1 year and 21–38% after 2 years.[156,157] Switching therapy from LVD to ADV may enhance the acquisition of another mutation and induce replication of HBV DNA.[158–160] On the other hand, combination therapy of LVD and ADV effectively suppressed viral replication and maintained high efficacy in LVD-resistant patients with chronic HBV infection.

ETV

Entecavir is a guanine analogue and Chang *et al.* have reported that ETV is effective in reducing the serum level of HBV DNA compared with LVD in HBeAg positive patients (Table 2).[159] The cumulative proportion of patients with undetectable HBV DNA (<300 copies/mL) increased to 81% after 1 year of therapy and 93% after 5 years of therapy.[160] After 1 year of treatment with ETV, the serum ALT level was normalized in approximately 70% of patients, and increased to 90% of patients after 5 years. Lai *et al.* have reported that ETV is more efficacious in HBeAg negative patients compared with LVD (Table 2).[161] ETV is the most potent of the currently available anti-HBV drugs because it affects multiple functions of the polymerase, including priming, reverse transcription and DNA elongation.[162]

Entecavir was licensed for the treatment of chronic hepatitis B in Japan in 2006. In nucleos(t)ide-naive patients, ETV is given at dose of 0.5 mg/day.

The rate of ETV resistance was extremely low in nucleoside-naive patients.[160,163,164] The incidence of ETV resistance in nucleos(t)ide analogue-naive patients was reported to be 1.2% at 3 years (Fig. 1).[160,163,164] HBeAg loss was observed in 8% of these patients. The response to ETV was lower in LVD-resistant patients than in nucleos(t)ide analogue-naive patients. In LVD-resistant patients, 20% of patients had undetectable HBV DNA levels after 48 weeks of ETV therapy, and the resistance rate to ETV was 26% at 3 years. Patients with HBeAg at the initiation of ETV had a resistance rate to ETV of 36% at 3 years. On the other hand, patients without HBeAg at the initiation of ETV did not have resistance to ETV at 3 years (Fig. 2).[160,165] In LVD-resistant patients, the risk of the development of resistance to ETV is much higher than those without LVD resistance.[160,165]

The resistance to ETV is principally associated with the mutations rtM250V, rtI169T or rtS202I in addition to the primary LVD resistance mutations rtM204V + rtL180M. The need for multiple mutations to induce ETV resistance suggests a higher genetic barrier to resistance and explains the low rate of resistance to ETV in nucleos(t)ide analogue-naive patients.

Table 2 Efficacy of nucleoside analogues for chronic hepatitis B

	Subject: HBeAg positive patients[159]							
	n	Change of HBV DNA (log copies/mL)		Negativity of HBV DNA of <300 copies/mL		Normalization of ALT	SC	
ETV 0.5 mg	354	−6.9	$P < 0.001$	67%	$P < 0.001$	68%	$P < 0.05$	21%	$P = 0.33$
LVD 100 mg	355	−5.4		36%		60%		18%	
	Subject: HBeAg negative patients[161]							
	n	Change of HBV DNA (log copies/mL)		Negativity of HBV DNA of <300 copies/mL		Normalization of ALT		
ETV 0.5 mg	325	−5.0	$P < 0.001$	90%	$P = 0.001$	78%	$P < 0.05$		
LVD 100 mg	323	−4.5		72%		71%			

ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; LVD, lamivudine; SC, seroconversion; VR, virological response.

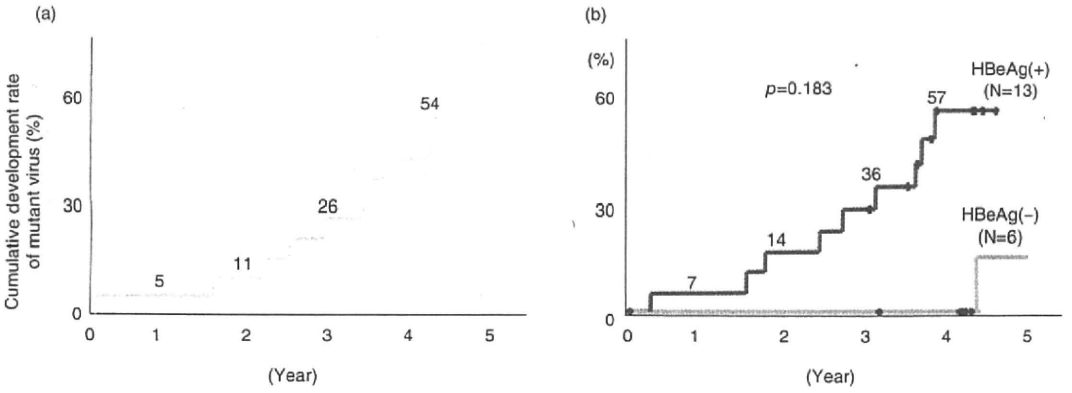

Figure 2 Cumulative development rate of mutant virus after the initiation of entecavir monotherapy in hepatitis B patients with resistance after the administration of lamivudine monotherapy.[164] (a) Cumulative development rate of mutant virus in all patients. (b) Cumulative development rate of mutant virus based on the difference of hepatitis B patients with positive hepatitis B e-antigen (HBeAg) and hepatitis B patients with negative HBeAg.

Consensus 9
Drug-resistant virus with specific mutations in the polymerase/reverse transcriptase gene emerges during nucleos(t)ide analogue therapy in chronic hepatitis B patients. The rtM204V/I and rtL180M mutations are associated with LVD resistance, the rtN236T and rtI233V or rtA181V with ADV resistance, and the rtM250V or rtT184G or rtS202I combined with rtM204V + rtL180M with ETV resistance. (Level 4, grade C.)

Recommendation 6
When patients with chronic hepatitis B are treated with nucleos(t)ide analogues, ETV should be given as the first-line drug because of its high efficacy and low emergence of viral resistant mutant. (Level 1b, grade A.)

Recommendation 7
The combination therapy of LVD and ADV is an effective treatment for LVD-resistant patients. (Level 1b, grade B.)

INTERFERON THERAPY FOR CHRONIC HEPATITIS B

INTERFERON (IFN) WAS the first antiviral treatment approved for chronic HBV infection. IFN-α and -β have a predominantly antiviral effect but also have an immunomodulatory effect and antiproliferative effect which is in contrast to direct antiviral agents such as nucleos(t)ide analogues. The duration of treatment is defined (usually 24–48 weeks) in IFN therapy. This finite duration of therapy is an advantage over direct antiviral agents which are usually given indefinitely. The long-term outcome of therapy is more precisely described in IFN compared to LVD due to its longer history of clinical usage.

Selection of patients

Factors associated with favorable response to IFN therapy are vigorously studied (Table 3). For HBeAg positive patients, high pretreatment ALT levels,[166] high grade of necroinflammation on liver histology and low serum HBV DNA level have consistently been shown to be predictive of favorable response.[167] Other predictive factors include female sex,[166] younger age,[168,169] and HBV genotype A versus D or B versus C.[169,170] Patients fulfilling these predictors are the best candidates for IFN treatment. For HBeAg negative patients, there is no consistent predictor of response. Adverse events such as severe infection or exacerbations of liver disease were common when IFN was given for decompensated cirrhosis. Thus, patients with decompensated cirrhosis should not be treated with IFN due to a risk of precipitating hepatic failure and fatal complications.[171,172]

Table 3 Predictive factors for response to interferon therapy

Predictive factors	HBeAg positive	HBeAg negative
Race	No correlation	No correlation
Age	No correlation or Younger	No correlation or Younger
Sex	No correlation or Female	No correlation or Female
ALT	Higher level	No correlation or Higher level
Activity	Higher grade	No correlation
Fibrosis	Conflicting	No correlation
HBV DNA titer	Lower titer	No correlation or lower titer
Genotype	A > D, B > C	A > D, B > C
Precore	Conflicting	No correlation
Core promoter	mutant	

ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

Recommendation 8
Younger age, high ALT levels, low HBV load, genotype A or B and high inflammatory activity in liver biopsy are predictive of good response to IFN. IFN therapy should be considered in patients fulfilling these predictors. (Level 2a, 2b, grade B.)

Recommendation 9
Interferon should be avoided for patients with decompensated cirrhosis. (Level 4, grade D.)

Standard IFN therapy in HBeAg positive chronic hepatitis B

A meta-analysis of 16 randomized controlled studies have shown that treatment with IFN-α for 16–24 weeks versus an untreated control is associated with higher rate of HBeAg loss (33% vs 12%), HBeAg seroconversion (difference of 18%), undetectable HBV DNA by hybridization or branched chain assay (37% vs 17%), HBsAg loss (7.8% vs 1.8%) and ALT normalization (difference of 23%) (Table 4).[173] A controlled trial has shown that extending therapy for up to 32 weeks in patients who remained HBeAg positive at the end of 16 weeks of therapy improved the rate of HBeAg seroconversion.[174] The durability of HBeAg seroconversion is more than 80%, and even delayed seroconversion could occur in 10–15% of patients 1–2 years after completion of therapy.[175–177] The loss of HBsAg is reported to occur in 12–65% of patients who cleared HBeAg.[175,178] However, this is a rare event in Asian patients.[176,177]

Consensus statement 10
10-1 In HBeAg positive patients, treatment with IFN versus untreated control is associated with higher rate of HBeAg loss, HBeAg seroconversion, undetectable HBV DNA, HBsAg loss and ALT normalization. Extension of therapy improves the rate of HBeAg seroconversion. (Level 1a,1b.)
10-2 Durability of HBeAg seroconversion is more than 80%. The loss of HBsAg is rare in Asian patients. (Level 1b.)

Standard IFN therapy in HBeAg negative chronic hepatitis B

Although the rate of response at the end of therapy is 60–90%, the durability of long-term response is less

Table 4 Standard interferon therapy for HBeAg positive chronic hepatitis B. Meta-analysis of 16 randomized controlled trials

	Interferon		Control	*P*-value
Loss of HBV DNA	37%		17%	0.0001
Loss of HBeAg	33%		12%	0.0001
Loss of HBsAg	7.8%		1.8%	0.001
Seroconversion		Difference of 18%		0.002
ALT normalization		Difference of 23%		0.0001

ALT, alanine aminotransferase; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus.

than 50%.[179,180] Longer duration of therapy is associated with improved durability of response: 10–15% with 4–6 months of therapy, 22–30% with 6–12 months of therapy and 30% with 24 months of therapy.[181–184]

Consensus statement 11

11-1 Durability of response is less than 50% in HBeAg negative patients. (Level 1b.)

11-2 Longer duration of therapy (>48 weeks) is associated with improved durability of response. (Level 2b.)

Pegylated IFN (PEG IFN)

Twenty four weeks of PEG IFN-α-2a monotherapy had higher rate of combined response (loss of HBeAg, suppression of HBV DNA <500 000 copies/mL and ALT normalization) compared to standard IFN-α-2a.[185] Another study with 24 weeks of PEG IFN-α-2b monotherapy also showed a higher rate of HBeAg loss and HBV DNA suppression compared to standard IFN-α-2b.[169]

Controlled studies comparing the 48 weeks of PEG IFN-α-2a and LVD in HBeAg positive and negative patients revealed that PEG IFN had a higher rate of sustained response.[170,171] Seroconversion of HBeAg (32% vs 19%), ALT normalization (41% vs 28% in HBeAg positives and 59% vs 44% in HBeAg negatives), HBV DNA suppression (HBV DNA <10 000 copies/mL, 32% vs 22% in HBeAg positives; HBV DNA <20 000 copies/mL, 43% vs 29% in HBeAg negatives) and negative HBV DNA (14% vs 5% in HBeAg positives and 19% vs 7% in HBeAg negatives) were more frequent in PEG IFN treated patients.

Differences were reported in outcome of the antiviral treatment of patients infected with different genotypes; genotype B is associated with a higher rate of antiviral response to IFN treatment than HBV genotype C among Asian patients with HBeAg positive chronic hepatitis B.[169,186,187] In multicenter trials comparing combination therapy of PEG IFN-α-2b and LVD versus PEG IFN-α-2b alone, it was shown that treatment with PEG IFN-α-2b is the best therapy to achieve HBsAg clearance in patients with genotype A compared with D.[188,189]

Combination or sequential therapy

Combination of two antiviral agents with different mechanisms of action seems a logical approach to improve efficacy. In fact, simultaneous combination of LVD and PEG IFN has a higher rate of HBV suppression, ALT normalization and less frequent emergence of LVD-resistant mutant virus compared to LVD alone. However, there is no difference in treatment response between the simultaneous combination of LVD and IFN or PEG IFN compared to IFN or PEG IFN alone (Table 5).[132,133,170]

There are several clinical trials of sequential therapy with LVD followed by IFN.[190–194] Common to all studies is that the sequential therapy had no advantage over IFN alone. Some studies have shown the suggestive evidence that sequential therapy had a higher rate of HBV suppression, ALT normalization and less frequent emergence of LVD-resistant mutant virus compared to LVD alone (Table 5).[190–194] However, because the study protocols and their results are variable, a conclusive result could not be drawn.

Table 5 Sequential therapy of lamivudine and interferon

		BR	SC	VR	LVD-R
Manesis *et al.* 2006	Sequential	39%	NA	28%	
($n = 36$)[190]	IFN	22%	NA	19%	
Shi *et al.* 2006	Sequential	53%	NA	14%	0%
($n = 162$)[191]	LVD	36%	NA	18%	23%
Yurdaydin *et al.* 2005	Sequential	51%	NA	54%	24%
($n = 78$)[193]	LVD	41%	NA	59%	53%
Sarin *et al.* 2005	Sequential	40%	40%	40%	15%
($n = 75$)[194]	LVD	14%	11%	16%	8%
Schalm *et al.* 2000	Sequential	50%	36%	55%	0%
($n = 226$)[192]	IFN	50%	22%	49%	0%
	LVD	63%	19%	63%	31%

BR, biochemical response; IFN, interferon; LVD, lamivudine; LVD-R, lamivudine resistant mutation; NA, not applicable because hepatitis B e-antigen patients are studied; SC, seroconversion; VR, virological response.

Long-term outcome

The end-point of antiviral therapy is to prevent liver cirrhosis and HCC. Meta-analysis of five studies including 935 patients revealed that IFN treatment significantly decreased the incidence of cirrhosis with the combined risk ratio of 0.65 (95% confidence interval [CI] = 0.47–0.91).[195] Meta-analysis of 11 studies including 2082 patients revealed that IFN treatment significantly decreased the incidence of HCC with the combined risk ratio of 0.59 (95% CI = 0.43–0.81).[195] These results suggest that IFN prevents progression of liver disease to liver cirrhosis or delays the development of HCC, as long as it is within 4–7 years of follow up which is the length of follow up in these studies. Sustained response to IFN therapy was associated with increased survival.[175,181,196,197] To further elucidate the impact of IFN on the natural course of chronic hepatitis B, studies with larger populations followed for longer periods may be needed.

Consensus statement 12

12-1 IFN therapy prevents progression to cirrhosis or the development of HCC. (Level 1a.)

12-2 IFN therapy is associated with improved survival. (Level 1b.)

Adverse effects

The most frequent adverse effects are flu-like symptoms, fatigue, myelosuppression and dermal reaction at the injection site. Others include alopecia, depression and thyroid dysfunction. Less frequent but severe adverse events include interstitial pneumonitis, exacerbation of underlying autoimmune disorders, cerebral vascular events and flare of hepatitis.

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Diagnostic and Treatment Algorithm of the Japanese Society of Hepatology: A Consensus-Based Practice Guideline

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Key Words
Hepatocellular carcinoma · Radiofrequency ablation · Surgical resection · Child-Pugh · JIS score

Abstract
In Japan, more than 70% of hepatocellular carcinomas (HCC) develop from hepatitis C virus infections and 15% are derived from hepatitis B infections. Since most have received close observation with e.g. ultrasound or enhanced computed tomography (CT) scan every 3–6 months before development of HCC, the HCC nodule was detected in the early stage in more than 60% of the patients. An algorithm for the HCC surveillance was shown as a Japanese clinical guideline of a scientific-based research group. At the joint symposium with JSH and the International Liver Cancer Association (ILCA), the algorithm of diagnosis and treatment for HCC was discussed using Answerpad. Several important discussions are described in this article.

Diagnosis of Early Hepatocellular Carcinoma

A consensus symposium of diagnosis and treatment for hepatocellular carcinoma (HCC) was held at the Annual Meeting of the Japanese Society of Hepatology (JSH) on June 4–5, 2009. This consensus-based practice guideline was a revision from that reported at the 2005 JSH Annual Meeting. More than 400 hepatologists including surgeons, radiologists and pathologists joined the symposium and consensus statements and recommendations were discussed using Answerpad. When more than 67% of the participants agreed with the statement, the statement was defined as established and described as a JSH consensus statement. More than 40 statements were discussed, which remain to be published.

In Japan, more than 70% of HCCs develop from hepatitis C virus infection and 15% are derived from hepatitis B infection. Since most had received close observation with e.g. ultrasound, enhanced computed tomography (CT) scan or enhanced magnetic resonance imaging (MRI) every 3–6 months before development of HCC, the HCC nodule was detected in the early stage in more than 60% of the patients. An algorithm for the HCC surveillance was shown as a Japanese clinical practice guideline of a scientific evidence-based research group supported

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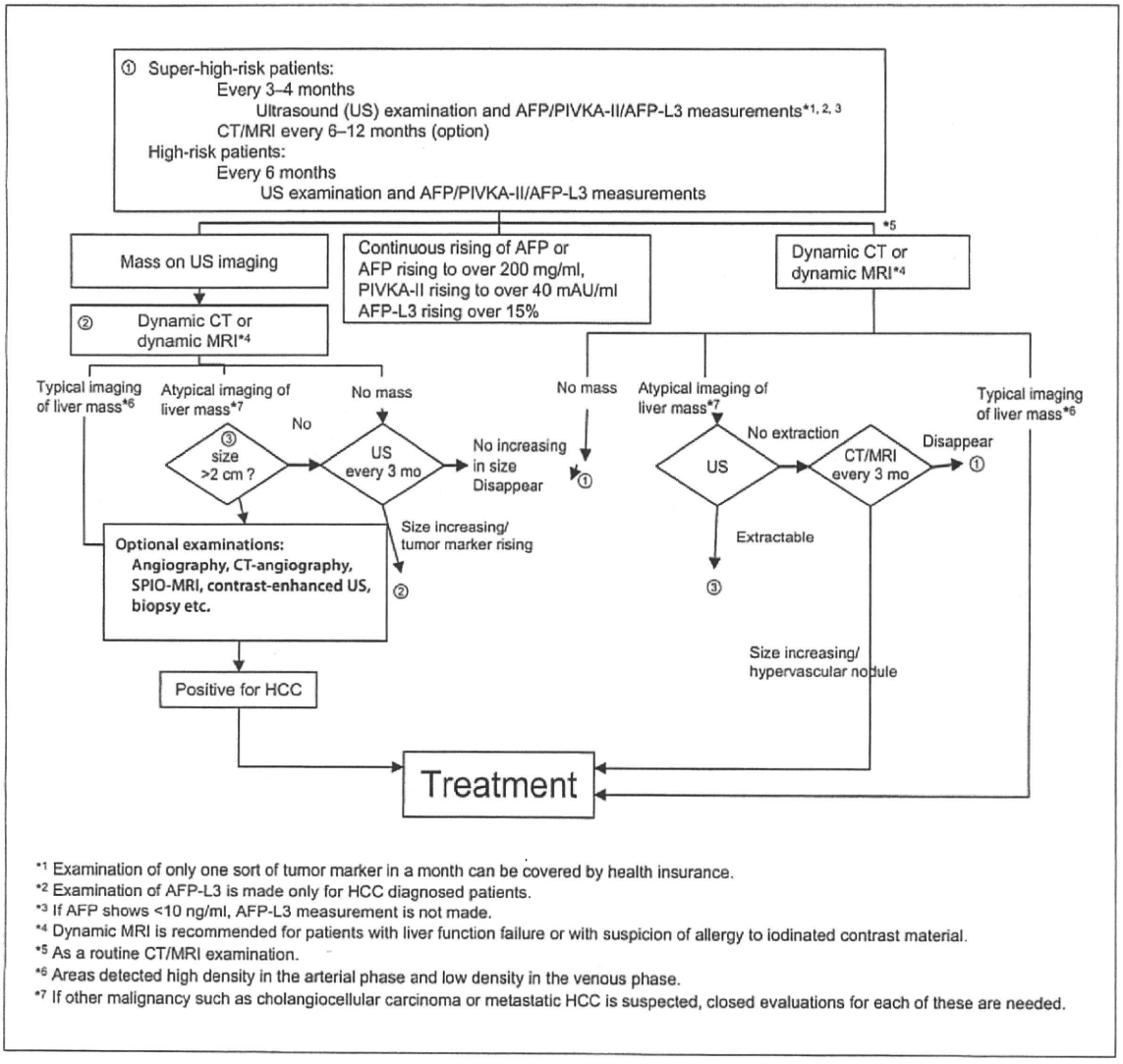


Fig. 1. Algorithm for the HCC surveillance 2005 (Japanese clinical practice guideline of a scientific evidence-based research group supported by the Japanese Ministry of Health, Labor and Welfare [taken from 1].

by the Japanese Ministry of Health, Labor and Welfare (Head: M. Makuuchi) [1] in 2005 (fig. 1).

At the joint symposium with JSH and the International Liver Cancer Association (ILCA), the algorithm of diagnosis and treatment for HCC was discussed using Answerpad. Forty-five hepatologists, surgeons, radiologists and pathologists participated in this meeting and voted the statement. Eight important statements were discussed and voted by Answerpad. The results described compare them with those of the JSH consensus meetings.

Statement 1

A needle biopsy of the hypervascular HCC nodule with 1.5 cm should not be done.

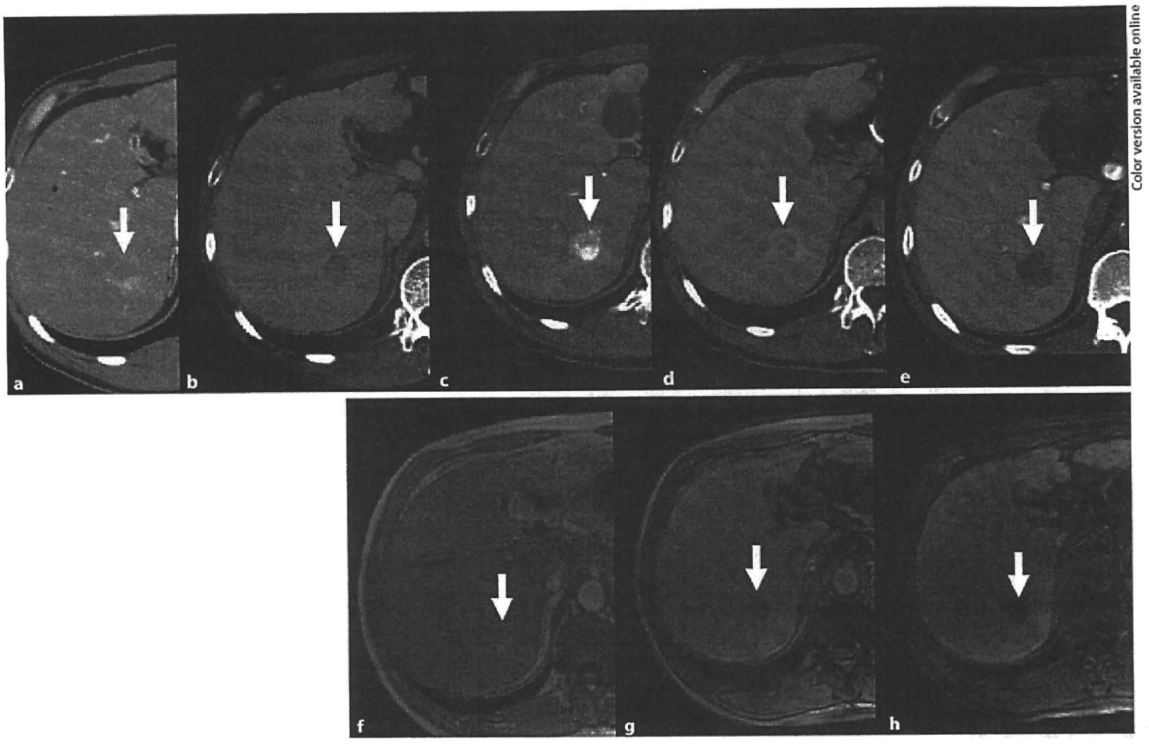


Fig. 2. Representative case of hypervascular early HCC in a 64-year-old male. There is a hypervascular nodule 1.8 cm in diameter in segment 7 during the arterial phase in the dynamic CT scan (**a**) which becomes a low-density area during the equilibrium phase (**b**). CTHA revealed a hypervascular region (**c**) which becomes a ringed enhancement, a so-called 'corona enhancement' in the late phase of CTHA (**d**). This nodule becomes a low-density area during CTAP (**e**). Gd-EPB-DTPA-enhanced MRI revealed a high-intensity area during the arterial phase (**f**) and a low-intensity area during the portal phase (**g**). Importantly, this nodule showed a low-intensity area in the T_1 hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI (**h**).

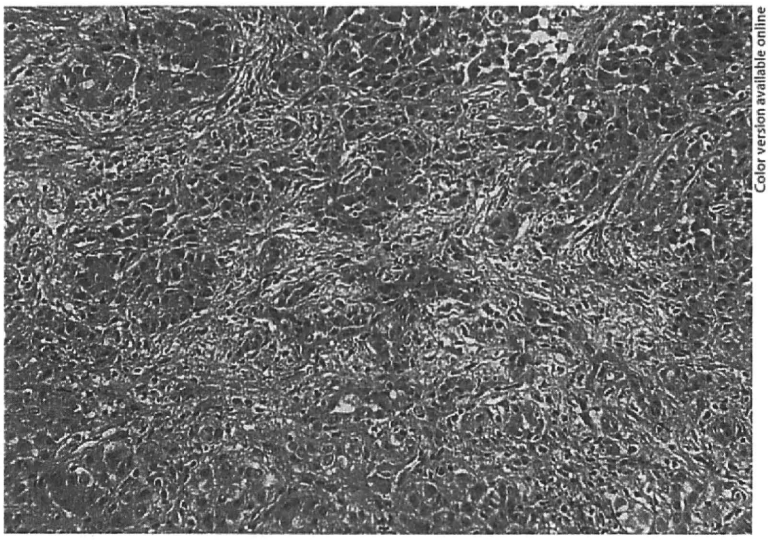
A typical case is shown in figure 2. A hypervascular nodule was observed at the arterial phase in a contrast-enhanced CT scan with a diameter of 1.8 cm in segment 7, which becomes a hypovascular region in the equilibrium phase. This nodule was defined as a hypervascular region during CT during hepatic arteriography (CTHA) and low-density area during CT during arterioportography (CTAP). Gadolinium (Gd)-EOB-DTPA MRI was carried out and the nodule of segment 7 became a low-intensity area in the hepatobiliary phase. A needle biopsy gives important information concerning pathological differentiation grade and biomarker expression; however, implantation of neoplastic cells to the tract or seeding has been reported [2, 3].

This statement was agreed on by 78% of the participants, but 22% disagreed. At the JSH consensus meeting, 91% of the participants agreed with this statement, and only 9% disagreed. Thus, most of the hepatologists who participated in both consensus meetings did not agree to undergo needle biopsy of the nodule when the nodule is hypervascular.

Biopsy of the nodule was done under guided ultrasound, which revealed moderately differentiated HCC (fig. 3). This nodule was treated by radiofrequency ablation (RFA), and complete necrosis was obtained.

Statement 2

A needle biopsy of the nodule should be done to the arterial hypovascular nodule with 1.0 cm when the nodule becomes a low-intensity area in the hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI.



Color version available online

Fig. 3. A needle biopsy of the nodule was done which revealed moderately differentiated HCC. HE. 200×.

Table 1. The JIS (Japan Integrated Score) was defined by adding the tumor TMN stage and Child-Pugh score

	Variable			
	0	1	2	3
Tumor stage (TMN)[1]	1	2	3	4
Child-Pugh score	A	B	C	

[1] Liver Cancer Study Group of Japan.

A typical case is shown in figure 4. The hypovascular nodule was detected at the arterial phase in a contrast-enhanced CT scan with a diameter of 1.5 cm in segment 8, which becomes also a hypovascular region in the equilibrium phase. This nodule was defined as a hypovascular region during CTHA and low-density area during CTAP. Gd-EOB-DTPA MRI was carried out, and the nodule of segment 8 became a low-intensity area in the hepatobiliary phase.

This statement was agreed on by 57% of the consensus meeting participants, but 43% disagreed with the statement. At the JSH consensus meeting, 47% of the participants agreed with this statement, and only 53% disagreed. Both of the voting results were similar.

A needle biopsy of the nodule was done which revealed well-differentiated HCC (fig. 5). When the hypovascular nodule was detected, it was difficult to obtain an accurate diagnosis without a needle biopsy and the strategy that was reported [4]. Since hypovascular nodules sometimes converted from malignant progression to overt HCC [5], it seems necessary to undertake a needle biopsy of the nodule.

Statement 3

For estimating the prognosis of patients with HCC, the most reliable staging system is the Japan Integrated Score (JIS).

The JIS scoring system was proposed by Kudo et al. [6] and was defined as adding the tumor TMN stage of the Japan Hepatocellular Cancer Study Group and Child-Pugh score as shown in table 1. In Japan, screening systems for the early detection of HCC have been established, e.g. periodic ultrasound, enhanced CT scan including measuring α-fetoprotein and prothombin induced by vitamin K deficiency. Thus, most HCC nodules were detected in the early stage. The JIS score has been validated in Japanese patients [7] and approved to be the best prognosis estimation of patients with HCC in Japan.

This statement was agreed on by 63% of the participants, but 37% disagreed at the ILCA consensus meeting. At the JSH consensus meeting, 71% of the participants agreed with this statement, and 29% disagreed.

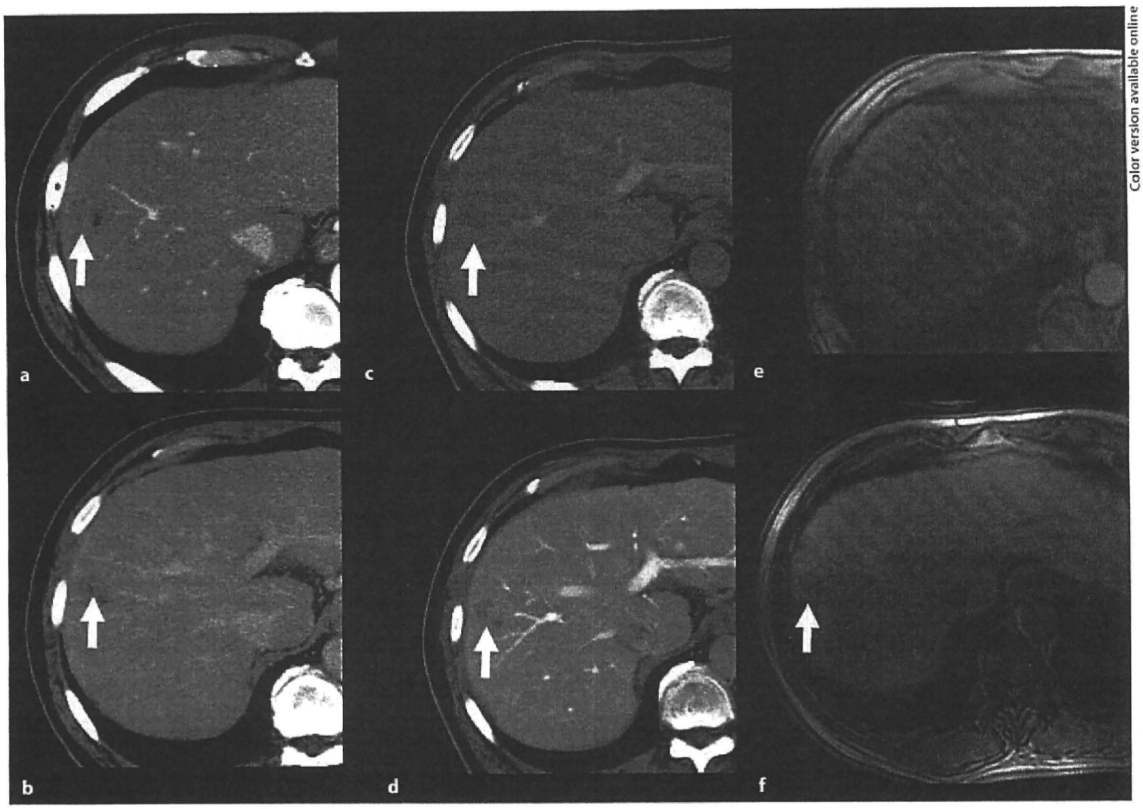


Fig. 4. A representative case of hypovascular early HCC in a 75-year-old male. There is a hypovascular nodule with a diameter of 1.5 cm in segment 8 during the arterial phase in the dynamic CT scan (**a**) which becomes a low-density area during the equilibrium phase (**b**). CTHA also revealed a hypovascular region (**c**). This nodule becomes a low-density area during CTAP (**d**). Superparamagnetic iron oxide-enhanced MRI was carried out, but a nodular region was not detected in the T_2* MRI image (**e**). Gd-EPB-DTPA-enhanced MRI showed a low-intensity area in the T_1 hepatobiliary phase by Gd-EOB-DTPA-enhanced MRI (**f**).

Treatment Algorithm of HCC

The treatment algorithm was discussed at the JSH consensus meeting in 2005. At this meeting the treatment algorithm was established by initially dividing the patients according to extrahepatic spread, Child-Pugh score, and vascular invasion (fig. 6). Next, they were divided by the nodule number and the vascularity of the nodule. When the single nodule was identified as being hypovascular, intensive follow-up or ablation was recommended. When the patient had 1–3 hypervascular nodules <3 cm in diameter, they should be treated by surgical resection or RFA. When the nodules are >3 cm, they should be treated by surgical resection or transarterial chemoembolization (TACE). When the patients have 4 or more HCC nodules, they should be treated by TACE or transarterial embolization (TAE). If the patients have 3 or less nodules <3 cm or a single nodule <5 cm which are divided within the Milan criteria, liver transplantation should be considered if the patients are younger than 65 years of age. If invasion to the portal or hepatic vein was observed, they should be treated by surgical resection, TAI or TACE.

When the patients were classified as having poor liver function with Child-Pugh C and the HCC nodules are within the Milan criteria, liver transplantation should be considered. Otherwise, palliative care should be chosen.

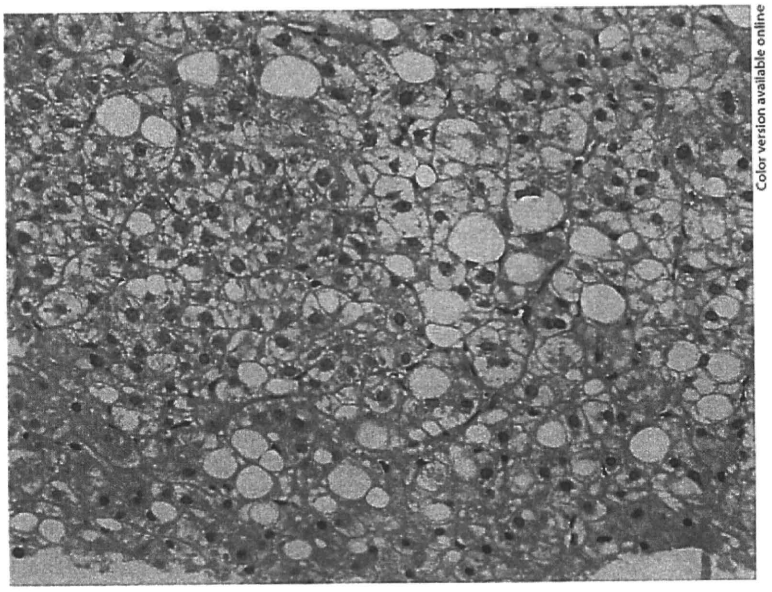


Fig. 5. A needle biopsy of the nodule was done which revealed a well-differentiated HCC. HE. 200×.

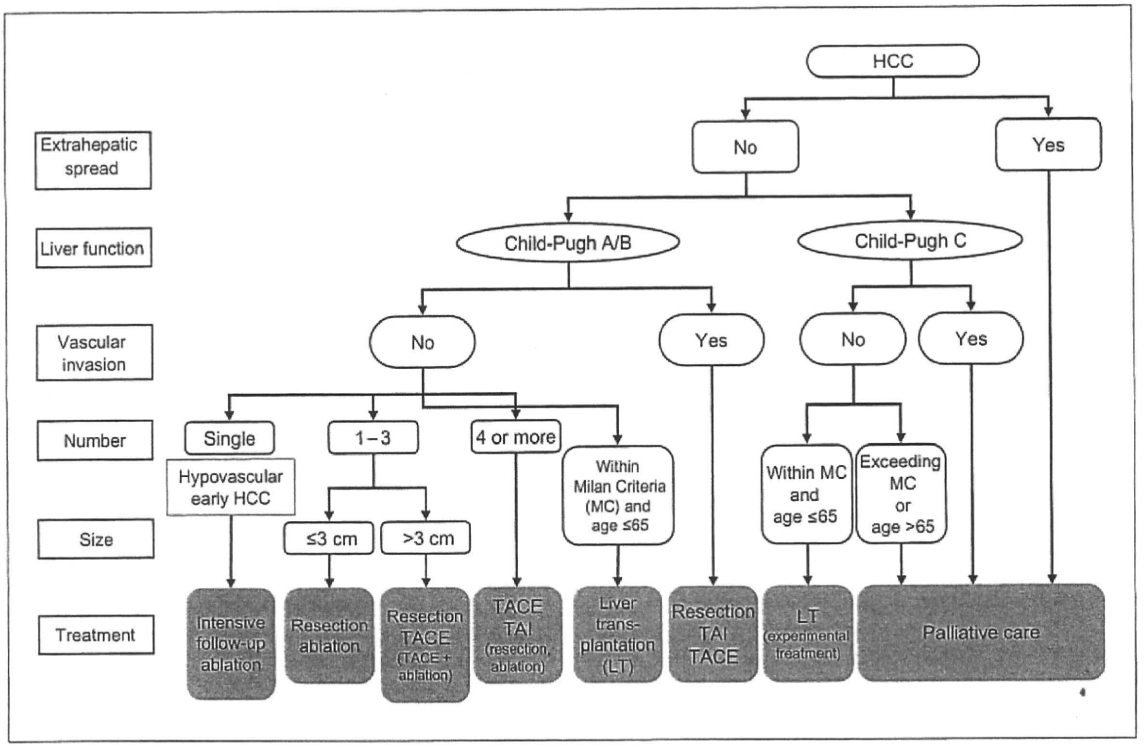


Fig. 6. Treatment algorithm for HCC (JSH consensus-based 2007).

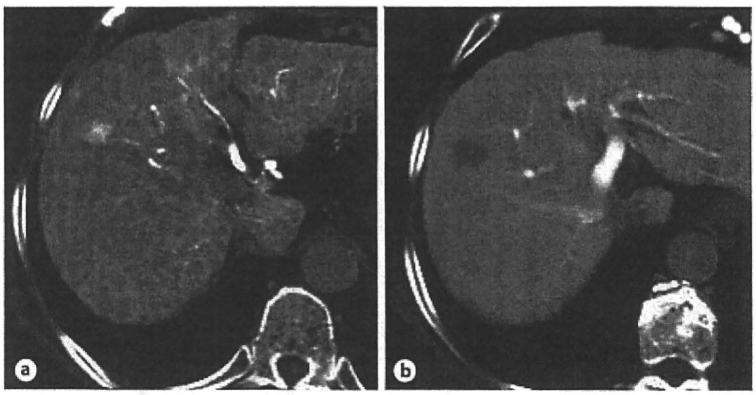


Fig. 7. A representative case with a hypervascular nodule by CTHA in segment 8 with a diameter of 1.8 cm (**a**). This nodule became a low-density area by CTAP (**b**). This patient has good liver function classified as Child-Pugh A.

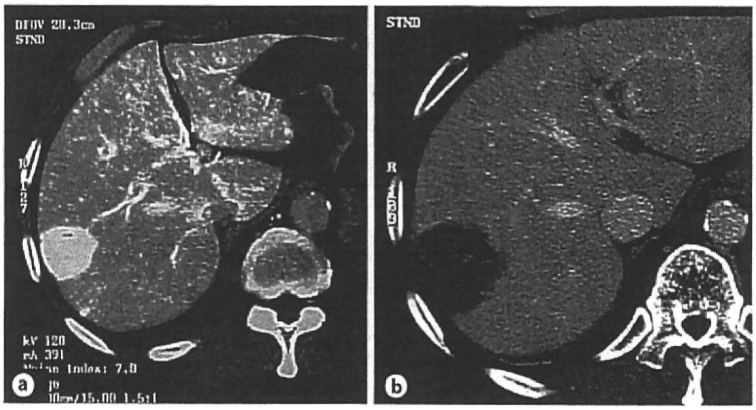


Fig. 8. A representative case with a hypervascular nodule by CTHA in segment 7 with a diameter of 3.0 cm (**a**). Locally complete curative necrosis was achieved by RFA (**b**).

Statement 4

Which treatment do you choose for the patient having a single HCC nodule <2 cm with Child-Pugh A?

A typical case of a 62-year-old male is shown in figure 7. A hypervascular small nodule was observed by CTHA at segment 8 with a diameter of 1.8 cm, which became a low-intensity area by CTAP. His liver function was classified as Child-Pugh A.

38% of the participants chose surgical resection, but 62% chose RFA. At the JSH consensus meeting, 44% of the participants chose surgical resection, but 56% chose RFA. When only surgeons were asked the same question, 80% of them chose surgical resection, but 20% chose RFA. This question was asked to only physicians at the JSH consensus meeting, and 32% chose surgical resection, and 68% chose RFA.

Overall survival was compared after surgical resection with RFA [8], in which no apparent difference was observed between the two groups. Thereafter, several reports including a large number of patients with HCC compared the survival or recurrence, but they are not randomized [9–11]. This is an important issue that needs to be clarified. Thus, randomized controlled trials are necessary including a large number of patients to clarify which treatment is superior between surgical resection and RFA.

Statement 5

Which treatment do you choose for a patient having a single HCC nodule <3 cm with Child-Pugh A?

A representative case of a 75-year-old male is shown in figure 8a. He had a single hypervascular nodule defined by CTHA at segment 7 with a diameter of 3 cm. His liver

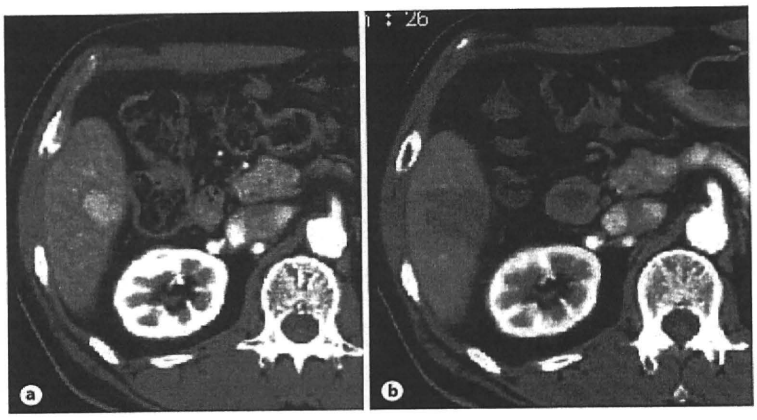


Fig. 9. A typical case with a single hypervascular HCC nodule in segment 6 with a diameter of 1.4 cm. He has a good liver function of Child-Pugh A (**a**). He was treated by RFA alone, and complete necrosis was obtained (**b**).

function was well preserved and he was classified as Child-Pugh A. The participants were asked this question. 74% of the participants chose surgical resection, but 26% chose RFA by the ILCA. At the JSH consensus meeting, 80% of the participants chose surgical resection, but 20% chose RFA as the first-line treatment.

Interestingly enough, most of the participants chose surgical resection when the nodule was as large as 3 cm. This hypervascular HCC nodule was treated by percutaneous RFA, and locally complete curative necrosis was obtained (fig. 8b).

Statement 6

RFA should be done after TACE to the hypervascular HCC nodule with a diameter of 2 cm.

A typical 62-year-old male with a 1.6-cm single hypervascular HCC nodule in segment 6 is shown in figure 9a. He has a good liver function with Child-Pugh A.

This statement was agreed on by 36% of the participants at the ILCA consensus meeting, but 64% disagreed. However, at the JSH consensus meeting, 51% of the participants agreed with this statement, but 49% disagreed.

This hypervascular HCC nodule was completely ablated by RFA alone (fig. 9b). It has been reported that TACE before RFA increased the ablated area, suggesting that overall survival will improve [12–14]; however, TACE may increase the adverse events by RFA. Whether TACE before RFA is beneficial for the patients should be examined by analyzing the overall survival of patients and comparing them to receiving TACE before RFA or without TACE before RFA.

Statement 7

Do you prescribe sorafenib as the first-line treatment option for the patients with advanced HCC in whom surgical resection, RFA or TACE is not indicated?

As sorafenib was approved in Japan in May 2009 [15], only a few hepatologists have experienced prescribing the medicine. Its usefulness after TACE in patients with advanced HCC is under investigation in the USA and Japan [16]. It will be included in the therapeutic algorithm for HCC, but it is still unclear to hepatologists to which patients the medicine should be prescribed.

At the ILCA consensus meeting, 61% of the participants agreed with this statement, but 30% disagreed. 9% of them did not have any opinion on the statement because they have no experience with sorafenib. At the JSH consensus meeting, 35% of the participants agreed with this statement, but 29% disagreed. 36% of the participants did not have any opinion because they have no experience with sorafenib.

The best indication for sorafenib should be investigated in the near future [17].

Statement 8

Overall survival should be the endpoint for the assessment of efficacy comparing ablation with surgical resection.

The recurrence rate after surgical resection or RFA was reported including a large number of patients, and the incidence of intrahepatic recurrence was higher after RFA than surgical resection [11]. However, overall survival was not different between the two groups. Thus, the problem is how to evaluate the outcome of surgical resection and RFA, and this question was proposed by hepatologists.