外の治療法が AFP-L3 分画の多寡により術後の生命予後を規定されるのに対し、治療法として外科切除を選択した症例に関しては、AFP-L3 分画の多寡によらず良好な治療成績を残していることを報告した。換言すれば、「癌の生物学的悪性度」の高い HCC 症例に対しては、外科切除を中心とした、より radical な治療法を選択することが予後改善につながることを示したことになり、従来のスコアリングシステムに AFP-L3 分画を評価項目として加えることによって、治療法選択と予後予測を一元的に行うことのできる理想的なシステム開発が可能であることが示唆された。

一般的に後向き研究では、対象症例の選択や除外の基準、検査方法、収集されるべき情報、治療方法、フォローアップ方法（期間や無再発確認の間隔や方法）等が施設間や年代で不均一であり、それにより、生存率の推定や、その有意差検定を行う際にバイアスが生じることがある。

平成 18 年度は、先に得られた後ろ向き研究の知見に対し確証的な結果を得るため、一定の基準の下で計測・データ収集できる前向き研究を行い、比較的短期間に評価可能な、無再発生存期間をアウトカムとして、腫瘍マーカーの多寡が患者の予後に及ぼす影響を評価した。

その結果、治療前後の AFP 濃度、AFP-L3 分画、PIVKA-II はともに治療後の無再発生存期間を有意に層別化し、治療前よりも治療後測定値での有意性が強いこと、L3 については PIVKA-II、AFP 低値例においても無再発生存期間を良好に層別化し、治療 2 ヶ月後の測定によって、優れた予後予測能力を発揮することを確認した。さらに、多変量解析では、HCC 再発の規定因子として、治療後の AFP-L3 が他のマーカーや腫瘍ステージと独立した最も有意な再発規定因子であることが明らかとなった。これら、前年度の知見と矛盾しない結果が得られた一方、治療法別に検討した結果では、外科切除とラジオ波焼灼術は、無再発生存の観点からは、AFP-L3 分画の高い群、低い群で治療成績が同等であると評価された。これは、生命予後をアウトカムとした前年度の後ろ向き研究により得られた、術前の AFP-L3 分画に影響を受けない治療法は手術療法のみである、という結果と乖離した結論であった。これは、経過観察期間が短いこと、登録症例数が少ないことが影響している可能性が十分に考えられる。このような、外科切除もラジオ波焼灼術も選択可能な症例において、いずれの治療がより適切であるかの結論とその選択基準を明確にすることは、本研究の最も重要な課題であると考えられる。次年度以降はこの問題に重点を置き、更なる症例の蓄積と追跡調査を行う予定である。

一方、もう一つの生物学的悪性度の指標として着目した hTERT を指標とした末梢血中癌細胞の検出に関しては、生命予後をアウトカムとした前年度の後ろ向き研究で、その治療前測定の意義が示唆されており、平成 18 年度は AFP-L3 と同様に比較的短期間に評価可能な無再発生存期間をアウトカムとして、患者の予後に及ぼす影響を前向きに評価した。その結果、hTERT 陽性症例数は治療前肝癌患者 94 例中では 9 例 (9.5%)、であり、既報の陽性症例率である約 55% (Clin. Cancer Res., 9: 3004-11, 2003) から期待される陽性率よりも低値であった。無再発期間に関する検討では治療前 hTERT 定性陰性者に比較して陽性者では無再発生存の短縮傾向 (p=0.33) を認めたが、有意な差は確認できず、この点も生命予後をアウトカムとした前年度の後ろ向き検討で確認されたものとは異なる結果であった。これは、登録症例数と観察期間、PCR

手技上の問題(偽陰性、偽陽性)に加え、抗体結合磁気 Beads を用いた定性法において用いている Ber-EP4 の肝癌細胞表出の頻度が当初予想していたよりも低いことが大きな要因であると考えられる。血中癌細胞由来 hTERT の検出については、これまで登録された症例の追跡調査を引き続き行う予定であるが、同時に、hTERT 測定手技の改良を検討していく必要があると考えられた。

E．結論

肝癌患者 190 例、249 回の治療データを前向きに解析した結果、治療後の AFP-L3 は他のマーカーや腫瘍ステージと独立した最も有意な再発規定因子($p<0.0001$)であることを確認した。血中肝癌細胞 hTERT 検出では、無再発生存における有意差は確認できなかったが($p=0.33$)、治療前の血液中癌細胞陽性症例の無再発生存率が低い傾向が認められた。

F．健康危険情報

なし

G．研究発表

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２．学会発表

なし

H. 知的財産権の出願・登録状況

１０．　特許取得

なし

１１．　実用新案登録

なし

１２．　その他

なし

研究成果の刊行に関する一覧表

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Machida T, Sato K, Takezawa J, Sohara N, Kakizaki S, **Takagi H**, Mori M.	Ruptured duodenal varices after endoscopic ligation of esophageal varices: An Autopsy Case	Gastrointestinal Endoscopy	63	352-354	2006

INTERNAL MEDICINE

□ CASE REPORT □

A Primary Follicular Lymphoma of the Duodenum Treated Successfully with Radiation Therapy

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Abstract

A 48-year-old man was admitted to our hospital because of repeated episodes of epigastralgia. Endoscopy showed multiple whitish granules extending from the 2nd to 3rd portion of the duodenum. Biopsy specimens showed well circumscribed follicles with a monotonous population of predominantly small cleaved cells that were positive for CD20, CD10 and BCL-2, but negative for CD5. A full staging study showed no abnormalities. The tumor was finally diagnosed according to the WHO classification as a stage I follicular lymphoma (FL), grade 1, of the duodenum and subsequently received irradiation to the involved area. After 3 years of follow-up, he is still in complete remission. Because FL arising in the duodenum has recently reported with increasing frequency, patients with multiple granules in the duodenum should be examined carefully.

Key words: follicular lymphoma, duodenum, radiation therapy, gastrointestinal tract

(DOI: 10.2169/internalmedicine.45.1464)

Introduction

The gastrointestinal (GI) tract is the most common extranodal site of origin for non-Hodgkin's lymphomas (NHLs), accounting for approximately 40% of all extranodal primary NHLs. The stomach is the most common primary site for NHL, followed by the colorectal region and the terminal ileum (1). However, the duodenum is rarely involved (2, 3).

Follicular lymphoma (FL) is a neoplasm of follicle center B-cells and is one of the most common subtypes of NHL. Most patients with FL present with nodal involvement, and extranodal presentation is uncommon. Although FL of the GI tract represents only about 1-3.6% of all GI tract lymphomas (3-5), FL arising in the duodenum has been reportedly occurring with increasing frequency (3, 6), and in fact recently there have been numerous case reports on this disease (7-11). Here, we present a case of stage I primary FL arising in the duodenum, which was diagnosed by biopsy specimens and treated successfully with irradiation to the involved area.

Case Report

A 48-year-old Japanese man presented with a 4-week history of epigastralgia. Initial endoscopic evaluation at another institution showed only gastric erosion; there was no evidence of duodenal abnormality. He was treated with antacids and obtained temporary relief from the symptoms. Later, however, the epigastralgia recurred, and he visited our hospital. Interview revealed that the patient had had poorly controlled diabetes for the previous ten years. Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. All laboratory findings, including the levels of lactate dehydrogenase and soluble IL-2 receptor, were within normal limits. Upper GI endoscopy revealed multiple whitish granules extending from the 2nd to 3rd portion of the duodenum

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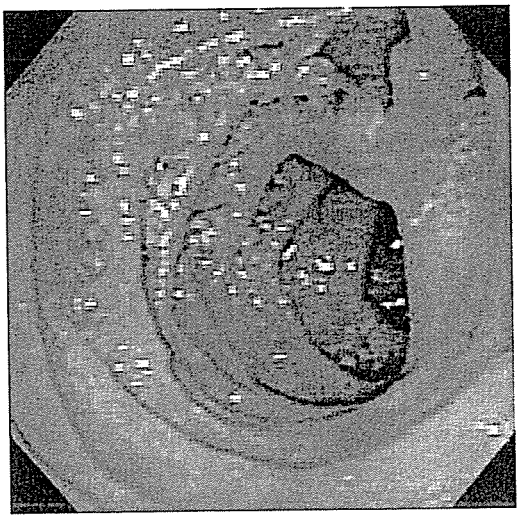

Figure 1. Endoscopic view of the duodenal follicular lymphoma. Multiple whitish granules extend from the 2nd to 3rd portion of the duodenum.

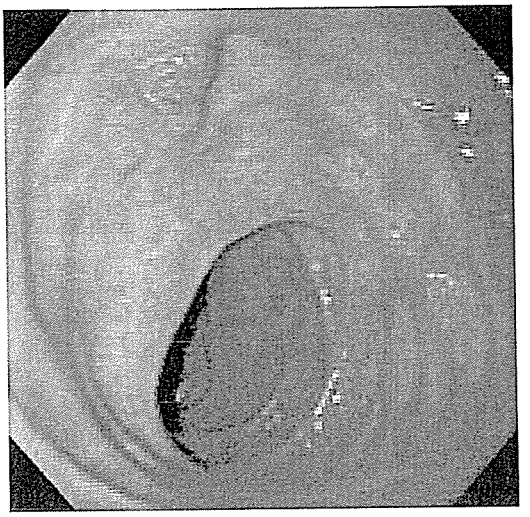

Figure 4. Nine months after the start of radiotherapy, endoscopic examination demonstrates disappearance of the granular lesions.

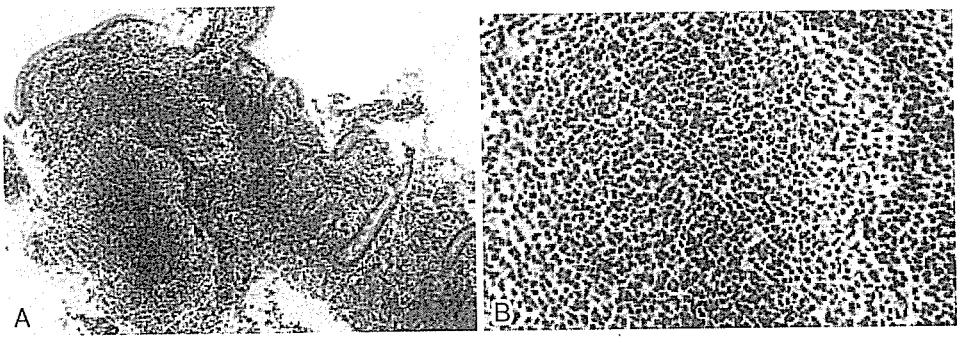

Figure 2. Histopathological examination of endoscopic biopsy specimens, showing a low-power view (A) and a high-power view (B). The biopsy specimens show well circumscribed follicles (A) composed of a monotonous population of predominantly small-cleaved cells (B).

(Fig. 1). Biopsy specimens showed well circumscribed follicles composed of a monotonous population of predominantly small-cleaved cells (Fig. 2) that were positive for CD 20, CD10 and BCL-2, but negative for CD5. The margin of the lesion revealed by endoscopy corresponded completely to that observed by microscopy. Rearrangement of the immunoglobulin heavy chain gene was confirmed by Southern blot analysis using tumor samples. Therefore, the tumor was diagnosed as a grade 1 FL, according to the WHO classification (12). Hypotonic duodenography showed thick and meandering folds, measuring about 50 mm, extending from the 2nd to 3rd portion of the duodenum (Fig. 3). Other examinations, including computed tomography, gallium scintigraphy, colonoscopy, endoscopic retrograde cholangiopancreatography, and bone marrow aspiration, showed no abnormalities. On the basis of these findings, the FL was evaluated as stage I.

The patient subsequently underwent irradiation to the involved area consisting of 30.6 Gy delivered in 1.8-Gy fractions. Nine months later, endoscopy revealed disappearance of the granular lesions (Fig. 4) and lack of lymphoma cells in biopsy specimens. Multiple biopsies of the duodenal mucosa during repeat endoscopies failed to demonstrate the presence of lymphoma cells. There was no evidence of recurrence during the 3 years of follow-up.

Discussion

FL is a rare histological subtype among primary GI tract NHLs. Recently, however, there has been increasing evidence that the incidence of FL is unexpectedly high in the duodenum in comparison with other GI sites. In the series reported by Yoshino et al (3), 5 of 8 cases of GI tract FL arose in the duodenum, and in another series reported by Shia et al (6), duodenal FL accounted for 10 of 26 cases of FL of the GI tract.

The clinical course of FL and treatment strategies differ according to the extent of disease (i.e., stage) at presentation. Although initial complete remission may be achieved by intensive therapies such as high-dose chemotherapy and/

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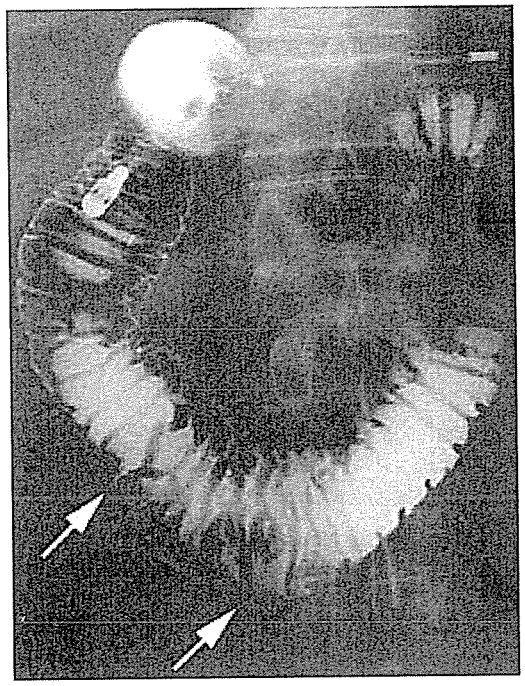

Figure 3. Hypotonic duodenography demonstrates thick and meandering folds (arrows) extending from the 2nd to 3rd portion of the duodenum.

or rituximab administration or chemoradiotherapy followed by stem cell transplantation, patients with disseminated (stage III and IV) FL usually relapse and have difficulty in achieving complete cure, whereas those with localized (stage I and II) FL are usually treated by radiation therapy or surgical resection and/or chemotherapy and often show long survival (13). Although the majority of cases of primary duodenal FL are treated by surgical resection, some are diagnosed only after surgical resection because of the difficulty in diagnosing FL from biopsy specimens (3). Therefore, for management of this disease, it is essential to make an accurate diagnosis and carry out accurate staging. The present case was diagnosed as grade 1 FL from biopsy specimens, and the margin of the lesion revealed by endoscopy corresponded completely to that observed by microscopy, i.e. it was judged to be a stage I primary FL extending from the 2nd to 3rd portion of the duodenum.

In this case, radiation therapy was chosen because surgical resection was considered to carry a high risk due to the patient's poorly controlled diabetes, and chemotherapy was not considered appropriate because the FL was localized. He received irradiation to the involved area consisting of 30.6 Gy delivered in 1.8-Gy fractions, without any adverse events, and has since been in complete remission for the last 3 years. Radiation therapy seems to be a safe and effective treatment modality for primary duodenal FL. However, Mac Manus et al reported that a few patients with localized FL suffered relapse, even decades after radiation therapy (14). Therefore, patients with FL need to be followed for as long as possible because of the risk of relapse.

In conclusion, we have reported a case of stage I primary FL arising in the duodenum, which was diagnosed by endoscopic biopsy and treated successfully with irradiation to the involved area. Patients with multiple granules in the duodenum should be examined carefully, especially in view of the fact that FL arising in the duodenum has recently been reported with increasing frequency.

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LIVER CANCER

Long-term outcomes of hepatectomy *vs* percutaneous ablation for treatment of hepatocellular carcinoma ≤4 cm

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Abstract

AIM: To determine which treatment modality - hepatectomy or percutaneous ablation - is more beneficial for patients with small hepatocellular carcinoma (HCC) (≤4 cm) in terms of long-term outcomes.

METHODS: A retrospective analysis of 149 patients with HCC ≤4 cm was conducted. Eighty-five patients underwent partial hepatectomy (anatomic in 47 and non-anatomic in 38) and 64 underwent percutaneous ablation (percutaneous ethanol injection in 37, radiofrequency ablation in 21, and microwave coagulation in 6). The median follow-up period was 69 mo.

RESULTS: Hepatectomy was associated with larger tumor size ($P<0.001$), whereas percutaneous ablation was significantly associated with impaired hepatic functional reserve. Local recurrence was less frequent following hepatectomy ($P<0.0001$). Survival was better following hepatectomy (median survival time: 122 mo) than following percutaneous ablation (median survival time: 66 mo; $P=0.0123$). When tumor size was divided into ≤2 cm *vs* >2 cm, the favorable effects of hepatectomy on long-term survival was seen only in patients with tumors >2 cm ($P=0.0001$). The Cox proportional hazards regression model revealed that hepatectomy ($P=0.006$) and tumors ≤2 cm ($P=0.017$) were independently associated with better survival.

CONCLUSION: Hepatectomy provides both better local control and better long-term survival for patients with HCC ≤4 cm compared with percutaneous ablation. Of the patients with HCC ≤4 cm, those with tumors >2 cm are good candidates for hepatectomy, provided that the hepatic functional reserve of the patient permits resection.

Key words: Liver neoplasms; Hepatocellular carcinoma; Hepatectomy; Percutaneous ablation; Prognosis; Multivariate analysis

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INTRODUCTION

Hepatectomy and percutaneous ablation are the treatments of choice for small hepatocellular carcinoma (HCC)[1,2]. Hepatectomy is recommended by surgeons, as this procedure removes portal venous thrombi in the adjacent liver[3], allows for better local control[4], and has better survival outcomes compared with percutaneous ablation[5,6]. In contrast, gastroenterologists and interventional radiologists advocate percutaneous ablation techniques including ethanol injection[7-9], microwave coagulation[10-12], and radiofrequency ablation[13-15], as these methods are not as invasive as hepatectomy[7-15], have a lower incidence of morbidity and mortality[7-13,15], are more feasible in patients with impaired hepatic functional reserve[7-15], and have similar survival outcomes compared with hepatectomy[7-9,15].

The aim of this study was to determine which treatment modality - hepatectomy or percutaneous ablation - is more beneficial for patients with small (≤4 cm) HCC in terms of long-term outcomes.

MATERIALS AND METHODS

Patients

From January 1990 to December 2002, 224 consecutive patients with HCC underwent either partial hepatectomy or percutaneous ablation therapy as an initial treatment at the Niigata University Medical and Dental Hospital. Of

these patients, 149 with HCC measuring ≤ 4 cm formed the basis of this retrospective study; they included 104 men and 45 women with a median age of 64 years (range: 29-83 years). Only HCCs measuring ≤ 4 cm were included in the current study, because percutaneous ablation therapy was the treatment modality mainly recommended for such tumors in our hospital. All patients were Japanese.

Treatment modalities

Of the 149 patients, 85 underwent a hepatectomy for HCC in the Division of Digestive and General Surgery. Hepatectomy. Procedures included non-anatomic hepatectomy in 38 patients, monosegmentectomy in 14, bisegmentectomy in 15, right hepatectomy in 14, and left hepatectomy in 4. In our department, the type of hepatectomy procedure selected was primarily based on the disappearance rate of indocyanine green (K_{ICG})[16,17], which is an indicator of hepatic functional reserve. The selection criteria were $K_{ICG} \geq 0.12$ for hemihepatectomy, $K_{ICG} \geq 0.10$ for bisegmentectomy, $K_{ICG} \geq 0.08$ for monosegmentectomy, and $K_{ICG} \geq 0.06$ for non-anatomic hepatectomy (including the enucleation of hepatic tumors).

The remaining 64 patients underwent a percutaneous ablation procedure for HCC in the Division of Gastroenterology and Hepatology. Hepatectomy was considered as a feasible option for 51 of these 64 patients and was offered as an alternative. However, all these patients preferred to undergo percutaneous ablation treatment. Hepatectomy was not considered feasible in the remaining 13 patients due to impaired hepatic functional reserve ($K_{ICG} < 0.06$); therefore, these patients were only offered percutaneous ablation treatment. Percutaneous ablation procedures included percutaneous ethanol injection (PEI) in 37 patients, radiofrequency ablation (RFA) in 21, and microwave coagulation therapy (MCT) in 6. In these patients, adequacy of the ablation was assured with dual-phase dynamic computed tomography (section thickness of 5 mm) within a month of the procedure. A microwave tissue coagulator (Microtaze® OT-110M; Alfresa-Pharma Co., Inc., Osaka, Japan) and an RF generator (Cool-tip® RF System, CMI Century Medical Co., Inc., Tokyo, Japan) were introduced in our hospital in 1995 and 2000, respectively.

Post-treatment follow-up

There were no mortalities 30 d post-treatment in the current study. Serum concentrations of alpha-fetoprotein were measured and abdominal ultrasonography and/or contrast-enhanced computed tomography was performed on all the patients approximately 1 mo after the treatment. Thereafter, patients were regularly monitored for recurrences in outpatient clinics every 3 mo by physical examination, laboratory tests, and imaging studies. When intrahepatic recurrences were detected, they were treated with either interventional radiological techniques, such as PEI, RFA, MCT, transarterial chemoembolization and hepatic arterial infusion, or repeat hepatectomy when indicated. Patients with disseminated recurrences and those in a debilitated state were treated with supportive care.

The follow-up period after the treatment was defined as the interval between the date of the initial treatment and that of the last follow-up, and ranged from 11 to 178 (median: 69) mo in the current study. The median follow-up period was 73 mo in patients who had undergone hepatectomy, and 61 mo in those who had undergone percutaneous ablation.

Definition of local recurrence after treatment

Local recurrence was defined as recurrences contiguous to resection margins in patients who had undergone hepatectomy, whereas in patients treated with percutaneous ablation, local recurrence was defined as recurrences contiguous to or within the ablated areas.

Laboratory examination

The following laboratory tests were performed before treatment: hepatitis B surface antigen; hepatitis C antibody; serum aspartate aminotransferase; serum alanine aminotransferase; the indocyanine green clearance test; and serum alpha-fetoprotein. Hepatitis B surface antigen and hepatitis C antibody in serum were detected by radioimmunoassay (Lumipulse II HBsAg; Fujirebio Co., Inc., Tokyo, Japan) and a second-generation enzyme-linked immunosorbent assay (Lumipulse II Ortho HCV; Ortho-Clinical Diagnostics Co., Inc., Tokyo, Japan), respectively. Indocyanine green (Diagnogreen; Daiichi Pharmaceutical Co., Inc., Tokyo, Japan) retention rate at 15 min after the injection of the dye (0.5 mg/kg) was used as an indicator of hepatic functional reserve, with a reference range of 10% or less[16-18]. Serum concentrations of alpha-fetoprotein were determined by enzyme immunoassay (Luminomaster AFP; Sankyo Yell Yakuhin Co., Ltd., Tokyo, Japan).

Pathologic examination

Resected specimens from all the patients who had undergone hepatectomy were submitted to the Department of Surgical Pathology in our hospital. Each specimen was examined to determine the number of hepatic tumors, tumor size, vascular invasion (gross or microscopic), and cirrhosis. Vascular invasion included both portal and hepatic venous invasion in the current study. Cirrhosis in the adjacent (non-tumorous) liver was diagnosed microscopically based on the presence of regenerative nodules surrounded by fibrous septa. The pathology of the liver was confirmed by fine-needle biopsy in all the patients undergoing percutaneous ablation. Among this group of patients, 41 patients had a fine-needle biopsy of the tumor.

Factors influencing outcomes after treatment

To determine the factors that may influence outcomes after the treatment, 13 conventional variables[19-22] were identified for univariate and multivariate analyses (Table 1). Vascular invasion and histologic grade were not chosen because they were often missed in patients undergoing percutaneous ablation.

Statistical analyses

Medical records and survival data were obtained for all the patients. The causes of death were determined from the medical records. Deaths from other causes were treated as uncensored cases. The Kaplan-Meier method was

used to estimate the cumulative incidences of events, and differences in these incidences were evaluated using the log rank test. The Cox proportional hazards regression model was performed to identify the factors that were independently associated with local recurrence and survival. In this model, a stepwise selection was used for variable selection with entry and removal limits of $P<0.1$ and $P>0.15$, respectively. The stability of each model was confirmed using a step-backward and step-forward fitting procedure, and variables identified as having an independent influence on local recurrence and survival were identical in both the procedures. Clinical features and pathologic tumor-related factors were compared between the two groups using Fisher's exact test. All statistical evaluations were performed using the SPSS 11.5J software package (SPSS Japan Inc., Tokyo, Japan). All tests were two-sided and P values of <0.05 were considered statistically significant.

RESULTS

Clinicopathologic characteristics according to treatment modality

A total of 125 hepatic tumors (median: one per patient; range: 1-14 tumors) were resected in patients undergoing hepatectomy, and a total of 100 tumors (median: one per patient; range: 1-5 tumors) were treated in patients undergoing percutaneous ablation.

Patients treated with hepatectomy had larger tumors than those treated with percutaneous ablation. Patients who had undergone percutaneous ablation were characterized by hepatitis C virus infection, cirrhosis, Child-Pugh classification B or C, an impaired indocyanine green retention rate at 15 min, and increased serum concentrations of aspartate aminotransferase and alanine aminotransferase, suggesting impaired hepatic functional reserve with active hepatitis in these patients (Table 1).

Table 1 Clinicopathologic characteristics of 149 patients with hepatocellular carcinoma according to treatment modality

Variable	Hepatectomy	Percutaneous ablation
Age (yr)		
≤65	56	33
>65	29	31
Gender		
Male	61	43
Female	24	21
HBsAg		
Negative	61	54
Positive	24	10
HCVAb		
Negative	38	11
Positive	47	53[b]
Cirrhosis		
Absent	38	13
Present	47	51[b]
Child-Pugh classification		
A	74	30
B plus C	11	34[b]
ICG R15 (%)		
≤10	52	10
>10	33	54[b]
AST(IU/L)		
≤50	48	17
>50	37	47[b]
ALT(IU/L)		
≤50	50	23
>50	35	41[b]
AFP (ng/mL)		
≤20	39	27
>20	46	37
No. of hepatic tumors		
Solitary	67	41
Multiple	18	23
Tumor size (cm)		
≤2	23	43
>2	62	21[b]

ICG R15: indocyanine green retention rate at 15 min. [b]$P<0.01$ between groups.

Factors influencing local recurrence

During the follow-up period, local recurrences developed in two patients who had undergone hepatectomy and 17 patients who had been treated with percutaneous ablation (10 treated with PEI and 7 treated with RFA). Univariate analysis revealed that treatment modality ($P<0.0001$), indocyanine green retention rate at 15 min $P=0.0005$), Child-Pugh classification ($P=0.0012$), serum alpha-fetoprotein level ($P=0.0072$), hepatitis C virus infection ($P = 0.0374$), and number of hepatic tumors ($P=0.0419$) were risk factors for local recurrence. Of these six variables, multivariate analyses revealed that treatment modality and serum alpha-fetoprotein level were the only independently significant variables (Table 2).

Table 2 Independent risk factors for local recurrence

Variable	Relative risk	95% CI	P value
Treatment modality			0.001
Hepatectomy	1.000		
Percutaneous ablation	13.442	3.102-58.254	
AFP (ng/mL)			0.014
≤20	1.000		
>20	4.711	1.370-16.195	

Factors influencing long-term survival

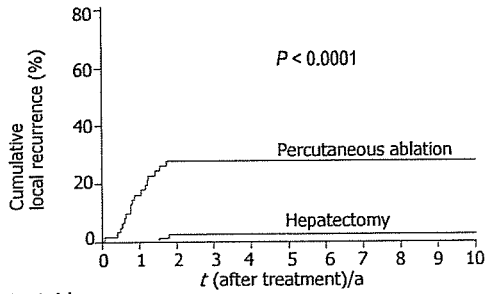
At the time of disease status assessment, 53 patients who had undergone hepatectomy were alive, and 32 had died. Thirty-four patients treated with percutaneous ablation were alive, and 30 had died. Univariate analysis revealed that Child-Pugh classification ($P=0.0010$), serum alpha-fetoprotein level ($P=0.0052$), treatment modality ($P = 0.0123$), serum aspartate aminotransferase ($P=0.0278$), tumor size ($P=0.0454$), and number of hepatic tumors ($P=0.0464$) were significant prognostic factors of long-term survival. Of these six variables, multivariate analyses revealed that treatment modality and tumor size were the only independent significant variables (Table 3).

Outcomes after treatment according to tumor size

Local recurrence was significantly less frequent in patients who had undergone hepatectomy than in those who had undergone percutaneous ablation ($P<0.0001$) (Figure 1). When the patients were divided into two groups according

Table 3 Independent factors influencing long-term survival

Variable	Relative risk	95% CI	*P* value
Treatment modality			0.006
Hepatectomy	1.000		
Percutaneous ablation	2.398	1.278-4.499	
Tumor size (cm)			0.017
≤2	1.000		
>2	2.159	1.148-4.060	
Child-Pugh classification			0.050
A	1.000		
B + C	1.773	1.000-3.142	
AFP (ng/mL)			0.072
≤20	1.000		
>20	1.713	0.952-3.084	



No. of patients at risk

Percutaneous ablation	64	51	35	25	19	17	12	8	5	3	2
Hepatectomy	85	80	71	59	45	35	31	26	21	17	12

Figure 1 Kaplan-Meier estimates of local recurrence. The incidence of local recurrence reached a plateau of 28% at 20 mo after percutaneous ablation, and a plateau of 3% at 22 mo after hepatectomy.

to tumor size (≤2 cm *vs* >2 cm), hepatectomy was found to be the more effective treatment for controlling local recurrence, but only in patients with HCC >2 cm ($P<0.0001$) (Figure 2). Survival after the treatment was significantly better in patients who had undergone hepatectomy than in those treated with percutaneous ablation ($P=0.0123$, Figure 3). Again, hepatectomy was the more effective treatment in terms of long-term survival, but only in patients with HCC >2 cm ($P=0.0001$, Figure 4).

Incidence of vascular invasion according to tumor size

Vascular invasion was more frequent in patients with tumors >2 cm (16/62, 26%) than in those with tumors ≤2 cm (1/23, 4%; $P=0.033$, Table 4).

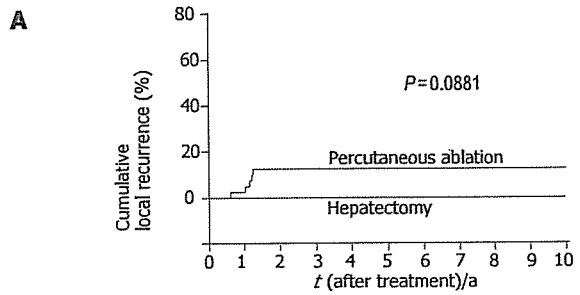
DISCUSSION

Selecting the correct treatment modality to suit individual patients with HCC remains a matter of debate[1,4,5]. This prompted us to conduct the current study, which has revealed that hepatectomy provided better outcomes for patients with HCC ≤4 cm than percutaneous ablation. This may partly be due to the fact that hepatic functional reserve was better in patients who had undergone hepatectomy. Despite this, we found that the incidence of local recurrence decreased and long-term survival increased independently after hepatectomy, indicating that

Table 4 Incidence of vascular invasion according to tumor size

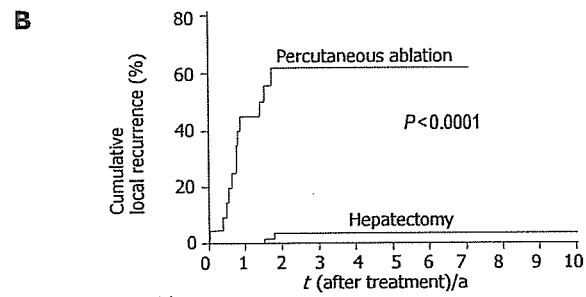
Tumor size (cm)	Vascular invasion (-)	Vascular invasion (+)	*P* value
≤2	22	1[1]	0.033
>2	46	16[2]	

[1]Portal venous invasion was noted. [2]Portal venous invasion in 10 patients, hepatic venous invasion in 3, and both portal and hepatic venous invasion in 3.



No. of patients at risk

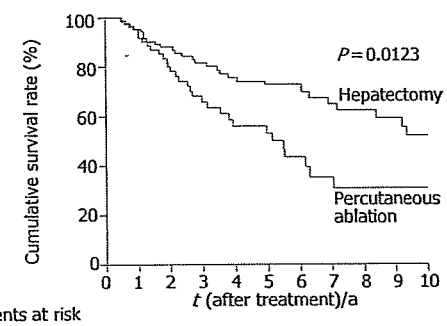
Percutaneous ablation	43	40	30	22	16	15	11	7	5	3	2
Hepatectomy	23	22	22	20	18	13	11	9	8	7	3



No. of patients at risk

Percutaneous ablation	21	11	5	3	3	2	1	1	0	0	0
Hepatectomy	62	58	49	39	27	22	20	17	13	10	9

Figure 2 Kaplan-Meier estimates of local recurrence by tumor size. A: Among tumors ≤2 cm, the incidence of local recurrence reached a plateau of 12% at 15 mo after percutaneous ablation, whereas no recurrences had occurred after hepatectomy; B: among tumors >2 cm, the incidence of local recurrence reached a plateau of 61% at 21 mo after percutaneous ablation, whereas it reached a plateau of 4% at 22 mo after hepatectomy.



No. of patients at risk

Hepatectomy	85	80	73	61	47	36	32	26	21	17	12
Percutaneous ablation	64	59	44	29	21	19	12	8	5	3	2

Figure 3 Kaplan-Meier estimates of survival. The median survival time was 122 mo with a 10-year survival rate of 53% in patients who had undergone hepatectomy. The median survival time was 66 mo with a 10-year survival rate of 31% in patients who had undergone percutaneous ablation.

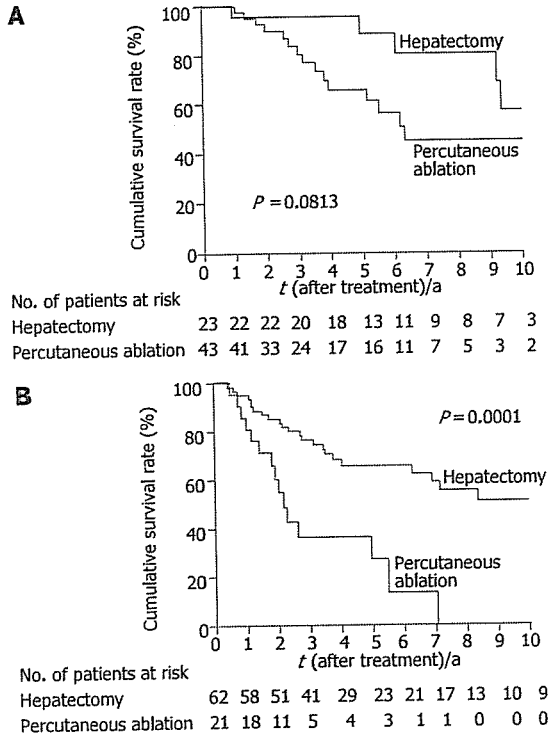


Figure 4 Kaplan-Meier estimates of survival by tumor size. A: Among patients with tumors ≤ 2 cm, survival was better following hepatectomy (median survival time of 122 mo; 10-year survival rate of 58%) than following percutaneous ablation (median survival time of 76 mo; 10-year survival rate of 45%); B: among patients with tumors >2 cm, survival was better following hepatectomy (median survival time of 126 mo; 10-year survival rate of 51%) than following percutaneous ablation (median survival time of 26 mo; 10-year survival rate of 0%).

this is an oncologically reliable treatment modality for HCC ≤ 4 cm.

Local recurrence was found to be more frequent after percutaneous ablation than after hepatectomy. Prospective, randomized controlled trials for PEI treatment of HCC ≤ 4 cm[23-25] demonstrated that cumulative 2-year local recurrence rates ranged from 33% to 45%. These rates are comparable with the 28% incidence of local recurrence after percutaneous ablation detected in the current study. Local recurrences after percutaneous ablation may be attributable to insufficient ablation of the primary tumor and/or the presence of portal or hepatic venous tumor thrombi in the adjacent liver[26,27]. Hepatectomy removes a rim of non-neoplastic liver parenchyma (a resection margin) together with the primary tumor, and thus eradicates both the primary tumor and venous tumor thrombi within the resection margin. This may explain better the outcomes following hepatectomy. In the current study, the beneficial effect of hepatectomy was prominent in a subgroup of patients with tumors >2 cm (Figures 2B and 4B), suggesting that these patients are good candidates for hepatectomy. Tumors >2 cm had a higher incidence of vascular invasion than tumors ≤ 2 cm (Table 4). Taken together, these findings suggest that the beneficial effect of hepatectomy is due to the clearance of venous tumor thrombi in the adjacent liver in addition to the complete removal of the primary tumor.

HCC mainly spreads *via* the portal and hepatic veins. Vascular invasion is an established adverse prognostic factor of HCC[19-21,28-30], and the incidence of vascular invasion increases as the tumor enlarges[30-33]. The current study confirmed this, with vascular invasion being more frequent in tumors >2 cm. Recent authors have suggested that tumors >2 cm are independently associated with local failure after RFA[34,35]. Considering that vascular invasion was less frequent in tumors ≤2 cm in our patients, percutaneous ablation appears to be an appropriate treatment modality for HCCs ≤2 cm. Despite this, outcomes for patients with HCCs ≤2 cm were better following hepatectomy than following percutaneous ablation. Due to the small sample size of this study, however, these differences were only marginally significant. We believe that hepatectomy may also be an appropriate treatment modality for HCCs ≤2 cm, provided that the patient is robust and that the hepatic functional reserve of the patient is at a level permitted for the resection.

Recent evidence suggests that high pre-treatment serum alpha-fetoprotein levels are associated with both the presence of portal venous invasion and intrahepatic recurrences after the treatment in HCC[26,36-41]. Serum alpha-fetoprotein levels were independently associated with local recurrences in the current study. The above findings suggest that high serum alpha-fetoprotein levels predict the presence of portal venous invasion, which may lead to treatment failure, in patients with HCC.

The current study has some limitations. First, it was a retrospective analysis of a small number of patients; second, the follow-up period in 64 patients was <60 mo; and third, percutaneous ablation therapy included three different treatment modalities. However, we believe that these limitations do not significantly influence the outcome of the study, as the marked differences between each group appear to overcome these biases.

In conclusion, hepatectomy provides both better local control and better long-term survival for patients with HCC ≤4 cm than percutaneous ablation, probably because hepatectomy eradicates both the primary tumor and venous tumor thrombi within the hepatectomy margin. Among the patients with HCC ≤4 cm, those with tumors >2 cm are good candidates for hepatectomy, provided that the level of hepatic functional reserve of the patient is suitable for resection.

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Original Paper

Common Clinicopathological Features of the Patients with Chronic Hepatitis B Virus Infection who Developed Hepatocellular Carcinoma after Seroconversion to Anti-HBs - A Consideration of the Pathogenesis of HBV-induced Hepatocellular Carcinoma and a Strategy to Inhibit It

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KEY WORDS:
Hepatocellular carcinoma; Hepatitis B virus; Anti-HBs; Liver cirrhosis; Reduced fibrosis

ABBREVIATIONS:
Anti-Hepatitis B surface Antigen (anti-HBs); Hepatitis B Virus (HBV); Hepatocellular Carcinoma (HCC)

ABSTRACT

Background/Aims: The incidence of hepatocellular carcinoma among patients who have seroconverted to anti-hepatitis B surface antigen (anti-HBs) remains controversial.

Methodology: We report four patients with chronic hepatitis B virus (HBV) infection who had cleared HBsAg and had developed anti-HBs at a later time, but who developed hepatocellular carcinoma (HCC) eventually.

Results: The common clinicopathological characteristics of the four patients were: An established diagnosis of precirrhosis or liver cirrhosis more than a decade previously, a long-standing normalization or stabilization at a low level of ALT values due to undetectable HBV DNA by the Amplicore Monitor assay, and a marked reduction of the fibrosis level in the non-tumorous liver obtained at HCC surgery or autopsy compared to the previous histology more than a decade previously. There was no fibrosis in the needle biopsy specimen from one patient.

Conclusions: Our findings suggest that HCC due to HBV can occur in the serologically-cured stage if progression to pre-cirrhosis or cirrhosis already has occurred, where the fibrosis level has improved considerably because of the long-term absence of active HBV viremia and inflammation. Active medical intervention to prevent liver cirrhosis for chronic hepatitis B may have an important role in the inhibition of HCC in patients with chronic hepatitis B.

INTRODUCTION

Appearance of anti-HBs following loss of HBsAg is considered to be a "serological cure" in general that occurs in the late stage of chronic HBV infection. The loss of HBsAg is a rare event and the incidence has been estimated to be 0.4% to 2% in Western countries (1,2) and 0.1% to 0.8% in Taiwan (3). The clinical prognosis of the patients who cleared serum HBsAg may be good (3-5). However, it still remains controversial in some recent reports (6,7). Because chronic liver inflammation is a cause of immune reaction against HBV, accelerated clearance of HBV antigens can reveal the early establishment of liver cirrhosis (3).

Clinicopathological features of hepatocellular carcinoma (HCC) due to HBV infection have been studied. Twenty percent to 50% of HBV HCC are not associated with liver cirrhosis, but most cases of HCV (hepatitis C virus) associated HCC accompany liver cirrhosis (8,9). HBV HCC is often found in patients with mild chronic hepatitis who have a good liver function and low ALT (alanine aminotransferase) levels (10,11). Integration of HBV genome into host chromosomal DNA or transactivating function of HBV genes may be implicated in direct cell transformation and involved in hepatocarcinogenesis occurring from liver with a low fibrosis level.

We previously reported two patients with chronic HBV infection in whom HCC had occurred almost at the same time as appearance of anti-HBs (12). They had a persistent normal level of ALT values for more than a decade with undetectable active HBV viremia. Notably, fibrosis level of the non-tumor part of the liver showed marked reduction when compared to that observed in the stage of active viral replication. We encountered another two patients who had HCC after the seroconversion to anti-HBs. Both patients also progressed to precirrhosis more than a decade ago and went through a non-HBV-viremic period until the development of HCC. Non-tumor part of the liver also showed marked reduction of fibrosis and no active inflammation.

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