2.『科学的根拠に基づく肝癌診療ガイドライン』作成と改訂の経緯*

長谷川　潔　　國土典宏**

〔要旨〕『科学的根拠に基づく肝癌診療ガイドライン』第3版は，初版・第2版と同様evidence-based medicine（EBM）の手法を用いて改訂された．まず，57個のClinical Question（CQ）を設定し，検索式を立て，2007年7月～2011年12月を対象に各CQに関連する論文を系統的に選択した．構造化抄録を作成，二次選択を経て，最終的に591篇が採択となった．これをもとに本文が執筆され，推奨グレードが決定された．改訂作業は客観性と再現性を確保しつつ，エビデンスを重視してすすめられた．

はじめに

『科学的根拠に基づく肝癌診療ガイドライン』の初版[1]は2005年2月に刊行されたが，いわゆるevidence-based medicine（EBM）の手法で策定された点が特徴で，この種のガイドラインの中ではもっとも早い時期に上梓されたものの一つである．初版は厚生労働省科学研究費（班長：幕内雅敏・現日本赤十字社医療センター院長）のサポートを受け，いわゆる班研究のかたちで作成されたが，第2版以降は日本肝臓学会の一事業として引き継がれ，2009年11月に第2版が刊行[2]（改訂委員会委員長：幕内雅敏）された．

本来，エビデンスが年代とともにかわっていくことを考慮し，EBMによるガイドラインは4～5年に一度の改訂が望ましいとされている．そこで，2011年9月に18名の委員，15名の専門委員，3名の特別委員からなる第3版改訂委員会（委員長：國土典宏・東京大学肝胆膵外科・人工臓器移植外科教授）〔表1〕を立ち上げた．最終的に17名となる実務協力者が加わり，総勢55名による約2年の作業を経て，2013年10月に第3版を刊行するにいたった[3]．改訂間隔は初版から第2版が4年9ヵ月，第2版から第3版が3年11ヵ月である．改訂の詳細は他稿の解説に委ねることとし，本稿では第3版の改訂の流れを初版・第2版と比較しつつ述べ，その中で生じた主たる問題点につき，合わせて説明したい．

I.『科学的根拠に基づく肝癌診療ガイドライン』作成の実際について

『科学的根拠に基づく肝癌診療ガイドライン』は初版以降，第3版にいたるまでEBMの手法を一貫して遵守している．まず，第3版改訂では第2版の51個のClinical Question（CQ）を見直すことから作業を始めた．このCQは肝細胞癌の診療

キーワード：検索式，構造化抄録，エビデンス，推奨グレード

* The revision of evidence-based clinical practice guidelines for hepatocellular carcinoma：the 3rd revision

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表1.『科学的根拠に基づく肝癌診療ガイドライン』第3版改訂委員会

・委員長
國土典宏（東京大学医学部肝胆膵外科・人工臓器移植外科教授）
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土谷　薫（武蔵野赤十字病院消化器科副部長）
中山壽之（日本大学医学部消化器外科専任講師）
福本　巧（神戸大学医学部肝胆膵外科准教授）
南　康範（近畿大学医学部消化器内科講師）
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における重要な問題点を取り上げたもので，基本的に疑問形で作成される．次にそれぞれのCQに対応するエビデンスを論文の中から抽出し，scientific statementとしてまとめ，CQに対する診断や治療面での対応に関する「推奨」を作成する．さらにエビデンスのレベルを判定し，それに基づ

表2. 各版における論文選択

	初　版	第2版	第3版
検索期間	1982～2002年	2002年10月～2007年6月 （ただし一部で1982年～）	2007年7月～2011年12月 （ただし一部で1982年～）
データベース	『PubMed』,『医学中央雑誌』	『PubMed』	『MEDLINE』,『PubMed』
検索総論文数	45,974篇	3,095篇	6,750篇
一次選択論文数	7,118篇	576篇	1,648篇
二次選択論文数	523篇	475篇	709篇
最終採択論文数	334篇	490篇 （初版から260篇，新規230篇）	591篇 （初版・第2版から241篇，新規350篇）

いて「推奨」や「根拠」の強さを決め，グレードとして示すといった過程をとる．「専門家の個人的な意見」はできるだけ排除して，エビデンスに基づいたコンセンサスを求めた．

初版では論文を一次選択し，そこから絞り込んでいく段階でresearch question（第2版以降のCQに該当）を設定した．第2版では，先にCQをある程度確定させてから論文検索にとりかかった点で初版と若干手順が異なるが，第3版は第2版のやり方に倣った．第2版のCQ 51個のうち13個が統廃合で除かれ，残り38個のうち17個が修正なしで採用，21個がなんらかの修正の後に採用，これらに新設CQ 19個が加わって，第3版では合計57個のCQの構成となった．

このCQをもとに検索式を作成し，論文データベースから各CQに関する論文を系統的に一次選択した．この検索式作成には相当の専門知識が必要で，本ガイドライン作成・改訂には図書館司書の方の協力をお願いしてきた．また，優れた検索式（必要かつ十分な論文を拾い上げられる）を設定するには適切なCQが必須で，論理的で具体的なCQを意識してつくっておくことが重要である．初版では1982～2002年の長い期間が対象となったため，45,974篇が初回検索対象となり，7,118篇もの論文が一次選択された．第2版では2002年10月～2007年6月が対象期間となり，3,095篇から576篇が，第3版では2007年7月～2011年12月を対象とし，6,750篇から1,648篇が一次選択された（表2）．第3版で一次選択論文が増えたのは，新規CQが19個と多く（第2版では7個），新規CQについては1982年にさかのぼって検索が行われたためであろう．このとき，対象期間の後（すなわち第3版では2012年1月以降）に発表された論文はいかに重要であっても，付記にとどめることにした．第2版改訂ではSHARP study[4]の結果をどう扱うかが問題となり，議論の末，推奨には取り入れなかったが，第3版でもこの原則を踏襲した．ただし，昨今のインターネット環境の進歩や電子ジャーナルの普及を鑑み，第3版では期間内にe-pub ahead printingとなった論文は検索対象に加えたが，第2版からの微修正である．

次に一次選択された論文につき，構造化抄録を作成し，論文のエビデンスの内容やレベルが一目で把握できるようにした．この過程で1,648篇から709篇に二次選択され，最終的には591篇が採択された．591篇のうち，初版・第2版からの繰り越しが241篇，残り350篇が新規採択となった．これらの作業の後，各CQに対する推奨文案が作成され，会議において吟味・修正の後，確定された．さらに推奨の根拠となるエビデンスの強さに応じて，推奨のグレードが決定された．草稿は2013年4月に完成し，同年5月，日本肝臓学会会員にウェブ上で公開され，パブリックコメントが公募された．また，第49回日本肝臓学会総会（会長：工藤正俊・近畿大学消化器内科教授）の特別企画として，2013年6月7日に公聴会が開催された．寄せられた意見は委員により検討され，一部は修正に反映された．日本肝臓学会の企画広報委員会・理事会の承認を得て，2回の校正の後，2013年10月に発刊された．今回の改訂作業中，合計8回の委員会が開かれ，ほぼ2年を費やした．今までと同

表3. 各版の構成

初　版	第2版	第3版
サーベイランス・診断アルゴリズム 治療アルゴリズム 第1章：予防 第2章：診断およびサーベイランス 第3章：手術 第4章：化学療法 第5章：肝動脈(化学)塞栓療法 第6章：穿刺局所療法	サーベイランス・診断アルゴリズム 治療アルゴリズム 第1章：予防 第2章：診断およびサーベイランス 第3章：手術 第4章：化学療法・放射線治療 第5章：肝動脈化学塞栓療法 第6章：経皮的局所療法	サーベイランス・診断アルゴリズム 治療アルゴリズム 第1章：予防 第2章：診断およびサーベイランス 第3章：手術 第4章：穿刺局所療法 第5章：肝動脈化学塞栓療法 第6章：化学療法 第7章：放射線治療 第8章：治療後のサーベイランス，再発予防，再発治療

様，検索式や構造化抄録はすべて公開し，改訂作業の客観性と再現性の担保としている．

Ⅱ．『科学的根拠に基づく肝癌診療ガイドライン』(第3版)の変更点

第3版もエビデンスを重視したEBMの手法による点では第2版までと同じ策定方針であるが，現状に合わせいくつか変更した点がある．まず，最近の化学療法と放射線治療のめざましい進歩をふまえ，第2版では両者あわせて一つの章であったのを，それぞれ独立した章として扱った．次に，第2版までは初発肝癌に対するCQしか設定されていなかったのに対し，再発への対応が臨床上重要な肝癌の特性を考慮し，第3版では「治療後のサーベイランス，再発予防，再発治療」という新章を設けた．章の順序を一部変更し，最終的に表3のように全部で8章という構成(第2版までは全6章)となった．さらに新たな試みとして医療経済の視点からの提言も時代の要請と考え，その専門家である福田敬先生(国立保健医療科学院)を委員にお迎えし，ガイドライン内容を吟味していただいた．前例がない中，手さぐりの検討となったが，ガイドライン策定における医療経済の視点の重要性は今後高まると思われる．

Ⅲ．第3版改訂後の課題

まず早急にやらねばならないのは，第3版の外部評価である．本来，ガイドラインの外部評価は発刊前に行い，その結果も合わせて同時公表すべきであるが，今回諸事情により間に合わなかった．現在，準備をすすめている．さらに英訳作業も予定している．本ガイドラインは批判もあるが，海外から注目されているので，第3版も第2版までと同様，英語論文の形で海外に第3版の内容を発信していきたい．

また，患者用に平易に解説したガイドラインの整備も残された課題である．現時点ではMedical Information Network Distribution Service (Minds)のホームページで本ガイドライン初版の一部の内容がわかりやすく紹介されており，一般の方も自由に閲覧可能となっている[5]．初版からみると，第3版はかなり内容がかわってきているので，こちらも対応していきたい．

おわりに

『科学的根拠に基づく肝癌診療ガイドライン』は初版以来，EBMの手法に則り，客観性の高いエビデンスを抽出し，根拠のない「思い込み」を排除するように構築されてきた．第3版もその基本方針に大きな変更なく，最新のエビデンスを盛り込むように留意した改訂となった．ただし，2013年10月の発刊時点で採択したエビデンスは2011年末までのものと，すでに2年弱の乖離が生じている．改訂に約2年を要することを考えると，発刊から2年後の2015年後半には次の改訂作業を開始する必要がある．

◆◆◆ 文献 ◆◆◆

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お知らせ

◆第30回日本静脈経腸栄養学会学術集会(会場ならびに会期変更のお知らせ)

会　　期：2015年2月12日(木)～13日(金)
会　　場：神戸国際会議場,神戸国際展示場,神戸ポートピアホテル
会　　長：井上善文(大阪大学臨床医工学融合研究教育センター栄養ディバイス未来医工学共同研究部門特任教授)
メインテーマ：臨床栄養の最前線――エビデンスとガイドラインに基づいた臨床経験の共有
学術事務局：〒565-0871　吹田市山田丘2-1産学連携本部A棟208
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Impact of Histologically Confirmed Lymph Node Metastases on Patient Survival After Surgical Resection for Hepatocellular Carcinoma

Report of a Japanese Nationwide Survey

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Objective: To clarify the clinical significance of resection of lymph node metastases in patients' hepatocellular carcinoma (HCC).

Background: Although the presence of lymph node metastasis form HCC has been considered as a systemic disease, prognosis after resection of them remains unknown.

Methods: From the database of a Japanese nationwide survey, 14,872 patients of HCC treated by surgical resection between 2000 and 2005 were enrolled. We modified the current Japanese staging system for HCC, by further dividing stage IVA into stage IVAnon-n1 and stage n1, according to the absence or presence of pathologically proven lymph node metastasis. Thus, the patients classified into 6 disease stages, that is, I (n = 1494), II (n = 8056), III (n = 4243), IVAnon-n1 (n = 701), n1 (n = 112), and IVB (n = 266), and their long-term outcomes were compared.

Results: The median follow-up period was 20.6 months. The 3-year overall survival rates of the patients with stage IVAnon-n1, stage n1, and stage IVB were 51.6%, 38.9% and 27.2%, respectively. A multivariate analysis showed that stage IVAnon-n1 would have a similar impact on the survival as stage n1 (hazard ratio: 0.88, 95% confidence interval: 0.59–1.33, $P = 0.555$), and that stage n1 still represented one class less advanced than stage IVB (hazard ratio: 0.52, 95% confidence interval: 0.34–0.80, $P = 0.003$).

Conclusions: The prognosis of patients with histologically node-positive HCC was similar to that of patients with locally advanced HCC (stage IVA), which supports the validity of the current Japanese staging system and also partially validates the system proposed by the UICC/AJCC.

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Keywords: hepatocellular carcinoma, lymph node metastasis, the UICC/AJCC staging system

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Although hepatocellular carcinoma (HCC) with lymph node metastasis has been considered as a systemic disease with a dismal prognosis, the actual impact of the node status on the patient outcome has never been thoroughly investigated. According to both the current Japanese (Table 1)[1] and UICC/AJCC staging systems (Table 2),[2,3] N1 (lymph node metastasis macroscopically suspected) with any T factor is classified as stage IVA, which represents the second worst stage of the disease. However, there have been few concrete data supporting the validity of these staging systems.

In patients with HCC, detection of enlarged lymph nodes around the liver is not rare, because accompanying liver inflammation (viral hepatitis, alcoholic hepatitis, steatohepatitis, etc) frequently induces reactive lymph node swelling.[4,5] It is often difficult to distinguish between benign reactive lymph node swelling and metastatic lymph node enlargement preoperatively, despite the recent remarkable advances in imaging technologies.[5,6] In addition, sampling of the hepatic hilar lymph nodes is avoided during surgery for HCC, because it has been known to increase the risk of postoperative refractory ascites.[7,8] Thus, the actual impact of resection of histologically proven lymph node metastases remains unknown.

Since 1965, the Liver Cancer Study Group of Japan has been conducting biannual nationwide surveys of patients with HCC; however, no data concerning HCC patients with histologically proven lymph node metastases have been accumulated. Therefore, we added several items related to the histological lymph node status to the questionnaire of the registry system in 2000. Because sufficient clinical data have been obtained over the 6 years since 2000, we conducted this retrospective study, based on prospectively gathered data, in the latest Japanese survey.

PATIENTS AND METHODS

With the cooperation of 795 institutions in Japan, patients with primary liver cancer are registered every 2 years and followed up prospectively in a nationwide survey conducted by the Liver Cancer Study Group of Japan. HCC is diagnosed on the basis of imaging studies, clinical data, and/or histopathological studies at each institution. Among the 57,444 patients with HCC who were newly registered with the survey between 2000 and 2005, a total of 14,872 patients who underwent surgical resection for HCC and for whom complete information concerning the disease stage, liver function, and prognosis was available were entered into this study. Then, the patients were

TABLE 1. The Japanese Staging System for HCC

Stages	T Factor	N Factor	M Factor
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVA	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

TABLE 2. The UICC/AJCC Staging System for HCC

Stages	T Factor	N Factor	M Factor
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

prospectively followed up at each institution. Although no definitive follow-up protocol was set, most liver surgeons observed the protocol shown in "Clinical Practice Guidelines for Hepatocellular Carcinoma,"[9] which recommends ultrasonography and serum tumor marker measurements every 3 or 4 months, and enhanced computed tomography or magnetic resonance imaging every 6 or 12 months. Although this study protocol was not submitted to the institutional review board of each institution participating in the nationwide survey, collection of the data and registering patients with HCC were conducted with the approval of each institution.

According to the fifth version of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, patients with histologically confirmed lymph node metastasis (labeled n1) in the absence of distant metastasis are classified as having stage IVA disease (Table 1)[1]; however, for this study, we further classified patients with stage IVA disease into stage IVAnon-n1 and stage n1 groups, to clarify the clinical significance of n1 (Table 3). Thus, on the basis of the disease stage, the study population (14,872 patients) was classified into 6 groups: stage I (n = 1,494), stage II (n = 8,056), stage III (n = 4,243), stage IVAnon-n1 (n = 701), stage n1 (n = 112), and stage IVB (n = 266). In this study, all patients classified as having stage n1 disease were treated by hepatic resection for HCC simultaneously.

Table 4 summarizes the baseline characteristics of the 6 groups. To clarify the differences among stages III, IVAnon-n1, n1, and IVB, pairwise *P* values are shown in Table 5. Table 6 shows the number and percentage of cases with n1 for each T factor, which indicates that even patients with T1 and T2 tumors, who would be classified as having stage I and stage II disease, respectively, in the absence of lymph node metastasis, could include several n1 cases.

The overall survival curves were plotted by the Kaplan-Meier method and compared by the log-rank test. In this study, recurrence-related data were not analyzed, because surgery performed in patients with stage n1 and stage IVB disease cannot be regarded as curative. The differences in the impact of each stage on the survival were estimated using a Cox proportional-hazards model including the following 10 covariates: age, gender, type of background hepatitis, platelet count ($<$ or $\geq 10 \times 10^4$ per μL), serum albumin level, serum total bilirubin level, indocyanine green retention rate at 15 minute ($<$ or $\geq$20%), serum alpha-fetoprotein level ($<$ or $\geq$20 ng/mL), serum des-γ-carboxy prothrombin level ($<$ or $\geq$40 AU/mL), and pathological differentiation grade of the tumor. The 10 covariates were chosen among the available factors in our database, because we regarded them as clinically important on the basis of previously published reports. The results of the multivariate analysis are expressed as hazard ratios calculated between consecutive stages with 95% confidence intervals. *P* values of less than 0.05 were considered to indicate statistical significance.

TABLE 3. The Classification Used in This Study

Stages	T Factor	N Factor	M Factor
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVAnon-nl	T4	N0	M0
Stage nl	Any T	n1	M0
Stage IVB	Any T	Any N	M1

n1; patologocally proven lymph node metastasis

RESULTS

The median follow-up period after treatment was 20.6 months, and the 25th and 75th percentiles were 8.7 and 38.1 months, respectively. The overall 3-/5-year survival rates of the patients with stage I, II, III, IVAnon-n1, n1, and IVB disease were 90.4%/77.8%, 80.8%/66.6%, 66.6%/49.5%, 51.6%/37.0%, 38.9%/29.5%, and 27.2%/22.0%, respectively (Fig. 1).

The multivariate analysis (Table 7) showed that the hazard ratio for survival of patients with stage IVAnon-n1 relative to patients with stage n1 disease was 0.88 (95% confidence interval: 0.59–1.33, $P = 0.555$), although that of patients with stage n1 disease relative to those with stage IVB disease was statistically significantly higher (0.52, 95% confidence interval: 0.34–0.80, $P = 0.003$). Except for the situations mentioned earlier, the hazard ratio for survival of patients with each disease stage relative to that of patients with one level higher disease stage was significantly low in all combinations, which indicated that the clinical impact of the stage factor on death increased in the order of the disease stage.

DISCUSSION

The results of this study indicate that the prognosis after resection of lymph node metastasis in patients with HCC, irrespective of the T factor in the TNM classification, would be equivalent to that of stage IVAnon-n1, and inferior to that of the prognosis associated with stages I to III. Our analysis also suggests that extrahepatic spread other than to the lymph nodes is associated with a significantly poorer prognosis than metastasis to the lymph nodes alone.

According to autopsy studies of HCC, the estimated incidence of lymph node metastasis in HCC patients, overall, is 30.3%,[10] whereas that in patients undergoing surgery is only 1% to 2%.[7,10,11] Although, until date, there have been few data on the clinical impact of lymph node metastasis in patients with HCC, on the basis of the results of small retrospective studies and clinical experience, it has been suspected that lymph node metastasis may be one of the worst prognostic factors in these patients. Uenishi et al[7] reported that of 504 patients, all 6 with lymph node metastasis died within 14 months of surgery. According to Sun et al[12] and Kobayashi et al,[13] the 3-year overall survival rates were 31% and 25.9%, respectively, in 49 and 21 HCC patients with lymph node metastasis. In this study, the 3-year survival rate of patients with lymph node metastasis of 38.9% was consistent with the 2 reports mentioned earlier.

TABLE 4. Baseline Characteristics

Variables	I n = 1494	II n = 8056	III n = 4243	IVAnon-n1 n = 701	n1 n = 112	IVB n = 266
Age, Median (interquartile range), yrs	66 (12)	67 (12)	67 (13)	65 (14)	66 (13.5)	62 (17)
Gender, No. (%)						
Male	1078 (72.2)	6143 (76.3)	3415 (80.5)	572 (81.6)	88 (78.6)	206 (77.4)
Female	416 (27.8)	1913 (23.7)	828 (19.5)	129 (19.5)	24 (21.4)	60 (22.6)
Hepatitis virus infection, No. (%)						
HBsAg(+)/HCV-Ab(−)	248 (16.6)	1320 (16.4)	776 (18.3)	165 (23.5)	19 (20.0)	72 (27.1)
HBsAg(−)/HCV-Ab(+)	969 (64.9)	4459 (55.4)	2314 (54.5)	346 (49.4)	56 (50.0)	96 (36.1)
HBsAg(+)/HCV-Ab(+)	29 (1.9)	143 (1.8)	71(1.7)	18 (2.6)	2(1.8)	6 (2.3)
HBsAg(−)/HCV-Ab(−)	189 (12.7)	1808 (22.4)	903 (21.3)	146 (20.8)	33 (32.4)	76 (28.6)
Unknown	59 (3.9)	326 (4.0)	179 (4.2)	26 (3.7)	2(1.8)	16 (6.0)
Serum albumin, g/dL*	3.9 (0.6)	3.9 (0.6)	3.9 (0.6)	3.9 (0.7)	3.8 (0.6)	3.8 (0.7)
Serum total bilirubin, mg/dL*	0.8 (0.4)	0.7 (0.4)	0.8 (0.4)	0.7 (0.4)	0.8 (0.4)	0.7(0.3)
Platelet count, No. (%)						
$\geq 10 \times 10$ per μL	961 (64.3)	5971 (74.1)	3208 (75.6)	564 (80.5)	91 (81.2)	226 (85.0)
$< 10 \times 10^4$ per μL	468 (31.3)	1814 (22.5)	890 (21.0)	118 (16.8)	16 (14.3)	29 (10.9)
Unknown,	65 (4.4)	271 (3.4)	145 (3.4)	19 (2.7)	5 (4.5)	11 (4.1)
ICG R15, No. (%)						
≥20%	467 (31.2)	2111 (26.2)	1128 (26.6)	157 (22.4)	26 (23.2)	56 (21.1)
<20% L	896 (60.0)	5190 (64.4)	2716 (64.0)	479 (68.3)	76 (67.9)	174 (65.4)
Unknown	131 (8.8)	755 (9.4)	399 (9.4)	65 (9.3)	10 (8.9)	36 (13.5)
Alpha-fetoprotein, No. (%)						
≥20 ng/mL	623 (41.7)	3645 (45.2)	2414 (56.9)	468 (66.7)	63 (56.2)	186 (69.9)
<20 ng/mL	795 (53.2)	4034 (50.1)	1619 (38.2)	203 (29.0)	42 (37.5)	66 (24.8)
Unknown	76 (5.1)	377 (4.7)	210 (4.9)	30 (4.3)	7(6.3)	14 (5.3)
Des-y-carboxy prothrombin, No. (%)						
≥40 AU/mL	401 (26.8)	3645 (45.2)	2414 (56.9)	468 (66.8)	63 (56.3)	186 (69.9)
<40 AU/mL	795 (53.2)	4034 (50.1)	1619 (38.2)	203 (28.9)	42 (37.5)	66 (24.8)
Unknown	298 (20.0)	357 (4.7)	210 (4.9)	30 (4.3)	7 (6.2)	14 (5.3)
Tumor differentiation grade, No. (%)						
Well	483 (32.3)	1668 (20.7)	612 (14.4)	53 (7.6)	2(1.8)	18 (6.8)
Moderate	731 (48.9)	4748 (58.9)	2537 (59.8)	416 (59.3)	54 (48.2)	134 (50.4)
Poor	101 (6.8)	668 (8.3)	529 (12.5)	139 (19.8)	34 (30.4)	62 (23.3)
Unknown	179 (12.0)	972(12.1)	565 (13.3)	93 (13.3)	22 (19.6)	52 (19.5)

HBsAg indicates hepatitis B virus antigen; HCV-Ab, hepatitis C virus antibody;
ICG R15, indocyanine green retention rate at 15 minutes.

TABLE 5. Pairwise P Value Among Stages III, IVA non-n1, n1, and IVB

Variable	III vs IVAnon-n1	IVAnon-n1 vs n1	n1 vs IVB
Age*	0.009	0.457	0.002
Gender†	0.490	0.447	0.810
Virus infection†	0.002	0.154	0.073
Serum albumin*	0.169	0.062	0.916
Serum bilirubin*	0.612	0.586	0.318
Platelet count†	0.009	0.547	0.346
ICG R15†	0.016	0.861	0.824
Alpha-fetoprotein†	0.000	0.046	0.010
Des-gamma-carboxy prothrombin†	0.000	0.002	0.000
Tumor differentiation grade‡	0.006	0.016	0.323

*t test.
†χ^2 test.
‡Mantel trend test.

TABLE 6. Association Between T and n Factors

	T1 n = 1426	T2 n = 7663	T3 n = 4110	T4 n = 709
n0, No. (%)	971 (68.1)	5275 (68.8)	2759 (67.1)	468 (66.0)
Unknown, No. (%)	450 (31.6)	2353 (30.7)	1295 (31.5)	219 (30.9)
n1, No. (%)	5 (0.3)	35 (0.5)	56 (1.4)	22 (3.1)

I	1494	1085	762	520	285	137	12
II	8056	5656	3706	2306	1236	556	49
III	4243	2720	1683	987	494	209	26
IV-A(non-n1)	701	377	206	119	53	25	25
n1	112	46	28	15	5	2	2
IV-B	266	102	47	24	14	6	6

FIGURE 1. Overall survival curves after surgery for hepatocellular carcinoma in patients with stage I, II, III, IVAnon-n1, n1, and IVB disease are demonstrated.

TABLE 7. Hazard Ratios

	Hazard Ratio	95% Confidence Interval	*P*
Stage I (vs II)	0.61	0.49–0.76	<0.001
Stage II (vs III)	0.56	0.51–0.62	<0.001
Stage III (vs IVAnon-n1)	0.69	0.58–0.81	<0.001
Stage IVAnon-n1 (vs n1)	0.88	0.59–1.33	0.555
Stage n1 (vs IVB)	0.52	0.34–0.80	0.003

Our data indicate that extrahepatic spread other than to lymph nodes is associated with an even poorer prognosis than spread to the lymph nodes alone. In both the Japanese and UICC/AJCC staging systems,[1–3] cases of M1 (meaning extrahepatic spread) are classified into the worst disease stage (IVB), irrespective of the T and N factors. The results of this study clearly supported the validity of separating lymph node metastasis from extrahepatic spread in the 2 currently used staging systems.

On the contrary, there was no significant difference in the prognosis between stage IVAnon-n1 and stage n1 in this study, which suggested that the outcome of patients with T4 (denoting multiple tumors, maximum tumor diameter >2 cm, and presence of vascular invasion) classified according to the Japanese system would be equivalent to those of patients with lymph node metastasis, irrespective of the T factor. On this point, the results of this study did not support the UICC/AJCC system, in which T4 cases without N1 or M1 are classified as stage IIIC, a disease stage lower than stage IVA.

One of the most important points of this study is that lymph node metastasis was microscopically confirmed in the resected specimens in all cases. This overcame the major problem of some previous studies in which pathological information was lacking,[11,13] as it is quite difficult to macroscopically distinguish true metastasis from reactive lymph node swelling. Because our study had the largest number of cases (>100) to date, with pathological confirmation, we expect that our results would be useful for estimating the true impact of lymph node metastasis on the prognosis.

On the contrary, the above advantage could be weighed down by several biases, which should be taken into consideration while interpreting our data. For example, there could have been a bias toward cases with good liver function in the study population, because liver resection could be performed in the patients. The impact of lymph node metastasis may be different in patients with moderate or poor liver function, which needs further study.

Caution should also be exercised while interpreting our data from the aspect that there were no clear criteria for dissection of lymph nodes during the operation in our series. Because of the difficulty in macroscopically distinguishing between benign and malignant lymph nodes, several cases with microscopic lymph node metastasis might have been misclassified into stages I, II, III, and IVAnon-n1 in this study. Some cases from the study populations, in which lymph node metastasis was found by intraoperative pathological examination on frozen sections and hepatic resection was abandoned, might have been dropped from the analysis. These limitations make it difficult to arrive at a definitive conclusion. To strictly evaluate the significance of the presence of lymph node metastasis in HCC patients, routine sampling of lymph nodes would, theoretically, be a suitable strategy. However, this would be unacceptable from the ethical standpoint, because routine sampling would place the patients at risk for refractory ascites and liver failure after surgery. Positron emission tomography using ^{18}F-fluorodeoxy glucose, which was developed recently, is also not very sensitive for differentiating between metastatic and inflammatory swelling of the lymph nodes, although it has been found to be useful to detect systemic metastases from cancer.

The clinical significance of resection of lymph node metastases in patients with HCC remains under debate.[12,14,15] It would also be difficult to arrive at a solution to this problem on the basis of the current data, because there was no uniform strategy to cope with swollen lymph nodes in this study. Another prospective investigation is therefore warranted.

In this study, the follow-up period and number of study were probably insufficient, because the interval between the change of the registry form and the collection of data was 6 years. However, at least, we are able to show the outcomes of surgical resection of HCC in more than 100 cases of pathologically confirmed lymph node metastases. Although further investigation would be useful, however, our results may also hold importance in the current situation.

CONCLUSIONS

In conclusion, the results of this study support the current staging system used in Japan, in which patients with lymph node metastasis, irrespective of the T stage, are classified as having stage IVA disease, a stage lower than M1 (extrahepatic spread). Our results provide only partial validation of the UICC/AJCC staging system.

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Prognostic Impact of Spontaneous Tumor Rupture in Patients With Hepatocellular Carcinoma

An Analysis of 1160 Cases From a Nationwide Survey

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Objective: The aim of the present study was to investigate the background characterisics of ruptured hepatocellular carcinoma (HCC) and to clarify the true impact of tumor rupture on patient prognosis in a large patient cohort.

Background: Spontaneous tumor rupture of HCC has been associated with a very poor patient prognosis and the current TNM staging systems classify ruptured HCC as T4 based on insufficient evidence.

Methods: In total, 1106 patients with ruptured HCC were extracted from the database of a nationwide survey conducted in Japan from 2000 to 2005. The clinicopathological parameters associated with HCC rupture were investigated using univariate and multivariate logistic regression models. The survival curves for ruptured and nonruptured HCC were generated and compared to evaluate the impact of the event (rupture) itself on patient prognosis and the TNM staging systems.

Results: The multivariate analyses showed that tumor rupture was associated with both a poor liver functional reserve and an advanced tumor status. Analyses of the survival curves stratified according to the baseline TNM staging showed that tumor rupture had an additional impact on the baseline survival curves without rupture, and the impact corresponded to the addition of 0.5 to 2 stages to the baseline tumor staging.

Conclusions: The present study suggested that tumor rupture itself had a negative impact on patient survival. However, its impact was not strong enough to cancel the effects of the other tumor-related parameters. Therefore, it may be appropriate to give additional stages to the baseline tumor staging in cases of ruptured HCC.

Keywords: Hepatocellular carcinoma, nationwide survey, patient outcome, spontaneous tumor rupture, TNM staging system

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The spontaneous rupture of hepatocellular carcinoma (HCC) is a life-threatening presentation of this disease. The incidence of spontaneous tumor rupture has been reported to be 10% of deaths from HCC in Japan,[1] but this figure decreased to 6.4% in a recent report,[2] probably in response to advances in imaging modalities and the development of a surveillance system for patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV). However, some primary cases are still found as a result of such catastrophic events. Previous studies have reported that the prognosis of ruptured HCC is dismal, and that spontaneous tumor rupture occurs at an adavanced tumor stage in patients with a poor liver functional reserve, although the mechanism of spontaneous tumor rupture remains unclear.[3] The 1-month mortality rate ranged from 34% to 71%, with a median survival period of 7 to 21 weeks in previous series.[1,4–17] As a result, the current TNM staging systems for HCC, including the fifth edition of the Liver Cancer Study Group of Japan (LCSGJ) classification[18] and the seventh edition of the AJCC/UICC (American Joint Committee on Cancer/Union for International Cancer Control) classification,[19] assign all ruptured HCC tumors to T4 (Tables 1 and 2). However, the true impact of tumor rupture itself on patient survival has not been clarified because of the small number of patients, especially patients in relatively early stages, enrolled in previous studies, and the significance of tumor rupture in the tumor staging system has been provisional.

In the present study, we used the LCSGJ database containing information from nationwide surveys in Japan and collected data for over 1000 patients with ruptured HCC. The aim of the present study was to identify the clinicopathological parameters associated with the spontaneous tumor rupture of HCC and to assess the true impact of tumor rupture on patient survival as well as on the current TNM staging systems.

METHODS

Japanese Nationwide Survey of HCC Patients

The LCSGJ has conducted biannual nationwide surveys of patients with HCC since 1970 and has updated the survival data of the enrolled patients. Eight hundred institutions in Japan have participated in the surveys and have answered more than 180 questionnaires regarding patient characteristics, diagnostic findings, treatment selection, treatment findings, and patient outcome. Since the 16th survey (2000–2001), questions regarding spontaneous tumor rupture have been added to conduct this cohort study. In the first step, the physicians at the participating institutions completed the questionnaire and checked the accuracy of the data. In the second step, the nationwide survey committee checked the data, and whenever there were unusual data, the participating institution was requested to confirm the data to ensure the accuracy of the data.

Patients

We used data collected from the 16th, 17th, and 18th LCSGJ nationwide surveys (2000–2005). During the study period, 57,444 new patients with HCC were registered and were prospectively followed up. Among the 57,444 patients, information concerning the status of spontaneous tumor rupture and the patient outcome was available for 49,708 patients; these patients comprised the study cohort of the present analyses. Spontaneous tumor rupture was observed in 1160 patients (2.3%, ruptured HCC group) and was not observed in 48,548 patients (97.7%, nonruptured HCC group). Tumor rupture was suspected in 315 patients, but these patients were excluded from the analyses. The patients were followed up until the end of 2005, and the patients who were alive at the end of the study period were censored.

Parameters

The parameters extracted from the database were as follows: (a) 2 patient demographic parameters (age, sex), (b) 13 background clinical data parameters [chronic hepatitis, liver cirrhosis, hepatitis B antigen (HBsAg), anti-hepatitis C antibody (HCVAb), alcohol abuse, encephalopathy, ascites, prothrombin time, platelet count, indocyanine green retention ratio at 15 minutes (ICGR15), liver damage according to the LCSGJ classification,[20] Child-Pugh grade,[21] and gastroesophageal varices], (c) 9 tumor-related parameters [presence of spontaneous tumor rupture, number of tumors, maximum tumor diameter, tumor distribution, the Eggel gross classification,[22] portal venous invasion, hepatic venous invasion, bile duct invasion, serum level of alpha-fetoprotein (AFP), and plasma level of des-gamma-carboxy prothrombin (DCP)], (d) main treatment method, and (e) patient outcome. The tumor-related variables were extracted from the pathological findings in the surgically resected cases, and from the radiological findings in the other cases. A tumor stage was assigned to each patient, excluding the parameter associated with spontaneous tumor rupture, according to both the LCSGJ classification (fifth edition) and the UICC classification (seventh edition).

TABLE 1. LCSGJ Classification (5th Edition)

T – Primary tumor					
Criteria	1. Solitary tumor				
	2. Diameter < 2 cm				
	3. No vascular or bile duct invasion				
T1	All 3 criteria are fullfilled				
T2	Two of the 3 criteria are fulfilled.				
T3	One of the 3 criteria are fulfilled.				
T4	None of the 3 criteria are fulfilled *or* **ruptured HCC**				
N – Lymph node metastasis					
N0	No lymph node metastasis				
N1	Lymph node metastasis				
M – Distant metastasis					
M0	No distant metastasis				
M1	Distant metastasis				
	Japanese TNM staging				
		T1	T2	T3	T4
	N0 and M0	I	II	III	IVA
	N1 and M0	IVA	IVA	IVA	IVA
	Any N and M1	IVB	IVB	IVB	IVB

Statistical Analysis

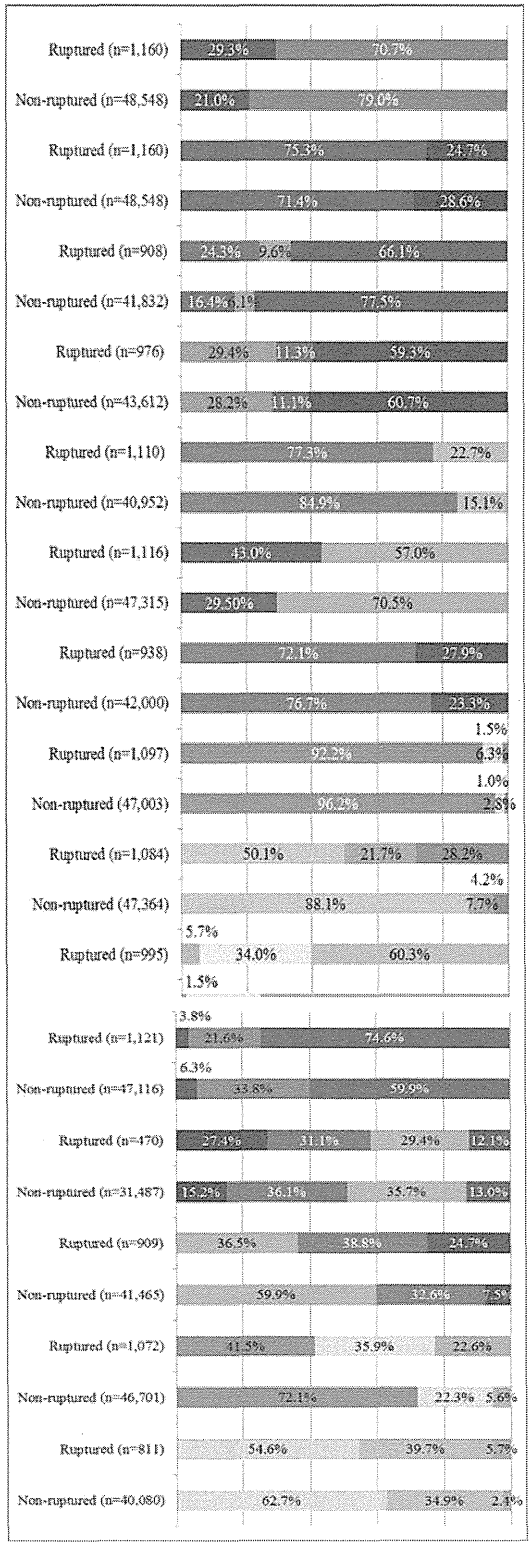
Each parameter was compared between the ruptured HCC group and the nonruptured HCC group using chi-square tests. Thereafter, a multivariate logistic regression analysis was performed to identify the parameters that were independently associated with spontaneous HCC tumor rupture. In the multivariate logistic regression analysis, parameters for which the values were missing for over 20% of the study population were excluded. Additional multivariate logistic regression analyses were conducted for subgroups stratified according to HBsAg and HCVAb status.

The patient survival curves were generated using the Kaplan-Meier method for each tumor stage, excluding the spontaneous tumor rupture parameter, according to the LCSGJ classification (fifth edition) and the UICC classification (seventh edition) separately for both the ruptured HCC group and the nonruptured HCC group. The differences among the curves were examined using the Cox proportional hazards analysis. Kaplan-Meier curves were also generated according to the main treatment methods and were compared. The analyses were conducted using SAS, Version 9.2. Differences were considered significant when the P value was less than 0.05.

TABLE 2. UICC Classification (7th Edition)

T – Primary tumor						
TX	Primary tumor cannot be assessed.					
T0	No evidence of primary tumor.					
T1	Solitary tumor without vascular invasion.					
T2	Solitary tumor with vascular invasion *or* multiple tumors, none more than 5 cm in greatest dimension.					
T3	Multiple tumors any more than 5 cm *or* tumor involving a major branch of the portal or hepatic vein(s).					
	T3a: Multiple tumors any more than 5 cm.					
	T3b: Tumors involving a major branch of the portal or hepatic vein(s).					
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder *or* **with perforation of visceral peritoneum**.					
N – Regional lymph nodes						
NX	Regional lymph nodes cannot be assessed.					
N0	No regional lymph node metastasis.					
N1	Regional lymph node metastasis.					
M – Distant metastasis						
M0	No distant metastasis.					
M1	Distant metastasis.					
UICC TNM staging						
		T1	T2	T3a	T3b	T4
	N0 and M0	I	II	IIIA	IIIB	IIIC
	N1 and M0	IVA	IVA	IVA	IVA	IVA
	Any N and M1	IVB	IVB	IVB	IVB	IVB

TABLE 3. Patient Demographics and Basic Clinical Data

Parameter	Ruptured (n = 1,160) Non-ruptured (n = 48,548)	P value (Chi-square)
Age (<60/≥60)		<0.0001
Sex (male/female)		0.0037
Chronic hepatitis (no/suspected/yes)		<0.0001
Liver cirrhosis (no/suspected/yes)		0.3632
HBsAg (negative/ positive)		<0.0001
HCVAb (negative/ positive)		<0.0001
Alcohol (no/yes)		0.0010
Encephalopathy (none/minimal/ moderate)		<0.0001
Ascites (no/controllable/ intractable)		<0.0001
Prothrombin time (%: <40/40-70/≥70)		<0.0001
Platelet count (x10^3: <50/50-100/≥100)		<0.0001
ICG R15 (<10%/ 10-20%/20-40%/ 40%-)		<0.0001
Liver damage (A/B/C)		<0.0001
Child-Pugh (A/B/C)		<0.0001
Gastroesophageal varices (none/ present/ruptured)		<0.0001

RESULTS

Parameters Associated With Spontaneous Tumor Rupture (Univariate Analyses)

The comparisons between the ruptured HCC group and the nonruptured HCC group showed that the following patient demographic and basic clinical data parameters were associated with spontaneous tumor rupture according to a univariate analysis: age, chronic hepatitis, HBsAg, HCVAb, alcohol, encephalopathy, ascites, prothrombin time, platelet count, ICGR15 value, liver damage, Child-Pugh grade, and gastroesophageal varices (Table 3). In other words, spontaneous tumor rupture was more frequently observed in patients with a younger age, positive HBsAg, greater alcohol intake, and a poorer liver functional reserve. On the other hand, spontaneous tumor rupture was also more frequently observed in patients with negative HCVAb, the absence of chronic hepatitis, a higher platelet count, and a better ICGR15 value.

The same analysis showed that the following tumor-related parameters were significantly associated with spontaneous tumor rupture according to a univariate analysis: the number of tumors, maximum tumor diameter, tumor distribution, the Eggel gross classification, portal invasion, venous invasion, bile duct invasion, serum AFP value, and plasma DCP value (Table 4). Namely, spontaneous tumor rupture occurred more frequently among patients with a more advanced tumor stage.

Parameters Associated With Spontaneous Tumor Rupture (Multivariate Analyses)

A multivariate analysis using logistic regression identified the following parameters as being independently associated with spontaneous tumor rupture: maximum tumor diameter [odds ratio (OR): 16.34 (>5 cm vs. ≤2 cm); 4.66 (2–5 cm vs. ≤2 cm); 3.50 (>5 cm vs. 2–5 cm)], Child-Pugh grade (OR: 2.57), plasma DCP value (OR: 1.66), platelet count (OR: 1.60), age (OR: 0.71), and the Eggel gross classification (OR: 1.42) (Table 5). The risk of spontaneous tumor rupture increased linearly with the increase in tumor size, and there were no clearcut thresholds. The model selected contained 25,404 cases.

Additional multiple logistic regression analyses were conducted for subgroups stratified according to HBsAg and HCVAb status: ie, an HBsAg(+) and HCVAB(−) group ($n = 6220$), an HBsAg(−) and HCVAb(+) group ($n = 32,097$), and an HBsAg(−) and HCVAb(−) group ($n = 8028$). As the number of patients who were positive for both HBsAg and HCVAb was relatively small compared with the other groups ($n = 894$), these patients were excluded from the subanalyses. The tumor size and Child-Pugh grade were independent significant parameters in all 3 subgroups. In the HBsAg(+) and HCVAb(−) group, the plasma DCP value was also associated with spontaneous tumor rupture; in the HBsAg(−) and HCVAb(+) group, tumor-related parameters (plasma DCP value, number of tumors, and

TABLE 4. Tumor-Related Data

Parameter	Ruptured (n = 1,160) Non-ruptured (n = 48,548)	P value (Chi-square)
Number of tumors (1/2/3 or more)	Ruptured (n=1,069): 42.8% 11.5% 45.7% Non-ruptured (n=47,070): 58.1% 17.9% 24.0%	<0.0001
Maximum tumor Diameter (cm: <2/2-5/≥5)	Ruptured (n=1,007): 26.3% 72.0% 1.7% Non-ruptured (n=46,121): 21.9% 54.5% 23.6%	<0.0001
Tumor distribution(unilobar/bilobar)	Ruptured (n=878): 44.5% 55.5% Non-ruptured (n=32,963): 66.0% 34.0%	<0.0001
Eggel's classification (nodular/massive/ diffuse)	Ruptured (n=1,060): 63.4% 25.7% 10.9% Non-ruptured (n=45,641): 88.9% 7.4% 3.7%	<0.0001
Portal invasion (negative/positive)	Ruptured (n=917): 61.6% 38.4% Non-ruptured (n=44,779): 88.0% 12.0%	<0.0001
Venous invasion (negative/positive)	Ruptured (n=802): 82.0% 18.0% Non-ruptured (n=43,390): 96.1% 3.9%	<0.0001
Bile duct invasion (negative/positive)	Ruptured (n=777): 92.3% 7.7% Non-ruptured (n=42,889): 97.8% 2.2%	<0.0001
AFP* (ng/mL: <15/15-200/200-400/≥400)	Ruptured (n=1,014): 22.0% 22.7% 5.0% 50.3% Non-ruptured (n=45,710): 36.6% 37.2% 5.9% 20.3%	<0.0001
DCP† (mAU/mL: <40/40-100/≥100)	Ruptured (n=849): 9.5% 7.0% 83.5% Non-ruptured (n=40,952): 41.7% 14.4% 43.9%	<0.0001

*Alpha-fetoprotein.
†Des-gamma-carboxy prothrombin.

TABLE 5. Predictive Variables for Spontaneous Tumor Rupture by Multivariate Analysis Using Logistic Regression Model ($n = 25,404$)

Parameter		Odds Ratio	95% CI	P
Maximum tumor diameter	>5 cm vs. ≤2 cm	16.34	7.05–37.87	<0.001
Maximum tumor diameter	2–5 cm vs. ≤2 cm	4.66	2.03–10.7	<0.001
Child-Pugh classification	A/B/C	2.57	2.16–3.05	<0.001
DCP*	mAU/mL	1.66	1.39–1.99	<0.001
Platelet count	$\times 10^4/\mu L$	1.60	1.27–2.03	<0.001
Age	≥60 vs. <60	0.71	0.54–0.93	0.012
Eggel classification	Massive vs. nodular	1.42	1.05–1.92	0.023

*Des-gamma-carboxy prothrombin.
Maximum tumor diameter >5 cm versus 2–5 cm: odds ratio = 3.50 (95% CI: 2.66–4.61), $P < 0.001$.

portal invasion) were identified as additional significant parameters; in the HBsAg(–) and HCVAB(–) group, only patient age (other than the tumor size and Child-Pugh grade) was marginally associated with tumor rupture (Table 6).

Impact of Spontaneous Tumor Rupture on Patient Survival and TNM Staging

The overall survival of the ruptured HCC group was significantly poorer, compared with that of the nonruptured HCC group [hazard ratio (HR): 2.10; 95% confidence interval (CI): 2.03–2.18; $P < 0.001$, Fig. 1]. The 6-month, 1-year, 3-year, and 5-year overall survival rates were 54.4%, 41.4%, 21.1%, and 13.3%, respectively, in the ruptured HCC group, and 90.2%, 84.1%, 63.0%, and 45.8%, respectively, in the nonruptured HCC group. The median survival time in the ruptured HCC group was 228 days (95% CI: 196–273 days).

As spontaneous tumor rupture occurred more frequently in patients with advanced stages of HCC in the abovementioned analyses, the survival curves were depicted according to the LCSGJ classification and the AJCC/UICC classification, excluding tumor rupture from the staging. The divided curves according to the LCSGJ classification and a verification of the differences among the curves are shown in Figure 2. The depicted survival curves of the ruptured stage II, ruptured stage III, ruptured stage IV-A, and ruptured stage IV-B patients were significantly separated. Only 7 patients had ruptured stage I disease, making this group unsuitable for inclusion in the statistical analyses. The survival curve for ruptured stage II HCC (ie, when stage II HCC ruptures) was situated in between the curves for nonruptured stage III HCC and nonruptured stage IV-A HCC, and was significantly different from these 2 curves (HR: 1.60 and $P < 0.001$ vs. nonruptured stage III; HR: 0.56 and $P < 0.001$ vs. nonruptured stage IV-A). The survival curve of ruptured stage III HCC was not different from that of nonruptured stage IV-A HCC (HR: 0.93, $P = 0.493$). The survival curve of ruptured stage IV-A HCC was situated between the curves for nonruptured stage IV-A HCC and nonruptured stage IV-B HCC and was significantly different from the 2 curves (HR: 1.59 and $P < 0.001$ vs. nonruptured stage IV-A; HR: 0.72 and $P = 0.016$ vs. nonruptured stage IV-B). The survival of patients with ruptured stage IV-B HCC was poorer than that of patients with nonruptured stage IV-B HCC, with a difference that was borderline significant (HR: 1.21, $P = 0.081$).

Similar analyses were conducted according to the AJCC/UICC classification (Fig. 3). However, the survival curves for ruptured stage II HCC and for ruptured stage III-A HCC were similar ($P = 0.826$), whereas the survival curves for ruptured stages III-B and IV-A were similar ($P = 0.192$). The survival curve for ruptured stage I HCC was situated between the curves for nonruptured stage II HCC and those for nonruptured stage III-A HCC, and was different from the 2 curves (HR: 1.61 and $P < 0.001$ vs. nonruptured stage II; HR: 0.81 and $P = 0.05$ vs. nonruptured stage III-A). The survival curves for ruptured stage II and stage III-A HCC were situated between the curves for nonruptured stage III-A HCC and those for nonruptured stage III-B HCC, and were not different from that for nonruptured stage III-B. The survival curves for ruptured stage III-B and IV-A HCC were poorer than that for nonruptured stage IV-B HCC, and the survival curve for ruptured stage IV-B HCC was much poorer than those for ruptured stage III-B and stage IV-A HCC.

Patient Survival Stratified According to Treatment Modalities

The survival of patients with ruptured HCC was estimated after stratification according to the main treatment modalities. The prognosis of patients who underwent a liver resection ($n = 298$) or local ablative therapy ($n = 32$) was better than that of the patients who received transcatheter arterial chemoembolization (TACE; $n = 489$), chemotherapy ($n = 65$), or best supportive care ($n = 275$) ($P < 0.001$), although the number of patients receiving local ablative therapy was relatively small (Fig. 4). The 1-, 3-, and 5-year overall survival rates after hepatic resection were 76.0%, 48.6%, and 33.9%, respectively, and the 1-, 3-, and 5-year overall survival rates after TACE were 39.7%, 14.1%, and 6.0%, respectively.

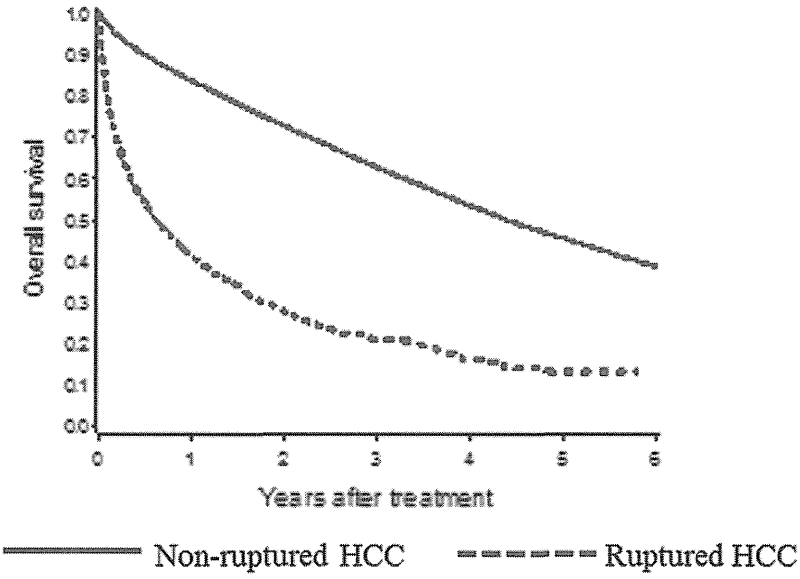
DISCUSSION

Previous studies have documented the clinical course as well as the treatment results of spontaneously ruptured HCC.[1–17] However, the largest series to date consisted of 172 cases,[1] mainly because spontaneous tumor rupture is a relatively rare event. As a result, it has been difficult to assess the true impact of tumor rupture on patient survival, and ruptured HCC has been assigned to T4 in the present TNM staging systems based on insufficient evidence. Therefore, to settle these problems, the LCSGJ started to gather information regarding the presence of spontaneous tumor rupture, beginning in 2000, and patients with spontaneous tumor rupture have been prospectively followed up. In the present study, we have collected data from 1106 HCC cases of spontaneous tumor rupture followed up for a maximum of 6 years. The maximum follow-up period of 6 years may be relatively short; however, because the outcome of ruptured HCC was generally poor, almost all the events occurred within 6 years (only 10 patients were at risk at 6 years). We therefore think that the clinical outcome of ruptured HCC is adequately represented by the data we obtained. It is true that the present study population was limited to Japanese patients and the dominant etiologies of the liver disease were HCV and HBV; nevertheless, we believe that our results are of significant value, and that they can be applied to HCC patients in epidemic areas of HBV and/or HCV infection and serve a fundamental reference data to study the behavior of HCC.

TABLE 6. Parameters Associated With Spontaneous Tumor Rupture Stratified by HBV and HCV Infection Status

		HBsAg (+) and HCVAb (–) (n = 6220)			HBsAg (–) and HCVAb (+) (n = 32,097)			HBsAg (–) and HCVAb (–) (n = 8028)		
Parameter	**Reference**	**Odds Ratio**	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***	**Odds Ratio**	**95% CI**	***P***
Age (≥60)	Age (<60)	0.72	0.44–1.17	0.19	0.67	0.36–1.25	0.21	0.54	0.28–1.04	0.064
Sex (female)	Sex (male)	0.82	0.50–1.33	0.424	0.46	0.17–1.21	0.114	0.88	0.37–2.07	0.765
Chronic hepatitis (yes)	Chronic hepatitis (no)	1.04	0.80–1.36	0.755	0.82	0.58–1.15	0.24	0.94	0.68–1.29	0.694
Alcohol (yes)	Alcohol (no)	0.98	0.61–1.56	0.923	0.55	0.25–1.20	0.133	1.43	0.73–2.77	0.295
Platelet count ($\times 10^3$)		1.05	0.75–1.48	0.776	1.89	0.90–3.97	0.094	1.41	0.65–3.07	0.387
Child-Pugh (A/B/C)		2.63	1.93–3.58	<0.001	2.20	1.26–3.85	0.006	2.14	1.24–3.71	0.006
AFP* (ng/mL)		1.12	0.94–1.34	0.199	1.07	0.83–1.37	0.608	1.19	0.92–1.53	0.187
DCP† (mAU/mL)		1.90	1.40–2.58	<0.001	1.85	1.08–3.17	0.025	1.15	0.72–1.84	0.549
Maximum tumor diameter (cm)		2.77	1.87–4.11	<0.001	5.54	2.61–11.73	<0.001	6.01	2.67–13.56	<0.001
Number of tumors		0.93	0.69–1.24	0.608	1.60	1.04–2.45	0.032	1.21	0.78–1.89	0.39
Portal invasion (positive)	Portal invasion (negative)	1.01	0.83–1.23	0.903	0.73	0.54–0.97	0.029	1.11	0.84–1.45	0.468
Venous invasion (positive)	Venous invasion (negative)	1.08	0.77–1.52	0.65	0.94	0.58–1.54	0.809	0.41	0.13–3.34	0.625
Bile duct invasion (positive)	Bile duct invasion (negative)	0.52	0.23–1.16	0.109	1.29	0.77–2.16	0.342	0.67	0.13–3.34	0.625
Eggel classification (massive)	Eggel classification (nodular)	1.68	0.98–2.90	0.06	1.06	0.52–2.16	0.881	1.54	0.73–3.28	0.26
Eggel classification (diffuse)	Eggel classification (nodular)	1.78	0.78–4.06	0.173	1.30	0.42–4.03	0.645	0.66	0.13–3.30	0.614
Gastroesophageal varices (none/present/ruptured)		1.03	0.81–1.32	0.792	0.82	0.52–1.28	0.373	0.90	0.57–1.42	0.646
Tumor distribution (bilobar)	Tumor distribution (unilobar)	0.80	0.48–1.35	0.405	1.22	0.60–2.48	0.586	0.74	0.33–1.68	0.47

*Alpha-fetoprotein.
†Des-gamma-carboxy prothrombin.



Non-ruptured HCC (n)	48548	29092	17339	10030	5067	2206	353
Ruptured HCC (n)	1160	335	145	70	30	10	10

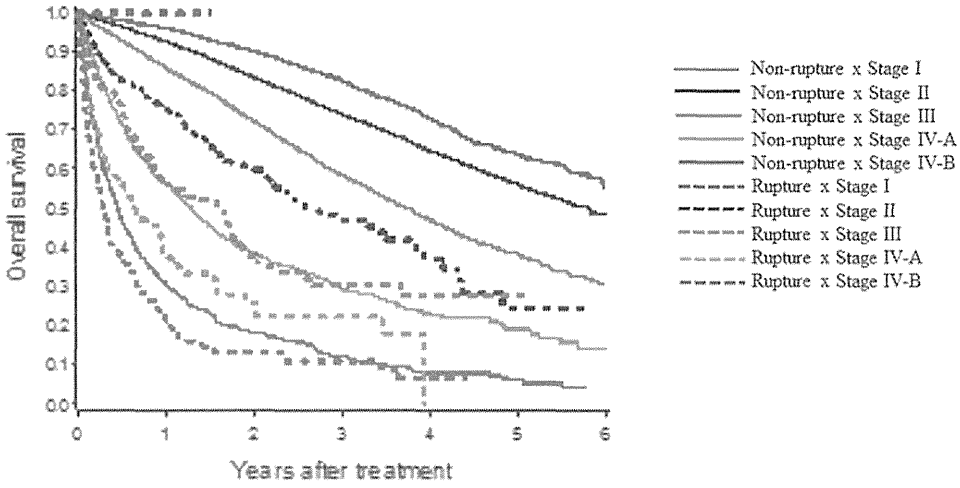
FIGURE 1. Overall survival curves in the ruptured HCC group (dotted blue line) and the nonruptured HCC group (solid blue line) ($P < 0.001$).

A comparison between ruptured HCC and nonruptured HCC revealed that spontaneous tumor rupture was more frequent among patients with a poor liver functional reserve, as reflected by the Child-Pugh grade and liver damage classification. On the other hand, spontaneous tumor rupture was more frequently observed among younger patients, and in HBV-infected livers, rather than chronically hepatitic or cirrhotic livers or HCV-infected livers. Furthermore, in the ruptured HCC patients, the platelet count was higher and the ICGR15 value was better, although the ICGR15 value was mainly estimated in patients undergoing liver resections. These results suggested that spontaneous tumor rupture occurred in a heterogeneous population of patients, and subsequent subanalyses showed that the clinicopathological parameters associated with tumor rupture differed among the subgroups when stratified according to the infectious status for HBV and/or HCV.

The analyses of tumor-related parameters showed that ruptured HCC represented a more advanced tumor stage, as reflected by the tumor size, tumor number, vascular invasion, and tumor marker values. These results are consistent with those in previous reports. A previous report indicated that tumors in contact with or protruding from the liver surface ruptured more frequently,[12] but the present surveys could not assess this issue, as detailed information regarding the location and shape of the ruptured tumors was not collected. Data collection regarding the shape of the HCC were not planned because a definition of "extrahepatically protruding HCC" had not been established at the time of study planning. A subsequent multivariate analysis showed that parameters related to both liver function and tumor status were identified as independent parameters associated with spontaneous tumor rupture. The HR was highest for the tumor size and was second highest for the Child-Pugh grade. Again, the liver functional data in the ruptured HCC group were obtained at the time of disease presentation, and thus, may differ from the baseline data obtained prior to rupture.

Similar to the previous reports, the outcome for ruptured HCC patients was poor compared with that for nonruptured HCC patients; to evaluate the true impact of the tumor rupture itself, we performed subsequent subgroup analyses stratified according to the TNM staging. The results stratified according to the LCSGJ TNM classification suggested that the tumor rupture itself had an additional negative impact on patient survival, and the impact was equivalent to an additional 0.5 to 1.5 stages added to the baseline TNM stage. Although the tumor rupture itself worsened the patient prognosis, the impact was not decisively strong so as to cancel the effect of other tumor-related parameters. In other words, when an HCC tumor in an earlier stage ruptures, a better survival can be expected as compared with that in an advanced-stage rupture. Therefore, assigning all the ruptured HCC to T4 may result in an overestimation of severity; rather, in cases of ruptured HCC, it may be adequate to add (0.5 in the case of stage IV-A, 1 in the case of stage III, or 1.5 in case of the stage II) additional stages to the baseline TNM stage, determined according to the tumor size, tumor number, vascular invasion, lymph node metastasis, and distant metastasis. Meanwhile, the survival curves of patients with tumor rupture were poorly stratified according to the AJCC/UICC TNM staging system. The survival curves for ruptured stage II HCC and for ruptured stage III-A HCC were similar, whereas those for ruptured stage III-B and stage IV-A HCC were similar. According to the present AJCC/UICC TNM staging system, ruptured HCC is assigned to stage III-C if no lymph node or distant metastases are present. However, the present analysis showed that it may not be appropriate to assign the same stage to all ruptured cases, but rather to add an additional 0.5 to 2 stages to the baseline TNM stage.

An overall survival analysis stratified according to the main treatment modality showed that liver resection and local ablative therapy could benefit patients, although the number of patients receiving local ablative therapy was still small ($n = 32$), possibly because of the large tumor size and the tumor location. As only data



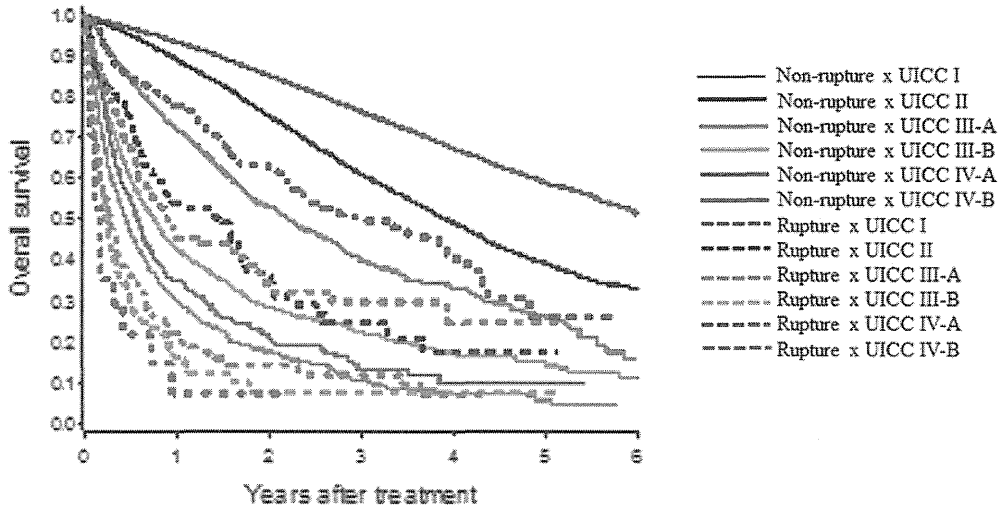
Non-rupture x Stage I (n)	6545	4549	2980	1832	981	440	63
Non-rupture x Stage II (n)	19783	13337	8250	4901	2528	1100	150
Non-rupture x Stage III (n)	10981	6720	3859	2120	996	405	59
Non-rupture x Stage IV-A (n)	1706	640	288	131	53	26	2
Non-rupture x Stage IV-B (n)	1353	267	97	42	21	6	2
Rupture x Stage I (n)	6	1	0	0	0	0	0
Rupture x Stage II (n)	267	145	73	36	14	4	0
Rupture x Stage III (n)	185	71	28	13	8	3	0
Rupture x Stage IV-A (n)	88	21	13	7	0	0	0
Rupture x Stage IV-B (n)	119	19	6	4	2	2	2

	Reference	Hazard ratio	95% C.I.	*P* value
Rupture x Stage II	Rupture x Stage I*	-	-	-
Rupture x Stage III	Rupture x Stage II	1.66	1.25-2.2	<.001
Rupture x Stage IV-A	Rupture x Stage III	1.72	1.24-2.38	0.001
Rupture x Stage IV-B	Rupture x Stage IV-A	1.67	1.21-2.31	0.002
Rupture x Stage II	Non-rupture x Stage III	1.60	1.31-1.94	<.001
	Non-rupture x Stage IV-A	0.56	0.46-0.68	<.001
Rupture x Stage III	Non-rupture x Stage III	2.65	2.15-3.26	<.001
	Non-rupture x Stage IV-A	0.93	0.75-1.15	0.493
	Non-rupture x Stage IV-B	0.42	0.34-0.52	<.001
Rupture x Stage IV-A	Non-rupture x Stage IV-A	1.59	1.22-2.07	<.001
	Non-rupture x Stage IV-B	0.72	0.56-0.94	0.016
Rupture x Stage IV-B	Non-rupture x Stage IV-B	1.21	0.98-1.49	0.081

* No event was observed in the 'Rupture x Stage I' subgroup.

FIGURE 2. (Upper component) Overall survival curves stratified according to the presence of tumor rupture, in combination with the baseline LCSGJ classification staging (stage I, II, III, IV-A, and IV-B). (Lower component) The differences among the survival curves examined using a Cox proportional hazards analysis.

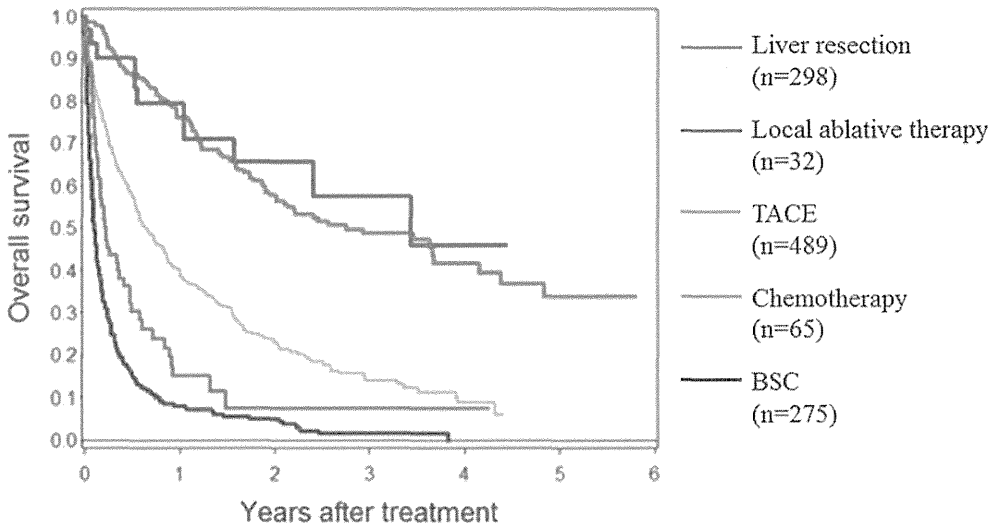
regarding the main treatment modality were available, the results of combination therapies, such as TACE plus liver resection, could not be assessed in the present series. Recent reports have shown that primary hemostasis using TACE followed by liver resection achieved the best treatment results;[17,23,24] indeed, in clinical settings in Japan, emergent TACE followed by hepatic resection is now the treatment of choice, if the general condition and liver function of the patient recovers after TACE.[25] A report on the latest nationwide survey in Japan documented that the 1-, 3-, and 5-year survival rates for all patients undergoing hepatic resection for HCC were 87.8%, 69.2%, and 53.4%, respectively.[2] The outcome of ruptured cases was somewhat poorer than that for all the resected cases; however, our results also suggested that, in selected cases, long-term survival can be expected if the patient's condition is tolerable to the curative treatment, ie, liver resection or local ablative therapy for the ruptured tumor.



Non-rupture x UICC I (n)	22062	14895	9365	5588	2889	1269	165
Non-rupture x UICC II (n)	12487	8043	4587	2517	1239	499	72
Non-rupture x UICC III-A (n)	2285	1102	537	269	129	47	4
Non-rupture x UICC III-B (n)	1497	416	176	97	41	22	2
Non-rupture x UICC IV-A (n)	381	82	36	11	4	4	0
Non-rupture x UICC IV-B (n)	1256	244	84	34	16	4	1
Rupture x UICC I (n)	228	128	65	32	13	4	0
Rupture x UICC II (n)	113	48	20	6	3	1	0
Rupture x UICC III-A (n)	129	35	16	9	4	4	0
Rupture x UICC III-B (n)	87	8	2	1	1	1	0
Rupture x UICC IV-A (n)	17	17	17	0	0	0	0
Rupture x UICC IV-B (n)	110	18	6	4	2	2	2

	Reference	Hazard ratio	95% C.I.	P value
Rupture x Stage II	Rupture x Stage I	2.13	1.55-2.93	<.001
Rupture x Stage III-A	Rupture x Stage II	1.04	0.74-1.47	0.826
Rupture x Stage III-B	Rupture x Stage III-A	3.26	2.32-4.58	<.001
Rupture x Stage IV-A	Rupture x Stage III-B	1.45	0.83-2.53	0.192
Rupture x Stage IV-B	Rupture x Stage III-B	0.71	0.52-0.98	0.035
	Rupture x Stage IV-A	0.49	0.28-0.85	0.011
Rupture x Stage I	Non-rupture x Stage II	1.61	1.3-1.99	<.001
	Non-rupture x Stage III-A	0.81	0.65-1.01	0.057
Rupture x Stage II	Non-rupture x Stage III-A	1.72	1.34-2.2	<.001
	Non-rupture x Stage III-B	0.78	0.61-1	0.051
Rupture x Stage III-A	Non-rupture x Stage III-A	1.78	1.38-2.3	<.001
	Non-rupture x Stage III-B	0.81	0.63-1.05	0.109
	Non-rupture x Stage IV-A	0.59	0.45-0.78	<.001
Rupture x Stage III-B	Non-rupture x Stage IV-B	1.60	1.25-2.04	<.001
Rupture x Stage IV-A	Non-rupture x Stage IV-B	2.32	1.39-3.87	0.001
Rupture x Stage IV-B	Non-rupture x Stage IV-B	1.14	0.92-1.42	0.236

FIGURE 3. (Upper component) Overall survival curves stratified according to the presence of tumor rupture, in combination with the baseline AJCC/UICC classification staging (Stage I, II, III-A, III-B, IV-A, and IV-B). (Lower component) The differences among the survival curves examined using a Cox proportional hazards analysis.



	Hazard ratio	95% C.I.	P value
BSC vs. liver resection	8.99	7.11-11.37	<0.001
Local ablative therapy vs. liver resection	0.87	0.47-1.63	0.671
TACE vs. liver resection	2.93	2.35-3.65	<0.001
Chemotherapy vs. liver resection	5.38	3.84-7.53	<0.001

BSC: best supportive care; TACE: transcatheter arterial chemoembolization

FIGURE 4. (Upper component) Overall survival curves stratified according to the main treatment modality. (Lower component) The differences among the survival curves examined using a Cox proportional hazards analysis.

CONCLUSIONS

In conclusion, we have investigated the parameters associated with spontaneous HCC rupture and have assessed the impact of tumor rupture on patient survival using information from a database containing nationwide survey data in Japan. Spontaneous tumor rupture had an additional negative impact on the baseline tumor status, and this impact corresponded to an additional 0.5 to 2.0 TNM stages. Our results provide important basic information for the next revision of the TNM staging system for HCC.

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