 0%, and third year 7.9% and 0%, respectively (Fig. 4). Local recurrence rate in patients after RFA therapy was remarkably higher than that of surgical therapy (log-rank test, $P = 0.053$).

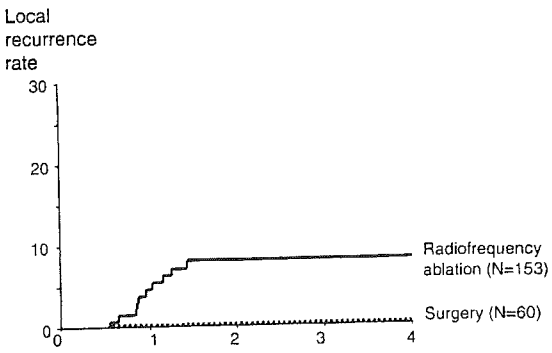

Fig. 4. Local recurrence rates in all the patients with radiofrequency ablation therapy and in those with surgical resection.

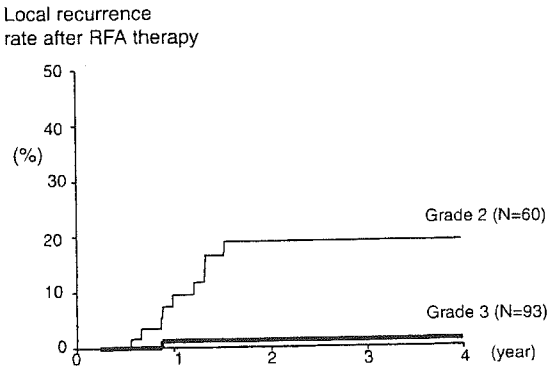

Fig. 5. Local recurrence rates after radiofrequency ablation according to the grade of necrosis area judged from dynamic computerized tomographies taken after therapy.

3.4. Relationship between necrotic area and recurrence rate after RFA therapy

Local recurrence rates were analyzed according to the judgment of final necrotic area classified into three categories. Cumulative recurrence rates after judgment of grade 2 necrosis ($N = 60$) and grade 3 necrosis ($N = 93$) were 9.6% and 1.2% at the end of the first year, 19.1% and 1.2% at the second year, and 19.1% and 1.2% at the third year, respectively (Fig. 5). The recurrence rate in the patients with grade 2 was significantly higher than those of grade 3 (log-rank test, $P = 0.0003$).

Among 91 patients who did not reach grade 3 necrosis after first therapy, 52 patients received additional ablation therapy to secure safety margin of 5 mm around the tumor. Although 31 (59.6%) of 52 patients attained grade 3 necrosis rate, the other 21 patients (40.4%) remained at grade 2. Local recurrence rates were assessed in the following three patient groups: grade 2 necrosis without additional ablation therapy (group A, $N = 39$), consequent grade 2 necrosis even after additional ablation therapy (group B, $N = 21$), eventual grade

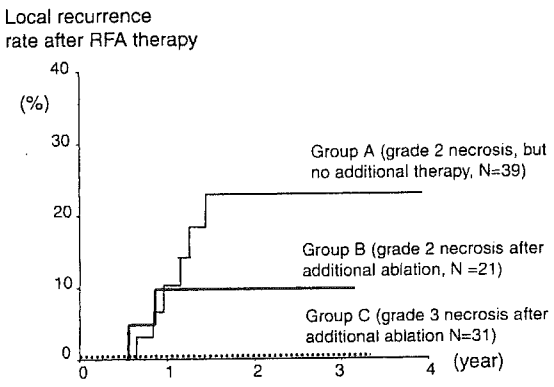

Fig. 6. Local recurrence rates in patients with grade 1 or 2 effect after initial radiofrequency ablation. Thirty-nine patients did not undergo treatment repetition (group A), 21 remained grade 2 in spite of re-treatment (group B), and 31 patients attained grade 3 necrosis after an additional ablation (group C).

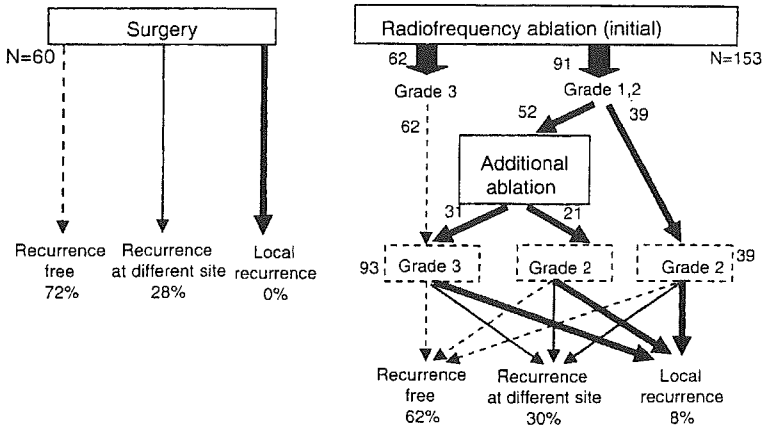

Fig. 7. Treatment and outcomes regarding to recurrence in the 213 patients with radiofrequency ablation or surgery.

3 necrosis with additional ablation (group C, $N=31$). Cumulative local recurrence rates in the group A, B, and C were 10.9%, 10.3%, and 0% at the end of the first year, 24.9%, 10.3%, and 0% at the second year, and 24.9%, 10.3%, and 0% at the third year, respectively (Fig. 6). The local recurrence rate was the highest in group A, and it was apparently lower in group B than in group A, and was the lowest in group C (log-rank test, $P=0.038$). Local recurrence rate from the 52 patients with repeated ablation was calculated as 4.2% at the end of the third year. That rate was lower than that of 39 patients without treatment repetition by 20.7%.

3.5. Treatment repetition and local recurrence rates

Although RFA therapy resulted in a higher local recurrence rate than surgical resection, median cost for surgical therapy was markedly higher than that of RFA therapy (Fig. 7). Since an additional therapy significantly reduced local recurrence rate in patients with grade 1 or 2 necrosis after initial RFA therapy, a simulated local recurrence rate was estimated when every patient without grade 3 necrosis received a supplementary ablation just after the first RFA therapy. Sixty-two (40.5%) of 153 patients achieved grade 3 necrosis after first RFA therapy and the other 91 patients (59.5%) remained at grades 1 or 2 necrosis. Treatment iteration improved an insufficient necrosis from grades of 1 or 2 to grade 3 by 59.6% (31/52 patients).

If every patient with grade 1 or 2 received additional ablation therapy, eventual rate of grade 3 necrosis after repeated procedures was estimated to be 76.0% (40.5% plus 59.5% multiplied by 59.6%), and the other 24.0% of patients remained at grade 2 necrosis even after repeated procedures. As a result, 76.0% of the patients would show a local recurrence with a rate of 1.2%, and the other 24.0% with a rate of 10.3%. Consequently, the local recurrence rate after repeated ablation at the end of the second year was calculated as 3.3% (1.2% multiplied by 76.0% plus 10.3% multiplied by 24.0%).

3.6. Side effects of radiofrequency ablation and surgery

The most common side effects observed during and after RFA were abdominal pain, fever, and mild aggravation of liver function tests. Varied degrees of abdominal pain during ablation were found in almost of the patients. Low-grade fever of 37–38 °C lasting for a few days was found in 46 patients (30.0%), and fever of 38 °C or more was found in the other 29 patients (19.0%). Seven patients (11.1%) showed vomiting at the time of treatment, but there was no significant deterioration in weight, symptoms or performance status. Transient elevation of serum aminotransferases for a week was seen in 131 patients (85.6%): 122 showed a figure twice as high as the values before treatment and 9 showed 1.5–1.9 times as high. Within a week after treatment, 20 patients (13.1%) showed a temporary elevation of total bilirubin level twice as high as pretreatment value. One patient developed a perforation of jejunum that required emergency surgery, and he left the hospital 26 days after RFA therapy. Two other patients developed biloma or intra-hepatic bile duct dilation without symptom, and they did not need any medication including antibiotics.

One patient developed biloma with infection after surgical resection and he needed to stay in the hospital until complete recovery for 138 days after surgery. Two patients developed prolonged ascites for a few months and the other one showed a transient aggravation of liver function tests with jaundice. One patient showed a significant bleeding requiring blood transfusion and re-laparotomy just after surgery.

Treatment-related death within six months after therapy was not found in the entire patient groups with RFA and also those with surgical resection.

3.7. Mortality

During a median follow-up period of 2.6 years, 10 patients (4.7%) died: 6 in the RFA therapy group and 4 in the surgery group. Among six patients in the RFA therapy group, two died

Table 3
Costs (Japanese Yen[a]) of diagnosis and treatment for small hepatocellular carcinoma, managed with single radiofrequency ablation, repeated percutaneous ablation, and surgical therapy

	Radiofrequency ablation (single Tx) ($N=101$)	Radiofrequency ablation (repeated Tx) ($N=52$)	Surgery ($N=60$)
Diagnosis and pretreatment check-ups: biochemistry, hematology, virology, US, CT, MRI, angiography, IVH before surgery, etc.	249600	249600	307700
Procedures for treatment: technique, anesthesia, medicines, machinery, and materials, etc.	143600	243600	438200
Post-treatment cares and examination: antibiotics, medicines, IVH, wound care, etc.; CT for judgment of efficacy	44400	80800	278000
Basic charge for admission	412300	512000	721200
Total cost (Yen[a])	849900	1086000	1745100

[a] Currency rate: $1.00 = ¥114.00 (October 2005).

from intra-hepatic cancer growth, three from liver failure, and one from sepsis, which was unrelated to liver disease. Among four patients in the surgery group, two died from intra-hepatic cancer growth, and two from metastatic tumor. The causes of death were not related to intra-hepatic tumor growth in 6 of the 10 patients.

3.8. Gross admission period

A median admission period for the RFA therapy was 26 days with a range of 11–112 days, including thorough imaging examinations before treatment, medical conferences, and evaluation of liver function and imagings after treatment: it was 24 days (11–57 days) when ablation therapy was performed only once in admission, and 29 days (15–112 days) when multiple procedures were carried out for a better necrosis rate. A median hospital stay after RFA therapy was 12 days with a range of 4–40 days, including an imaging study with CT for evaluation of the effects of the therapy: unless additional therapy was required on the CT evaluation for the first therapy, median hospital stay was 6 days with a range of 4–21 days.

A median admission period for the treatment with surgical resection was 52 days (range, 28–187 days), and median period of hospital stay after surgery was 26 days (range, 16–138 days). The admission period in surgical therapy was significantly longer than that of RFA (Mann–Whitney U-test, $P<0.001$).

3.9. Net cost for treatment

Net cost required for examination and treatment of HCC were estimated in both treatment arms, excluding examination and treatment of other diseases than HCC.

Net costs required for examination and treatment in RFA therapy and surgery were ¥867,200 and ¥1,745,100, respectively. It was ¥849,900 when RFA therapy was performed once as a treatment of HCC during a median admission period of 24 days, and was ¥1,086,000 when a repeated percutaneous ablation therapy was performed during a median period of 30 days (Table 3).

3.10. Cost-effectiveness of RFA and surgery

Medical cost for surgical resection of a small HCC was ¥1,745,100. Mean cost of RFA therapy per person was ¥930,100 (single therapy in 101 patients and multiple therapies in 52 patients). Since evaluation and treatment for local recurrence were required in 7.9% of patients with RFA therapy within 2 years, supplementary cost should be taken into account in the group: Mean cost for RFA therapy per person was ¥1,003,500 with an additional cost for local recurrence.

When the rates of multicentric tumor occurrence and intrahepatic tumor metastasis were supposed to be same between the RFA group and surgery group, RFA therapy cut the cost by ¥741,600 per patient with a small HCC, compared to surgical resection.

4. Discussion

Recently in Japan, as a result of recognition of high carcinogenesis rate in patients with cirrhosis and vigorous check-ups for the high risk patients with ultrasonography, small HCCs have often been found during the follow-up period of cirrhosis. The treatment strategy for these small multiple tumors should, therefore, be established as fast as possible. Since survival period of patients with HCC chiefly depends on the growth of the tumor, and since most of the patients with small HCC eventually die from progression of the tumor, more radical and reasonable ways of therapy should be applied for every patient.

RFA is one of the most effective therapies for a small HCC; it is not only less invasive but a less expensive manner of treat-