Table 1 Patient characteristics ($n = 25$)

Characteristics	Number of patients	%
Age (years)		
Median	67	
Range	47–79	
Sex		
Male	20	80
Female	5	20
Eastern Cooperative Oncology Group performance status		
0	21	84
1	4	16
Hepatitis B surface antigen		
Positive	4	16
Hepatitis C antibody		
Positive	15	60
Child-Pugh classification		
A	17	68
B	8	32
Prior treatments		
Present	13	52
Resection	4	16
Local ablation	5	20
TACE	10	40
Portal vein invasion		
Main	19	76
First branch	6	24
Tumor distribution		
Unilateral	8	32
Bilateral	17	68
Ascites		
Present	6	24
Alpha-fetoprotein (ng/mL)		
Median	1,075	
Range	11.3–386,300	
PIVKAII (mAU/mL)		
Median	1,600	
Range	18–423,350	

TACE transcatheter arterial chemoembolization, *PIVKAII* protein induced by vitamin K absence or antagonist-II

account of death due to hepatic failure (1 patient), variceal rupture (1 patient), or accidental perforation of the colon (1 patient)), and one patient remains alive without tumor progression. The median progression-free survival was 3.6 months. All patients were included in the survival assessment. Of the 25 patients, 21 died. The causes of death were tumor progression (18 patients), hepatic failure (1 patient), rupture of esophageal varices (1 patient), and accidental perforation of the colon (1 patient). The median survival time and 1-, 2-, and 3-year survival rates of the patients were 7.1 months and 36, 20, and 20 %, respectively (Fig. 1). The median survival time was 45.4 months in the patients who showed complete or partial response, and four of these patients survived for more than 3 years; on the other hand, the median survival time in the patients who showed stable or progressive disease was 5.8 months.

Adverse events

The adverse events occurring in the patients enrolled in this study are summarized in Table 2. The adverse events represent the maximum grade occurring in the patients during the entire course of therapy. Grade 3–4 leukocytopenia, neutropenia, and thrombocytopenia occurred in 5 (20 %), 2 (8 %), and 4 (16 %) of the patients, respectively; however, they were all transient and recovered fully without treatment. The major non-hematological adverse events were elevations of the serum AST and ALT levels. Grade 3–4 AST and ALT elevations were observed in 11 (44 %) and 6 (24 %) of the patients, respectively. However, the levels returned to the initial levels within one month without any additional treatment. No cumulative adverse events were seen in this patient series. One patient developed perforation of the colon on day 37 after the commencement of the first cycle; however, this was judged as an accidental event not causally related to the treatment. There were no other serious non-hematological adverse events.

Discussion

HAIC is widely undertaken in Japan for patients with advanced HCC who are not suitable candidates for

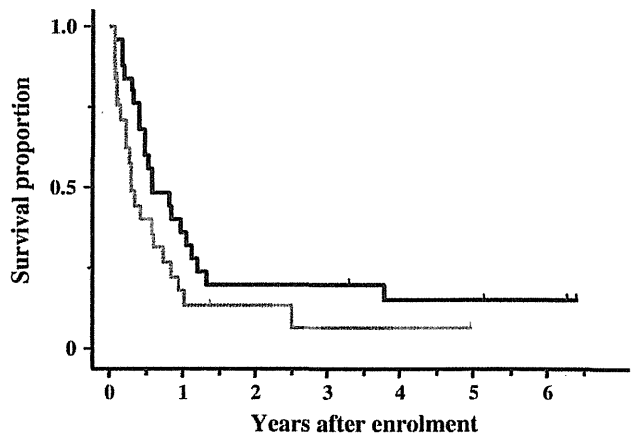

Fig. 1 Overall survival (*black line*) and progression-free survival (*gray line*) curves of the 25 patients of advanced hepatocellular carcinoma with tumor thrombosis in the main and/or first branch of the portal vein treated by hepatic arterial infusion chemotherapy using cisplatin. *Tick marks* indicate censored cases

Table 2 Adverse events

	Grade				
	1	2	3	4	3–4 (%)
Hemoglobin	6	7	0	0	0
Leukocytes	7	9	5	0	20
Neutrophils	6	7	2	0	8
Platelets	6	6	4	0	16
Nausea	10	5	0	0	0
Vomiting	9	1	0	0	0
Anorexia	13	6	0	0	0
Fatigue	8	3	0	0	0
Fever	3	0	0	0	0
Diarrhea	0	0	0	0	0
Abdominal pain	2	0	0	0	0
Weight loss	2	1	0	0	0
Total bilirubin	10	5	0	0	0
Hypoalbuminemia	6	7	0	0	0
AST	1	3	10	1	44
ALT	3	5	5	1	24
Alkaline phosphatase	3	0	0	0	0
Creatinine	3	2	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase

resection, local ablative therapies, or transcatheter arterial chemoembolization, such as those with complicating PVTT [3, 4]. HAIC is usually administered using one of the following three well-reported regimens: cisplatin alone [11, 24], 5-FU plus cisplatin [12–15], and 5-FU plus interferon [16–20]. The efficacies of these regimens for HCC patients with PVTT are shown in Table 3 [11–20]. The reported response rates and disease control rates are approximately 20–40 % and 50–80 %, respectively, and the reported median survival is in the range of 7–12 months. However, optimum regimen for patients of advanced HCC with PVTT still remains controversial. Recently, a randomized phase II trial comparing 5-FU and interferon with best salvage therapy (BST), such as 5-FU plus cisplatin or cisplatin alone, has been reported [27]. Although the response rate was quite similar in both groups, the patients treated with 5-FU and interferon seemed to show inferior disease control and overall survival rates as compared to those treated by BST. Thus, the optimal regimen for HAIC has not yet been clarified. Transarterial radioembolization with yttrium-90 microspheres is one of the good options for HCC with PVTT, and the treatment efficacy has been reported to be favorable (Table 3) [28, 29]. However, this treatment has not been established as standard therapy, because the survival benefit has not been clarified by randomized trials.

In this study, cisplatin was selected as the trial chemotherapeutic agent for HAIC, because it is widely used in Japan, it can be administered by short infusion, and it requires no indwelling reservoir system for hepatic arterial infusion, unlike 5-FU plus cisplatin or 5-FU plus interferon. The response and disease control rates to HAIC with cisplatin in this study were 28 and 76 %, respectively, and the median overall survival time was 7.1 months. These results are comparable to previous reports (Table 3). Besides, in the patients who achieved complete or partial response, the median survival time was 45.4 months and four of them survived for more than 3 years. In previous reports also, the prognoses in the responders to HAIC were extremely favorable [11–13, 15–17, 19]. Thus, HAIC sometimes causes favorable tumor shrinkage, and a markedly prolonged survival time can be expected in such patients. If the tumor response to HAIC can be predicted prior to the start of the treatment, more appropriate selection of suitable candidates for HAIC may be possible. Therefore, identification of reliable markers to predict a favorable response to HAIC is warranted.

In comparison with systemic administration of anticancer agents, HAIC allows high local concentrations of anticancer drugs to be achieved, with reduced systemic distribution, thereby increasing the activity of the anticancer drug and reducing the likelihood of systemic adverse effects. With regard to the toxicity, the toxicity of HAIC with cisplatin was very mild. The main grade 3–4 adverse events were leukocytopenia (27 %), neutropenia (47 %), increased AST (40 %), and increased ALT (20 %). These adverse events were transient and reversed without any specific treatments. Furthermore, no cumulative or serious adverse events were seen in this study. Therefore, this treatment was considered to be well tolerated and even patients with Child-Pugh B could be included as candidates for this treatment.

HAIC is considered as one of the valid treatment options for advanced HCC, because it has been shown to exert a favorable effect with mild toxicities in advanced HCC patients with PVTT. However, it has not been acknowledged as a standard therapy for advanced HCC, because no chemotherapeutic agent or regimen has yet been shown to confer a survival benefit sufficient for adoption as a standard therapy [1–4]. On the other hand, sorafenib has been acknowledged as a standard agent for the treatment of patients with advanced HCC, including HCC with vascular invasion and extrahepatic metastases, because two pivotal phase III trials comparing sorafenib versus placebo have shown the survival benefit afforded by sorafenib [7, 8]. Sorafenib has a limited tumor shrinkage effect, but is capable of prolonging the time-to-progression and the overall survival. In the comparison of the efficacy between HAIC with cisplatin and sorafenib (Table 3), the efficacy of cisplatin seemed to be equivalent to that of sorafenib [7, 30]; therefore, cisplatin may be one of the promising

Table 3 Treatment efficacy of hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis

Regimen	*n*	RR (%)	DCR (%)	Median TTP/PFS (months)	Median OS (months)	1-year OS (%)	2-year OS (%)	3-year OS (%)	Median OS for responder (months)	References
Yttrium 90 (Child-Pugh A)	35	50	NA	5.6	10.4	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90 (Child-Pugh B)	57	28	NA	5.9	5.6	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90	76	NA	NA	NA	10.0	NA	NA	NA	NA	Sangro et al. [29]
Sorafenib[a]	108	NA	38.9	4.1	8.1	NA	NA	NA	NA	Bruix et al. [7]
Sorafenib[a]	44	NA	24	NA	4.4	NA	NA	NA	NA	Kang et al. [30]
5-FU/Cisplatin	48	48	77	NA	10.2	45.0	31.0	25.0	31.6	Ando et al. [12]
5-FU/Cisplatin	38	8	66	NA	6.0	21.0	NA	NA	NA	Cheong et al. [14]
5-FU/Cisplatin	18	33	72	NA	NA	28.0	NA	NA	15.0	Lai et al. [13]
5-FU/Cisplatin	52	39	65	4.1	15.9	53.3	34.8	26.1	40.7	Ueshima et al. [15]
5-FU/IFNα	55	44	51	5.2	11.8	48.9	28.6	16.4	24.4	Ota et al. [16]
5-FU/IFNα	116	52	54	NA	NA	34.0	18.0	NA	59 % (2 years)	Obi et al. [17]
5-FU/IFNα	31	29	55	5.8	7.5	29.0	5.6	NA	NA	Uka et al. [18]
5-FU/IFNα	102	39	47	2.0	9.0	36.8	21.2	10.8	25.0	Nagano et al. [19]
5-FU/IFNα	57	25	58	3.3	10.5	NA	NA	NA	NA	Yamashita et al. [20]
Cisplatin	24	21	25	NA	7.0	38.0	16.0	NA	37.3	Kondo et al. [11]
Current study (Cisplatin)	25	27	72	3.6	7.1	36	20	20	45.4	Ikeda

RR response rate, *DCR* disease control rate, *TTP* time to progression, *PFS* progression-free survival, *OS* overall survival, *5FU* 5-fluorouracil, *IFN* interferon, *NA* not available

[a] The study included the patients with macrovascular invasion

regimens for advanced HCC with PVTT. In addition, sorafenib and cisplatin have different toxicity profiles, except for causing liver dysfunction. Sorafenib and cisplatin have been reported to exert a synergistic effect against liver cancer in preclinical research [31, 32], and some clinical trials of combined regimens of sorafenib and cisplatin have been performed in patients with gastric cancer [33], nasopharyngeal carcinoma [34], and lung cancer [35]. Therefore, combined use of the two drugs may yield superior results. Furthermore, a randomized controlled trial comparing sorafenib plus HAIC with sorafenib could clarify the additional effect of HAIC and establish HAIC as a standard treatment for advanced HCC. Therefore, a phase I trial of sorafenib plus HAIC with cisplatin has already been conducted, and a randomized phase II trial of sorafenib plus HAIC with cisplatin versus sorafenib alone (UMIN000005703) is ongoing.

This study involved some limitations. First, the number of enrolled patients was not so high, and the results should be interpreted with some caution. Secondly, 10 patients received chemoembolization as prior therapy. This might lead to resistance to HAIC with cisplatin. Finally, as this was a single-arm phase II trial, the survival benefit of HAIC with cisplatin could not be clarified. All of these limitations argue for the conduct of a randomized trial to further compare this treatment with standard therapy in advanced HCC patients with PVTT.

In conclusion, HAIC with cisplatin exerts moderate activity with mild toxicity in HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment. At present, a randomized controlled trial of HAIC using a combination of cisplatin and sorafenib is under way.

Acknowledgments This work was supported in part by Grants-in-Aid for Cancer Research and for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan and National Cancer Center Research and Development Fund (23-A-22).

Conflict of interest None.

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J Gastroenterol
DOI 10.1007/s00535-013-0853-7

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Efficacy of sorafenib in patients with hepatocellular carcinoma refractory to transcatheter arterial chemoembolization

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Received: 5 March 2013 / Accepted: 9 June 2013

Abstract
Background The efficacy of sorafenib for hepatocellular carcinoma (HCC) patients refractory to transcatheter arterial chemoembolization (TACE) has not yet been clarified. We investigated the efficacy of sorafenib in HCC patients who were refractory to TACE (sorafenib group) and retrospectively compared the results with those of patients treated with hepatic arterial infusion chemotherapy using cisplatin (cisplatin group).
Methods We evaluated the anti-tumor effect, the time to progression, and the overall survival in 48 patients in the sorafenib group and 66 patients in the cisplatin group.
Results The disease control rate to sorafenib was 60.4 %, the median time to progression was 3.9 months, and the median survival time was 16.4 months in patients who were refractory to TACE. When compared with the cisplatin group, significant differences in the patient characteristics were not observed between the two groups with the exception of patient age; however, the disease control rate (cisplatin group 28.8 %, $P = 0.001$), time to progression (cisplatin group: median 2.0 months, hazard ratio 0.44, $P < 0.01$), and overall survival (cisplatin group: median 8.6 months, hazard ratio 0.57, $P < 0.001$) were significantly superior in the sorafenib group. The multivariate analysis also showed the sorafenib treatment to be the most significant factor contributing to prolongation of time to progression and overall survival.
Conclusions Sorafenib showed favorable treatment results in patients refractory to TACE. When compared with hepatic arterial infusion chemotherapy using cisplatin, sorafenib demonstrated a significantly higher disease control rate, a longer time to progression and increased overall survival.

Keywords Hepatocellular carcinoma · Sorafenib · Cisplatin · Chemotherapy · Hepatic arterial infusion chemotherapy

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. HCC is highly prevalent in African and Asian countries, and its incidence has recently been increasing in western countries [1, 2]. For patients with unresectable HCC who are not candidates for curative treatments, such as resection, transplantation, or local ablation, transcatheter arterial chemoembolization (TACE) is the main therapeutic option [1, 2]. A clear survival benefit for patients with unresectable HCC who are treated with TACE has been shown in several randomized controlled trials and a meta-analysis [3, 4]. Chemotherapy has been recognized as a palliative treatment option for patients with highly advanced HCC in whom TACE is not indicated.

Sorafenib is a multikinase inhibitor of Raf kinase, which is involved in cancer cell proliferation, as well as vascular

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Published online: 23 June 2013

endothelial growth factor receptor-2/-3 (VEGFR-2/-3) and platelet-derived growth factor receptor beta (PDGFR-β), which is involved in peritumor neovascularization [5, 6]. In two pivotal international phase 3 trials of sorafenib vs. placebo, the so-called SHARP trial [7] and the Asia-Pacific trial [8], sorafenib demonstrated a prolonged overall survival and time-to-progression, compared with a placebo, in patients with advanced hepatocellular carcinoma (HCC). Therefore, sorafenib has been acknowledged as a standard therapy for advanced HCC.

In the therapeutic strategy of the Barcelona Clinic Liver Cancer Study Group [5], sorafenib was indicated for patients with extrahepatic metastasis and/or vascular invasion of Stage C disease (advanced stage), patients with a performance status (PS) of 1–2, and those with Stage B (intermediate stage) multifocal HCC refractory to TACE. In the 2010 updated version of the consensus-based clinical practice guidelines for the management of HCC proposed by the Japan Society of Hepatology [9, 10], patients with extrahepatic metastasis, with macrovascular invasion, and who were refractory to TACE are listed in the algorithm for treatment with sorafenib. The main indications for sorafenib are, therefore, considered to be patients who are refractory to TACE, those who have vascular invasion, or those who have extrahepatic metastasis. Subgroup analyses of the SHARP trial [7] and the Asia-Pacific trial [8] showed the treatment efficacies in patients with vascular invasion and extrahepatic metastasis. However, those in patients who are refractory to TACE have not been reported so far, although the outcome of patients with prior TACE has been reported [11, 12].

Before the introduction of sorafenib, hepatic arterial infusion chemotherapy was mainly performed in Japan for patients with advanced HCC [13–21], including those refractory to TACE [13, 14]. However, no consensus on a standard therapy has been achieved because large-scale prospective studies and randomized controlled studies have not been conducted and the survival benefit has not been clarified [10]. In this study, we clarified the efficacy of sorafenib in patients who were refractory to TACE (sorafenib group) and retrospectively compared the anti-tumor effect, time to progression, and overall survival between the sorafenib group and patients who were refractory to TACE and who were treated with hepatic arterial infusion chemotherapy using cisplatin (cisplatin group).

Patients and methods

Patients

Forty-eight consecutive chemotherapy-naive patients who were refractory to TACE without extrahepatic metastasis were extracted from 205 patients treated with sorafenib at the National Cancer Center Hospital East (East Hospital) between April 2009 and December 2011. Sixty-six of the 84 chemo-naive patients who were refractory to TACE and were treated with hepatic arterial infusion chemotherapy using cisplatin at the National Cancer Center Hospital and the East Hospital between July 2004 and September 2008, the period before the approval of sorafenib in Japan, were enrolled in the cisplatin group after excluding 18 patients with extrahepatic metastasis or the moderate retention of ascites. In this series, the total number of TACE sessions was 478, while the median number of TACE sessions was 4 (range 1–16). In previous TACE sessions, an emulsion containing an anticancer agent and lipiodol followed by gelatin sponge particles were used. In the present series, epirubicin was used for 394 sessions, adriamycin was used for 29 sessions, and mitomycin C was used for 12 sessions; the anticancer agent was unknown for 43 sessions. Patients who were refractory to TACE were defined as those showing progression or a tumor shrinkage rate of <25 % of the hypervascular lesions as visualized using dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) after 1–3 months of TACE [13]. The TACE-refractory status of individual patients was discussed at a weekly tumor board conference. HCC was diagnosed based on the presence of histopathological findings or imaging findings that were characteristic of HCC together with an increase in the serum α-fetoprotein level. The diameter of the tumor and the presence/absence of extrahepatic metastasis were confirmed using dynamic CT/MRI, ultrasound, or chest X-ray/CT prior to treatment. In our hospital, sorafenib is indicated for the treatment of patients with highly advanced HCC with a Child–Pugh score of either A or B. Informed consent for each treatment was obtained from all the patients before the initiation of treatment. This clinical study was conducted with the approval of the Ethics Committee of the National Cancer Center and was conducted in accordance with the ethical principals stated in the Japanese ethics guideline for epidemiological research.

Treatments

An oral dose of sorafenib at 400 mg was administered twice daily, after breakfast and dinner (800 mg/day). Treatment was continued as long as tolerability was observed without obvious disease progression. The dose was reduced or withdrawn and treatment was continued depending on the severity of adverse events. A dose increase up to 800 mg/day was permitted when the dose increase was judged possible in patients in whom the dose had been reduced.

For hepatic arterial infusion chemotherapy using cisplatin, intra-arterial cisplatin at a dose of 65 mg/m^2 was

administered over 20–40 min via a catheter inserted into the feeding arteries of the tumors. Treatment was repeated every 4–6 weeks for up to 6 courses until disease progression or unacceptable toxicities occurred. An infusion of 3,000 mL or more was administered on the day of treatment, and an infusion of 1,000 mL or more was continued for 3 days after administration to reduce renal toxicity caused by cisplatin; a diuretic (mannitol, furosemide, etc.) was administered as necessary to ensure an adequate urine volume.

Assessment and statistical analyses

Dynamic CT or MRI was used to confirm the anti-tumor effect every 1–2 months. The anti-tumor effect was evaluated using the Response Evaluation Criteria in Solid Tumors, version 1.0 (RECIST) [22], to judge the best overall response. The time to progression was defined as the period from the date of the start of treatment until the date of the confirmation of tumor progression by radiological evaluation or the day on which obvious tumor progression was judged to have occurred based on the clinical symptoms. Overall survival was defined as the period from the day of the start of treatment until the date of death or the final date of confirmed survival. A χ^2 test or Wilcoxon test was used to compare the patient characteristics and the anti-tumor effect between the sorafenib and the hepatic arterial infusion chemotherapy using cisplatin groups, and the Kaplan–Meier method was used to calculate the time to progression and the overall survival; the log-rank test was used to analyze differences between the groups. In a multivariate analysis, a Cox regression was used to analyze factors with $P < 0.10$ using a univariate analysis. $P < 0.05$ was judged to be statistically significant. JMP version 9.0 (SAS Institute Inc.) was used for the above statistical analyses.

Results

Patient characteristics

Table 1 shows the patient characteristics before each treatment. Age was significantly higher in the sorafenib group, although the medians were very similar (sorafenib group 71 years, cisplatin group 69 years). Although the Eastern Cooperative Oncology Group PS, the maximum tumor diameter, total bilirubin, AST, and ALT tended to be slightly worse in the cisplatin group, significant differences were not observed in the other parameters between the two groups. The median number of treatments in the cisplatin group was 2 (range 1–6 times). As a subsequent treatment, other systemic chemotherapy was performed in 14 patients, hepatic arterial infusion chemotherapy using cisplatin was performed in 7 patients, TACE was performed in 4 patients, and hepatic arterial infusion chemotherapy using 5-FU + interferon and radiotherapy was performed in one patient each in the sorafenib group; meanwhile, TACE was performed in 15 patients, hepatic arterial infusion chemotherapy using epirubicin was performed in 4 patients, other systemic chemotherapy was performed in 4 patients, hepatic arterial infusion chemotherapy using 5-FU + interferon was performed in 2 patients, and radiotherapy was performed in one patient in the cisplatin group. The median observation period was 9.4 months (range 2.1–31.6 months) in the sorafenib group and 7.5 months (range 0.8–43.1 months) in the cisplatin group; this difference was not statistically significant ($P = 0.44$).

Efficacy

The best overall response in the sorafenib group was evaluated as a complete response (CR) in one patient, a partial response (PR) in 2 patients, stable disease (SD) in 26 patients, progressive disease (PD) in 16 patients, and not evaluable (NE) in 3 patients. The response rate (CR + PR) was 6.3 % [95 % confidence interval (CI) 1.3–17.2 %], and the disease control rate (CD + PR + SD) was 60.4 % (95 % CI 45.3–74.2 %). The median time to progression and the progression-free rate at 6- and 12-months were 3.9 months, 32.6 %, and 12.1 %, respectively, while the median overall survival and the survival rate at 6-, 12-, and 24-months was 16.4 months, 88.9 %, 55.3 %, and 32.5 %, respectively, in the sorafenib group.

The best overall response in the cisplatin group was evaluated as a CR in 1 patient, PR in 0 patients, SD in 18 patients, PD in 39 patients, and NE in 8 patients. The response rate was 1.5 % (95 % CI 0.04–8.2 %), and a significant difference in the response rate, compared with the sorafenib group, was not observed ($P = 0.40$). The disease control rate was 28.8 % (95 % CI 18.3–41.3 %), which was significantly higher in the sorafenib group ($P = 0.001$). The median time to progression and the progression-free rate at 6- and 12-months in the cisplatin group was 2.0 months, 15.9 %, and 4.8 %, respectively, showing a significantly superior result in the sorafenib group (hazard ratio 0.44, $P < 0.01$) (Fig. 1). At the time of analysis, 21 patients had died because of tumor progression, and 1 patient had died because of hepatic failure in the sorafenib group. Additionally, 60 patients had died because of tumor progression, and 4 patients had died because of hepatic failure in the cisplatin group. The median survival time and the survival rate at 6-, 12-, and 24-months in the cisplatin group were 8.6 months, 62.0 %, 35.2 %, and 11.3 %, respectively, showing a significantly superior result in the sorafenib group (hazard ratio: 0.57,

Table 1 Patient characteristics

	Sorafenib		Cisplatin		*P* value
	n	(%)	*n*	(%)	
All patients	48	–	66	–	
Age (years)					
Median [range]	71	[53–83]	69	[40–82]	0.04
Sex					
Male	43	(90)	52	(79)	
Female	5	(10)	14	(21)	1.00
Performance status					
0	43	(90)	49	(74)	
1	5	(10)	17	(26)	0.07
HCVAb (positive)	32	(67)	45	(68)	1.00
HBsAg (positive)	7	(15)	8	(12)	0.92
Prior resection (present)	12	(25)	27	(41)	0.11
Prior ablation (present)	19	(40)	29	(44)	1.00
No. of prior TACE sessions					
Median [range]	4	[1–9]	4	[1–17]	0.86
Maximum tumor diameter (mm)					
Median [range]	30.5	[10–150]	40	[12–110]	0.07
Number of tumors					
1–3	8	(17)	13	(20)	0.32
≥4	40	(83)	53	(80)	0.64
Portal vein invasion (present)	9	(19)	16	(24)	0.64
Hepatic vein invasion (present)	3	(6)	4	(6)	0.99
Stage[a]					
II or III	38	(79)	49	(74)	
IVa	10	(21)	17	(26)	0.70
Ascites (present)	9	(19)	17	(26)	0.51
Child–Pugh class					
A	32	(67)	36	(55)	
B	16	(33)	30	(45)	0.27
Total bilirubin (mg/dL)					
Median [range]	0.9	[0.3–2.1]	1.1	[0.2–3.0]	0.02
Albumin (g/dL)					
Median [range]	3.5	[2.3–4.8]	3.3	[2.4–4.5]	0.21
AST (U/L)					
Median [range]	54	[20–165]	88	[35–287]	0.04
ALT (U/L)					
Median [range]	43	[10–139]	62	[22–187]	0.05
Prothrombin time (%)					
Median [range]	78	[40–107]	73	[48–104]	0.39
α-Fetoprotein (ng/mL)					
Median [range]	70.3	[1.3–218876]	324.3	[1.7–210200]	0.59
PIVKAII (mAU/mL)					
Median [range]	505.5	[11–291330]	438	[11–96390]	0.65
Subsequent treatments (present)	27	(56)	26	(39)	0.11

HCVAb hepatitis C viral antibody, *HBsAg* hepatitis B surface antigen, *TACE* transcatheter arterial chemoembolization, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PIVKAII* protein induced by vitamin K absence or antagonists-II

[a] Japanese classification of primary liver cancer

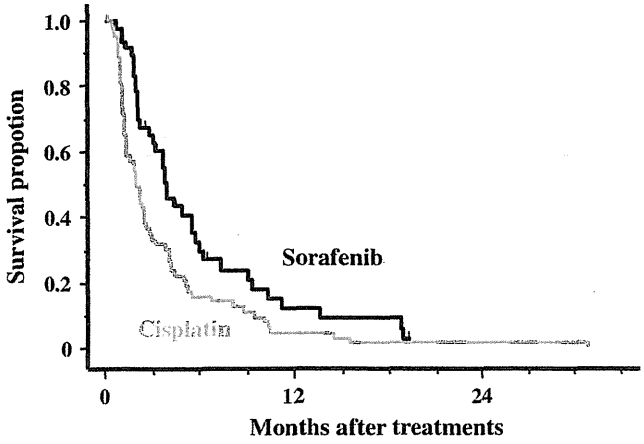

Fig. 1 Comparison of time to progression between sorafenib and hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to transcatheter arterial chemoembolization (TACE)

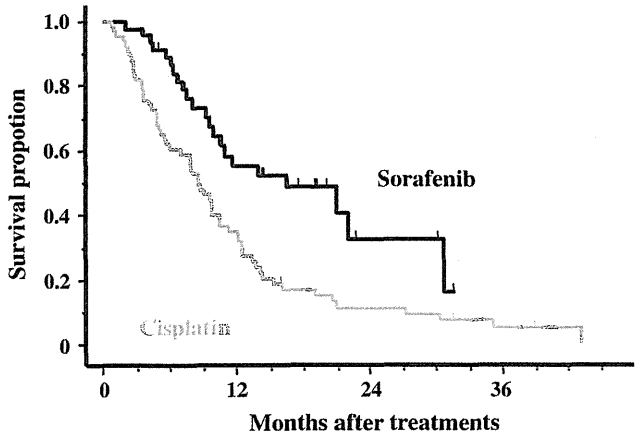

Fig. 2 Comparison of overall survival between sorafenib and hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to TACE

$P < 0.001$) (Fig. 2). The same analysis was performed for patients limited to Child–Pugh A, since sorafenib is widely recommended for the treatment of patients with Child–Pugh A. The results were similar, although the disease control rate and the time to progression were not statistically significant (data not shown).

Toxicity

Serious adverse events (SAE) occurred in two patients (1 patient, grade 4 hepatic encephalopathy; 1 patient, grade 3 erythema multiforme) in the sorafenib group, but none of the patients in the cisplatin group experienced an SAE. Thirty-eight patients (79 %) required a sorafenib dose reduction because of adverse events, such as liver dysfunction, hand-foot syndrome, or rashes, and treatment was discontinued in 7 patients (14 %) because of adverse events, such as liver dysfunction, hepatic encephalopathy, or erythema multiforme. On the other hand, none of the patients required a cisplatin dose reduction, and treatment was discontinued in 6 patients (9.1 %) because of adverse events, such as liver dysfunction, fatigue, or nausea/anorexia.

Predictive factors of time to progression and overall survival

Univariate analyses were performed to identify the factors that contributed to the prolongation of time to progression in patients who were refractory to TACE (Table 2). The univariate analyses showed that the significant factors that contributed to the prolongation of the time to progression ($P < 0.10$) were an age >65 years, a PS of 0, a maximum tumor diameter ≤3.0 cm, the absence of hepatic vein invasion, the absence of ascites, a bilirubin level ≤1.2 mg/dL, an α-fetoprotein level <1,000 ng/mL, and sorafenib treatment. A multivariate analysis was performed for the factors that showed a significant tendency ($P < 0.10$) in the univariate analysis, and the absence of hepatic vein invasion and sorafenib treatment were significant independent factors that contributed to the prolongation of the time to progression (Table 3). Univariate analyses were performed to identify the factors that contributed to survival prolongation in patients who were refractory to TACE (Table 2). The univariate analyses showed that the significant factors that contributed to the prolongation of survival ($P < 0.10$) were an age >65 years, a PS of 0, a maximum tumor diameter of ≤3.0 cm, 3 or fewer tumors, the absence of hepatic vein invasion, Child–Pugh class A, the absence of ascites, an albumin level >3.5 g/dL, a bilirubin level ≤1.2 mg/dL, an AST level <100 U/L, an α-fetoprotein level <1,000 ng/mL, a protein induced by vitamin K absence or antagonist-II (PIVKA-II) level <1,000 mAU/mL, and sorafenib treatment. A multivariate analysis was performed for the factors showing a significant tendency at $P < 0.10$, and the significant independent favorable prognosis factors were a PS of 0, 3 or fewer tumors, Child–Pugh A, an α-fetoprotein level <1,000 ng/mL, a PIVKA-II level <1,000 mAU/mL, and treatment with sorafenib (Table 3). Treatment with sorafenib had the smallest hazard ratio among these prognostic factors.

Discussion

Patients with vascular invasion, extrahepatic metastasis, and who are refractory to TACE are good candidates for sorafenib [5, 9, 10]. However, the efficacy of sorafenib in patients who are refractory to TACE has not been previously reported, although the outcome of patients with prior

Table 2 Univariate analysis of time to progression and overall survival time in patients refractory to transcatheter arterial chemoembolization treated with sorafenib or intra-arterial cisplatin

	n	Time to progression			Overall survival		
		Median (months)	Hazard ratio	*P* value	Median (months)	Hazard ratio	*P* value
Sex							
Female	19	2.9	1.01 (0.60–1.68)	0.98	10.5	0.92 (0.51–1.68)	0.79
Male	95	2.6			9.8		
Age (years)							
≤65	33	2.0	1.41 (0.92–2.14)	0.11	8.0	1.65 (1.03–2.66)	0.03
>65	81	3.0			11.4		
Performance status							
0	92	3.2	0.58 (0.35–0.95)	0.03	11.4	0.38 (0.22–0.66)	<0.001
1–2	22	1.6			4.8		
HCVAb							
Negative	37	2.8	0.82 (0.53–1.25)	0.35	9.9	0.72 (0.45–1.18)	0.19
Positive	77	2.5			9.8		
HBsAg							
Negative	99	3.0	0.86 (0.50–1.50)	0.60	9.9	1.09 (0.54–2.17)	0.82
Positive	15	2.1			9.8		
Maximum tumor diameter (cm)							
≤3.0	39	4.0	0.65 (0.43–0.99)	0.04	12.3	0.56 (0.34–0.83)	0.02
>3.0	75	2.2			8.7		
No. of tumors							
≤3	21	4.4	0.78 (0.48–1.29)	0.33	13.8	0.68 (0.39–1.19)	0.06
>3	93	2.4			8.0		
Portal vein invasion							
Present	25	3.2	0.89 (0.55–1.43)	0.62	5.4	1.34 (0.79–2.27)	0.23
Absent	89	2.6			8.7		
Hepatic vein invasion							
Present	7	2.5	2.12 (0.97–4.66)	0.05	4.8	2.17 (0.94–5.03)	0.13
Absent	107	2.8			9.2		
Stage[a]							
II or III	87	2.8	0.94 (0.59–1.48)	0.77	11.6	0.64 (0.39–1.07)	0.08
IV	27	2.5			6.2		
Child–Pugh class							
A	68	3.2	0.84 (0.56–1.26)	0.39	9.5	0.65 (0.41–1.01)	0.08
B	46	2.2			7.8		
Ascites							
Present	26	2.2	1.56 (0.98–2.47)	0.06	5.6	2.15 (1.32–3.53)	0.01
Absent	88	2.9			9.2		
Albumin (g/dL)							
≤3.5	76	2.4	1.17 (0.78–1.77)	0.44	7.8	1.90 (1.16–3.11)	0.02
>3.5	38	3.8			10.6		
Total bilirubin (mg/dL)							
≤1.2	81	3.2	0.66 (0.42–1.02)	0.06	11.6	0.42 (0.26–0.66)	<0.001
>1.2	33	1.6			4.8		
Prothrombin time (%)							
<70	42	2.9	0.95 (0.63–1.42)	0.79	10.5	0.93 (0.59–1.47)	0.77
≥70	72	2.5			9.9		

Table 2 continued

	n	Time to progression			Overall survival		
		Median (months)	Hazard ratio	*P* value	Median (months)	Hazard ratio	*P* value
AST (U/L)							
<100	82	3.0	0.86 (0.55–1.35)	0.50	12.3	0.44 (0.27–0.70)	<0.001
≥100	32	2.2			5.5		
ALT (U/L)							
<100	97	2.6	0.90 (0.52–1.56)	0.70	9.9	0.85 (0.44–1.57)	0.59
≥100	17	2.5			8.5		
α-Fetoprotein (ng/mL)							
<1,000	71	3.8	0.60 (0.40–0.91)	0.01	12.2	0.61 (0.39–0.96)	0.03
≥1,000	43	2.1			7.1		
PIVKA-II (mAU/mL)							
<1,000	67	3.1	0.78 (0.52–1.16)	0.22	10.6	0.62 (0.40–0.96)	0.03
≥1,000	45	2.1			9.5		
Treatments							
Sorafenib	48	3.9	0.57 (0.38–0.86)	0.01	16.4	0.44 (0.27–0.72)	<0.001
Cisplatin	66	2.0			8.6		

HCVAb hepatitis C viral antibody, *HBsAg* hepatitis B surface antigen, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PIVKAII* protein induced by vitamin K absence or antagonists-II

[a] Japanese classification of primary liver cancer

Table 3 Multivariate analysis of overall survival and time to progression in patients refractory to TACE

	Hazard ratio	*P* value
Time to progression		
Hepatic vein invasion: present	0.41 (0.19–0.91)	0.03
Treatment: sorafenib	0.55 (0.37–0.83)	0.004
Overall survival		
Performance status: 0	0.46 (0.27–0.81)	0.006
No. of tumors: ≤3	0.51 (0.29–0.91)	0.02
Child–Pugh class: A	0.44 (0.27–0.71)	0.001
α-Fetoprotein: <1,000 ng/mL	0.52 (0.22–0.84)	0.008
PIVKA-II: <1,000 mAU/mL	0.47 (0.29–0.76)	0.002
Treatment: sorafenib	0.42 (0.25–0.77)	0.001

TACE has been reported [11, 12]. We retrospectively evaluated the efficacy of sorafenib in patients who were refractory to TACE. The following data were obtained: the response rate (CR + PR) was 6.3 %, the disease control rate (CD + PR + SD) was 60.4 %, and the median time to progression was 3.9 months; these results were comparable to those obtained for sorafenib to date [7, 8]. The median survival time of 16.4 months was regarded as favorable. The patients who were refractory to TACE have a lower frequency of vascular invasion, which is a significant predictor of a poor prognosis in patients with advanced HCC. In addition, most of the TACE refractory patients had an intermediate BCLC stage. The TACE refractory patients in this study (proportion of advanced stage 33 %) had a better BCLC stage than the patients in previous trials (proportion of advanced stage SHARP, 82 %; Asia-Pacific trial, 95.3 %). Favorable tendencies, therefore, might be shown for the overall survival of a subgroup of patients who are refractory to TACE among advanced HCC patients in whom sorafenib treatment is indicated.

A definition of "refractory to TACE" has not yet been established. In this study, the definition of "refractory to TACE" was regarded as progression or a tumor shrinkage rate of <25 % in hypervascular lesions as visualized using dynamic CT and/or MRI after 1–3 months of TACE. According to the consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology 2010 [5], however, "refractory to TACE" is defined as two or over consecutive incomplete necrotic reactions or the appearance of a new lesion, vascular invasion, or extrahepatic metastases. Although a consensus has not been reached among clinicians, this is a critical issue when considering a conversion from TACE to sorafenib treatment in patients with unresectable HCC.

In the present study, sorafenib was compared with hepatic arterial infusion chemotherapy using cisplatin, which was used before the introduction of sorafenib. A consensus on a standard therapy has not been attained for hepatic arterial infusion chemotherapy, since its survival benefit has not been elucidated [10]. However, this regimen is still frequently used in Japan, because favorable antitumor effects and long-term survivals have been seen in a

few patients [15–21]. Nonetheless, hepatic arterial infusion chemotherapy has not been reported to have favorable results in patients who are refractory to TACE [13, 14]. Regarding hepatic arterial infusion chemotherapy using cisplatin in patients who were refractory to TACE ($n = 84$), the response rate at out-patient hospitals was 3.6 %, the median time to progression was 1.7 months, and the median overall survival period was 7.1 months [13], while the results of a phase II study of hepatic arterial infusion chemotherapy using cisplatin in patients with unresectable HCC ($n = 80$) were favorable, with a response rate of 33.8 % and a 1-year survival rate of 67.5 % [15]. One possible reason for the difference between these studies might be differences in the characteristics of the study populations. Most patients in the phase II trial of cisplatin were TACE-naïve, whereas only patients with TACE-refractory disease were included in the present study. Thus, hepatic arterial infusion chemotherapy may not be expected to show favorable therapeutic results when the patients are limited to those refractory to TACE, although the reason remains unknown. Therefore, the results were compared with those for patients who were refractory to TACE and were treated with sorafenib. Although the patient age was significantly higher in the sorafenib group and the PS and tumor size was slightly worse in the cisplatin group, no other significant differences in the patient characteristics were observed between the two groups. The response rate was comparable, but the sorafenib group showed significantly higher results for the disease control rate, time to progression, and overall survival. We also performed a multivariate analysis to examine the factors that contributed to the time to progression and overall survival in patients who were refractory to TACE, and treatment with sorafenib was one of the significant factors. These results suggest that sorafenib, rather than hepatic arterial infusion chemotherapy using cisplatin, might be the treatment of first choice in patients who are refractory to TACE. This outcome might not have much impact in overseas settings, where hepatic arterial infusion chemotherapy is less popular, but it is quite disappointing in Japan, since hepatic arterial infusion chemotherapy using cisplatin was expected to show a therapeutic effect comparable to that of sorafenib.

The present study has some limitations. First, the results for sorafenib treatment in patients who were refractory to TACE were obtained as part of a single-site, retrospective study. A prospective study enrolling only patients who are refractory to TACE should be performed in the future to verify the efficacy of sorafenib in patients who are refractory to TACE. Second, the periods of treatment differed between the sorafenib group and the cisplatin group. Third, the influence of subsequent treatment on the overall survival cannot be denied. Hepatic arterial infusion chemotherapy using cisplatin was administered as a subsequent treatment in 7 patients in the sorafenib group, whereas patients in the cisplatin group were not treated with sorafenib. Still, the anti-tumor effect of hepatic arterial infusion chemotherapy using cisplatin following sorafenib was PD in all the patients, and the impact would have been negligible. Finally, considering the possible selection bias in therapeutic policy after the introduction of sorafenib, we selected patients with different periods of treatment, but the results might also have been affected by the difference in periods. Also, no significant differences in the patient characteristics, except for age, total bilirubin, and AST, were seen between the sorafenib and the hepatic arterial infusion chemotherapy using cisplatin group, but subtle differences in the patient characteristics might have affected the favorable results for sorafenib, since this study was a retrospective comparison.

In conclusion, sorafenib showed a favorable efficacy in patients who were refractory to TACE, resulting in a significantly higher disease control rate, longer time to progression, and longer overall survival compared with hepatic arterial infusion chemotherapy using cisplatin. Thus, sorafenib, rather than hepatic arterial infusion chemotherapy, should be considered as the first-line therapy for patients who are refractory to TACE in the future.

Acknowledgments This work was supported in part by Grants-in-Aid for Cancer Research and for the Third-Term Comprehensive 10-Year Strategy for Cancer Control from the Ministry of Health, Labour, and Welfare of Japan.

Conflict of interest The authors declare that they have no conflict of interest.

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European Journal of Radiology 83 (2014) e23–e35

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Primary staging of laryngeal and hypopharyngeal cancer: CT, MR imaging and dual-energy CT

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ARTICLE INFO

Article history:
Received 12 April 2013
Received in revised form 23 July 2013
Accepted 20 October 2013

Keywords:
Laryngeal cancer
Hypopharyngeal cancer
Computed tomography
Magnetic resonance imaging
Dual-energy CT
Staging

ABSTRACT

Laryngeal and hypopharyngeal cancer, in particular T4a disease associated with cartilage invasion and extralaryngeal spread, needs to be evaluated accurately because treatment can impact heavily on a patient's quality of life. Reliable imaging tools are therefore indispensible. CT offers high spatial and temporal resolution and remains the preferred imaging modality. Although cartilage invasion can be diagnosed with acceptable accuracy by applying defined criteria for combinations of erosion, lysis and transmural extralaryngeal spread, iodine-enhanced tumors and non-ossified cartilage are sometimes difficult to distinguish. MR offers high contrast resolution for images without motion artifacts, although inflammatory changes in cartilage sometimes resemble cartilage invasion. With dual-energy CT, combined iodine overlay images and weighted average images can be used for evaluation of cartilage invasion, since iodine enhancement is evident in tumor tissue but not in cartilage. Extralaryngeal spread can be evaluated from CT, MR or dual-energy CT images and the routes of tumor spread into the extralaryngeal soft tissue must be considered; (1) via the thyrohyoid membrane along the superior laryngeal neurovascular bundle, (2) via the inferior pharyngeal constrictor muscle, and (3) via the cricothyroid membrane. Radiologists need to understand the advantages and limitations of each imaging modality for staging of laryngeal and hypopharyngeal cancer.

1. Introduction

Laryngeal and hypopharyngeal cancers are common malignant tumors in the head and neck, and most of such cases are squamous cell carcinomas [1]. In view of the functional and social importance of the larynx, any decision about the optimal management strategy for laryngeal or hypopharyngeal cancer must involve consideration of both potential survival and the functional consequences of any given treatment approach. Patients with T1, T2 and limited cartilage invasion disease can be considered positively for organ-preserving procedures such as radiation therapy alone, a combination of chemotherapy and radiation therapy, and function-preserving partial laryngectomy procedures [2–6]. Patients with T4a disease, particularly when the tumor extends through the cartilage into the soft tissue of the neck, often need aggressive treatments such as total laryngectomy [2,7,8], because the risks of recurrence and cartilage necrosis after radiotherapy alone are high [2–4]. Both CT and MR imaging are routinely used to differentiate between limited and gross cartilage invasion. However, cartilage invasion is sometimes overestimated, resulting in unnecessary total laryngectomies in some patients [9,10].

Currently, dual-energy CT is being investigated in several clinical fields [11–15], including the evaluation of head and neck cancer [16]. Since treatment is decided according to the precise extent and invasion pattern of a tumor, the findings of these imaging procedures play a crucial role in any multidisciplinary approach for management of laryngeal and hypopharyngeal cancer [17–19]. Rapid technological developments in recent years have made it necessary for all members of multidisciplinary teams to understand the

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http://dx.doi.org/10.1016/j.ejrad.2013.10.022

Table 1
Primary tumor (T) staging according to the American Joint Committee on Cancer (AJCC) 7th edition (modified version by author).

	Laryngeal cancer			Hypopharyngeal cancer
	Supraglottic	Glottic	Subglottic	
T1	One subsite	(a) One vocal cord (b) both vocal cords	Limited to subglottis	≤2 cm and limited to one subsite
T2	More than one subsite	Extends to supra/sub glottis Impaired vocal cord mobility	Extends to glottis	>2–4 cm or more than one subsite
T3	PGS/PES or vocal cord fixation Inner cortex of thyroid cartilage Extends to postcricoid	PGS or vocal cord fixation Inner cortex of thyroid cartilage	Vocal cord fixation	>4 cm or vocal cord fixation
T4a	Tumor invades through the thyroid cartilage or extra-laryngeal spread		Tumor invades thyroid/cricoid cartilage or extra-laryngeal spread	
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures			

Note: PGS = paraglottic space; PES = preepiglottic space.

potential applications, limitations, and appropriate criteria of these imaging modalities.

In this article, we review the significant role of imaging for staging of laryngeal and hypopharyngeal cancer. We discuss the appearances of T4a disease on conventional CT and MR images and illustrate how dual-energy CT can be applied for evaluation of laryngeal and hypopharyngeal cancer.

2. Primary tumor staging (T) of laryngeal and hypopharyngeal cancer

The system for staging of primary laryngeal (glottic, supraglottic and subglottic) and hypopharyngeal cancer is outlined in Table 1 (American Joint Committee on Cancer 2010) [20]. Clinical staging of the primary site is based on involvement of various subsites of the larynx or adjacent regions of the pharynx and vocal cord mobility. Assessment of the primary tumor is initially accomplished by clinical inspection, using indirect mirror and direct endoscopic examination with a fiberoptic nasolaryngoscope. However, these tumors have a tendency to spread submucosally, and this extension into deeply seated tissue planes can be easily missed by clinical examination alone [8,17,19]. Therefore, clinicians rely on imaging to predict which patients will have T3–4 disease. Even if the primary tumor has been clinically diagnosed as T1–2 disease on the basis of inspection, imaging is an important adjunct to exclude any T3–4 factor features or the presence of submucosal extension [8,21–23]. Therefore, cross-sectional imaging using CT or MR imaging is mandatory for completing the staging process, and should be included in the diagnostic workup.

For laryngeal cancer, the first imaging criterion that defines T3 lesions is extension into the paraglottic and/or preepiglottic space, irrespective of vocal cord mobility. In addition, tumor erosion limited to the inner cortex of the thyroid cartilage indicates a T3 lesion, whereas erosion of the outer cortex of the thyroid cartilage define a T4a tumor. For hypopharyngeal cancer, unlike the larynx, criteria that define T3 lesions are based on vocal cord mobility and tumor diameter only. Hypopharyngeal cancer with invasion of the thyroid or cricoid cartilage indicates a T4a lesion, even in cases of localized cartilage invasion. In any event, accurate staging requires diagnosis of subtle cartilage invasion.

Extralaryngeal tumor spread is also one of the important predictors of T4a disease, with or without cartilage invasion, in laryngeal and hypopharyngeal cancer.

3. Technical considerations for CT, MR imaging and dual-energy CT

3.1. Conventional CT

CT is the preferred imaging method for staging of laryngeal and hypopharyngeal cancer. The images are obtained with the patient supine and during quiet respiration (not while holding the breath). The neck should be in slight extension, and the head is aligned along the cephalocaudal axis to allow comparison of symmetrical structures. Malpositioning may create an appearance that simulates disease. Every effort should be made to make the patient feel comfortable. When a small tumor is suspected, the patient may be scanned during a modified Vasalva maneuver or during phonation to open the piriform sinuses [24,25]. Typically, a 100-mL injection of 300 mgI/mL iodinated contrast medium is injected at a rate of 2.5 mL/s and the scan is initiated 70 s after the start of the injection, proceeding in a cranio-caudal direction. The scan range is set from the base of the skull to the bottom of the neck. Reconstructed images are generated as frontal and coronal sections parallel and vertical to the vocal cords from 1 cm above the hyoid bone to the inferior margin of the cricoid cartilage (2-mm thickness and 16-cm field of view).

3.2. MR imaging

MR imaging is also obtained with the patient supine and during quiet respiration. Axial T2-weighted fast spin echo (FSE) and T1-weighted FSE images are obtained with a scan orientation parallel to the true vocal cords. Typical image parameters for a standard examination include a slice thickness of 3 mm with a 1-mm intersection gap. Additional axial fat-saturated T1-weighted fast field echo (FFE) images after intravenous administration of gadolinium chelates are obtained routinely. When evaluations using CT alone are insufficient to determine cartilage invasion, the following 3D sequences are additionally performed within the area from 1 cm above the hyoid bone to the inferior margin of the cricoid cartilage: a 3D-T2-weighted image (3D-T2WI) is acquired in the transverse plane with a 3D volume isotropic T2-weighted acquisition (VISTA) sequence (TR/TE, 1,100/91 with Driven Equilibrium [DRIVE] technique; flip angle, 90; field of view, 230 mm; matrix, 190 × 448; slice thickness/gap, 1.5 mm/0 mm). A 3D-T1-weighted image (3D-T1WI) is then acquired in the transverse plane with a 3D Turbo Field Echo (TFE) sequence unenhanced (TR/TE, 6/2.3; flip angle,

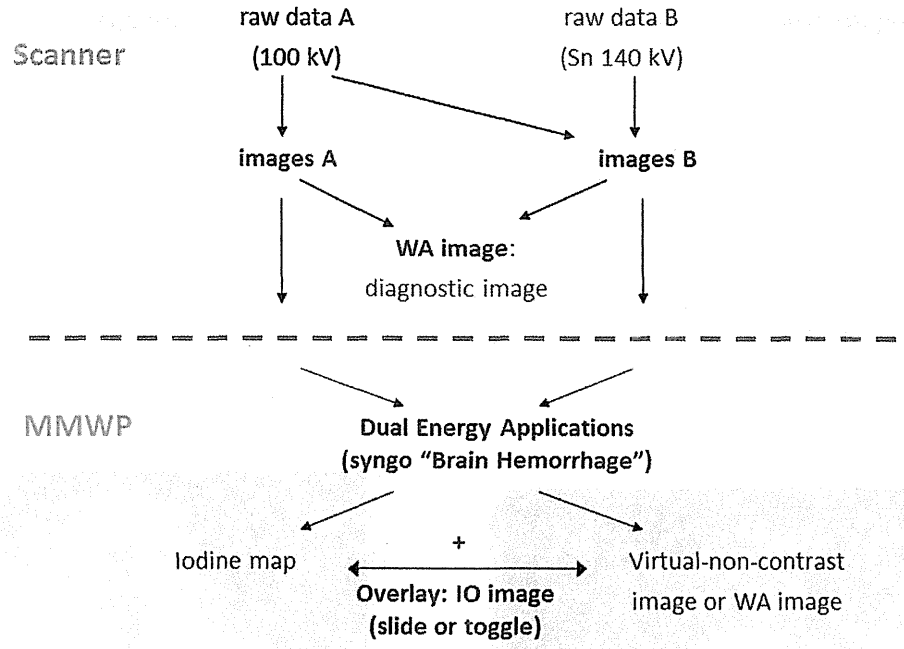

Fig. 1. Flow chart showing an overview of post-processing. Weighted-average (WA) CT images are generated by fusing data sets acquired with different tube voltages (100 and 140 kV). WA images resemble conventional CT images. Iodine overlay (IO) images are generated by fusing virtual non-contrast images and iodine images at a ratio of 0.5.

15; field of view, 230 mm; matrix, 224 × 224; slice thickness/gap, 1.0 mm/0 mm) and fat saturated contrast-enhanced (TR/TE, 6/1.15; flip angle, 15; field of view, 230 mm; matrix, 224 × 224; slice thickness/gap, 1.0 mm/0 mm). Images in the coronal or sagittal plane may be obtained in order to evaluate certain anatomic spaces, such as the preepiglottic space in the sagittal plane, or the paraglottic space and the ventricle in the coronal plane.

3.3. Dual-energy CT

3.3.1. Basic principles

Single-energy CT generates images based on the X-ray absorption coefficient of scanned tissues, and according to their density the tissues are assigned a CT value and displayed as a grey scale. As a result, it may be difficult to differentiate materials of different chemical composition, such as iodine and bone or iodine-enhanced lesions and cartilage, as they have the same CT value on CT images [8,26]. This difficulty can be overcome for some materials using dual-energy CT [15,27,28] which exploits the dependence of the absorption coefficient on the energy of the X-ray spectrum, or kV setting, used for the scan [13,29–31]. For example, materials such as iodine have lower CT values at high X-ray energies than at low X-ray energies, whereas fat tissue shows the opposite behavior. The CT value of water, soft tissue and blood stays almost constant at all X-ray energies.

In practice, two CT images taken at different tube voltages, typically 80 or 100 kV and 140 kV, are sufficient to classify many tissues. Different scan techniques have been developed to acquire dual-energy CT data sets; dual-source dual-energy CT, dual-energy CT with fast kilovolt switching, and multilayered-detector dual-energy CT [32,33]. Here, we limit our discussion to dual-source dual-energy CT [33,34], used at our institution.

Several algorithms can be used to extract material information and generate material maps or remove materials from images. A three-material decomposition algorithm applied to each voxel of an iodine-enhanced dual-energy CT image set makes it possible to compute iodine maps and virtual non-contrast images. Three materials have to be predefined for this algorithm according to the scanned body area: for example iodine, soft tissue and air are chosen for lung imaging [14], and iodine, fat and tissue for liver imaging [33]. For the head-neck region, the materials are set to iodine, brain parenchyma and hemorrhage [12,16].

3.3.2. Dual-energy CT protocol

For dual-source dual-energy CT scans using 128-slice dual-source CT (SOMATOM Definition Flash; Siemens Healthcare, Forchheim, Germany), the following parameters are applied: 100 and 140 kV tube voltages with a 0.4-mm tin filter (labeled as Sn140 kV), 200 and 200 effective mAs, 0.33-s rotation time, 32 × 0.6-mm collimation with a z-flying focal spot, and a pitch of 0.6. The tin filter blocks low-energy X-rays from the 140 kV spectrum, thus reducing radiation to the patient and enhancing energy separation of X-rays from the low and high kV X-ray tubes. These parameters result in an average CT dose index of 14–15 mGy, which is equivalent to that of single-energy CT scans. Noise needs to be minimized to ensure precise three-material decomposition in the head and neck, where many heterogeneous structures such as cartilage, soft tissues and air in the trachea require a high image resolution. A voltage combination of 100 kV and Sn140 kV, rather than 80 and 140 kV, is chosen to minimize noise while maximizing the separation of the X-ray tubes' energy spectra. The methods of contrast material injection are the same as for conventional CT.

3.3.3. Image reconstruction and post-processing

The image reconstruction and post-processing flow is shown in Fig. 1: two sets of raw data (100 kV and Sn140 kV) are separately reconstructed from the acquired dual-energy data using a 1-mm slice thickness and 0.7-mm increment, and a third, WA image set is generated at the same time, linearly weighing and fusing each pixel of the 100-kV and Sn140 kV data (p100 and p140, respectively) at the default ratio of $w = 0.5$ according to the following formula: $[w \times \text{p100}] + [(1 - w) \times \text{p140}]$. A medium sharp D30f kernel is applied for all reconstructions. WA images are used as diagnostic images since they are equivalent in terms of image quality to single-energy 120 kV CT images [35,36].

Next, the images are post-processed on a separate workstation (MMWP; Siemens Healthcare), and three-material-decomposition analysis (Syngo Dual Energy, Brain Hemorrhage; Siemens

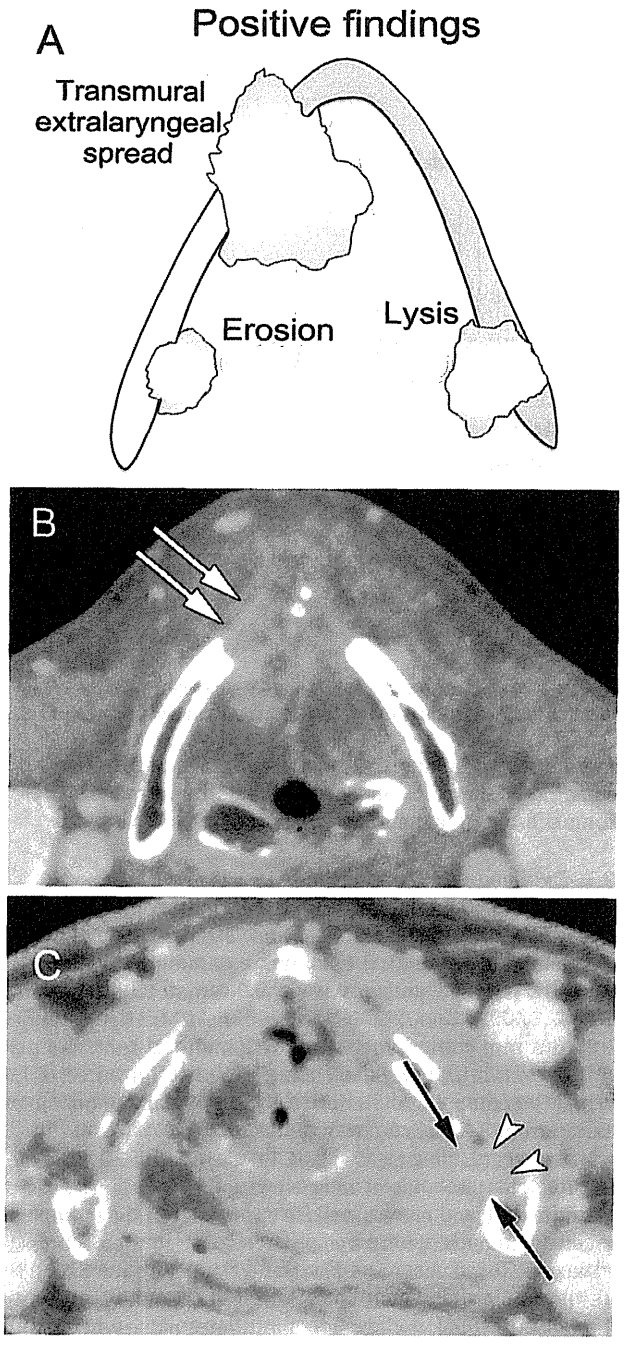

Fig. 2. (A) Drawing to illustrate the criteria for evaluation of thyroid cartilage invasion. Erosion is defined as invasion beyond the inner cortex without reaching the outer cortex (less than half of the cartilage width), lysis is defined as almost reaching the outer cortex but with preservation of the cortex, and extralaryngeal spread is defined as all-layer invasion through both the inner and outer cortex (penetration) of the cartilage, including the extralaryngeal soft tissues. (B) Positive finding of invasion through the outer cortex of the thyroid cartilage in a 56-year-old man with glottic cancer. Axial contrast-enhanced CT image at the level of the vocal cords shows tumor invasion into the thyroid cartilage, spreading into the extralaryngeal soft tissue (white arrows). (C) Positive finding of thyroid cartilage lysis in a 69-year-old man with hypopharyngeal cancer. Axial contrast-enhanced CT image at the glottic level shows a tumor mass arising from the left piriform sinus. The inner cortex of the left thyroid cartilage shows disappearance of a thin hypo-attenuated line between the tumor and the cartilage (arrows), and substitution of cartilage with tumor tissue as demonstrated by CT attenuation (arrowheads).

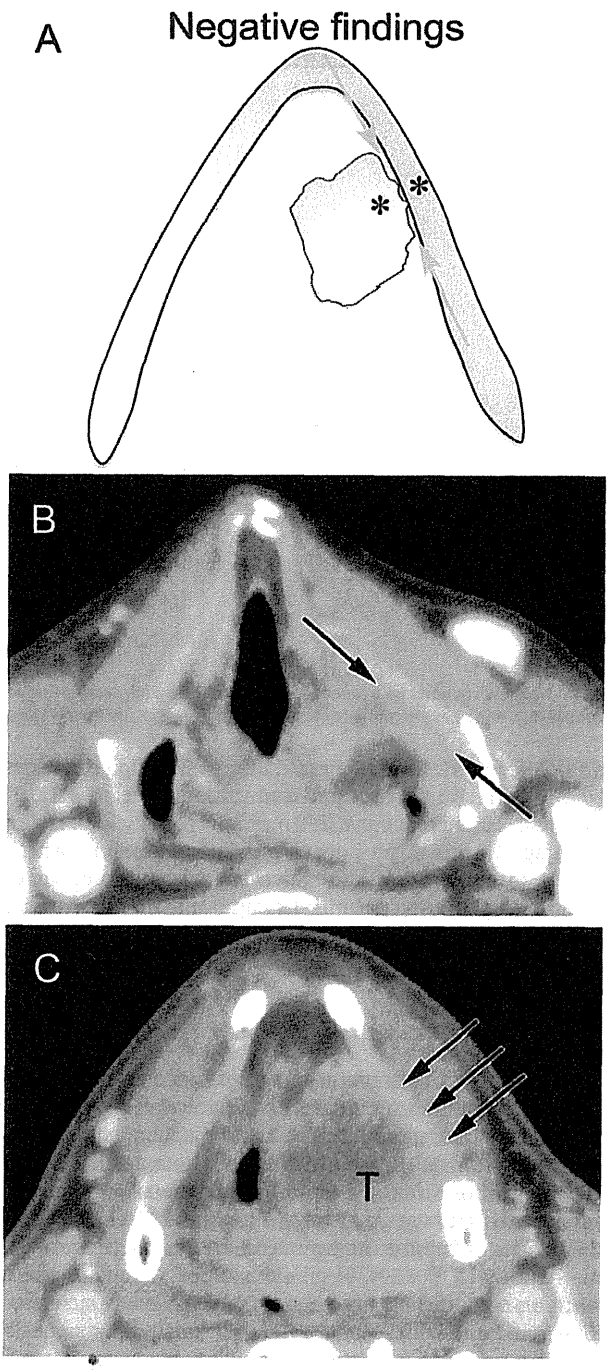

Fig. 3. (A) Drawing to illustrate the criteria for negative thyroid cartilage invasion based on two concurrent findings: (1) perfect or almost continuously defined thin hypo-attenuated line between the tumor and the cartilage (arrows), (2) difference in CT attenuation between non-ossifying cartilage and the tumor (asterisks). (B) Negative finding of thyroid cartilage invasion in a 67-year-old man with hypopharyngeal cancer. Axial contrast-enhanced CT image at the level of the false vocal cords shows a tumor mass arising from the left piriform sinus, but preservation of a dark line between the tumor and the cartilage is evident (arrows). (C) Negative finding of thyroid cartilage invasion in a 61-year-old man with hypopharyngeal cancer. Axial contrast-enhanced CT image at the supraglottic level shows a tumor mass arising from the left piriform sinus. CT attenuation of the non-ossifying cartilage (arrows) is different from that of the tumor (T).

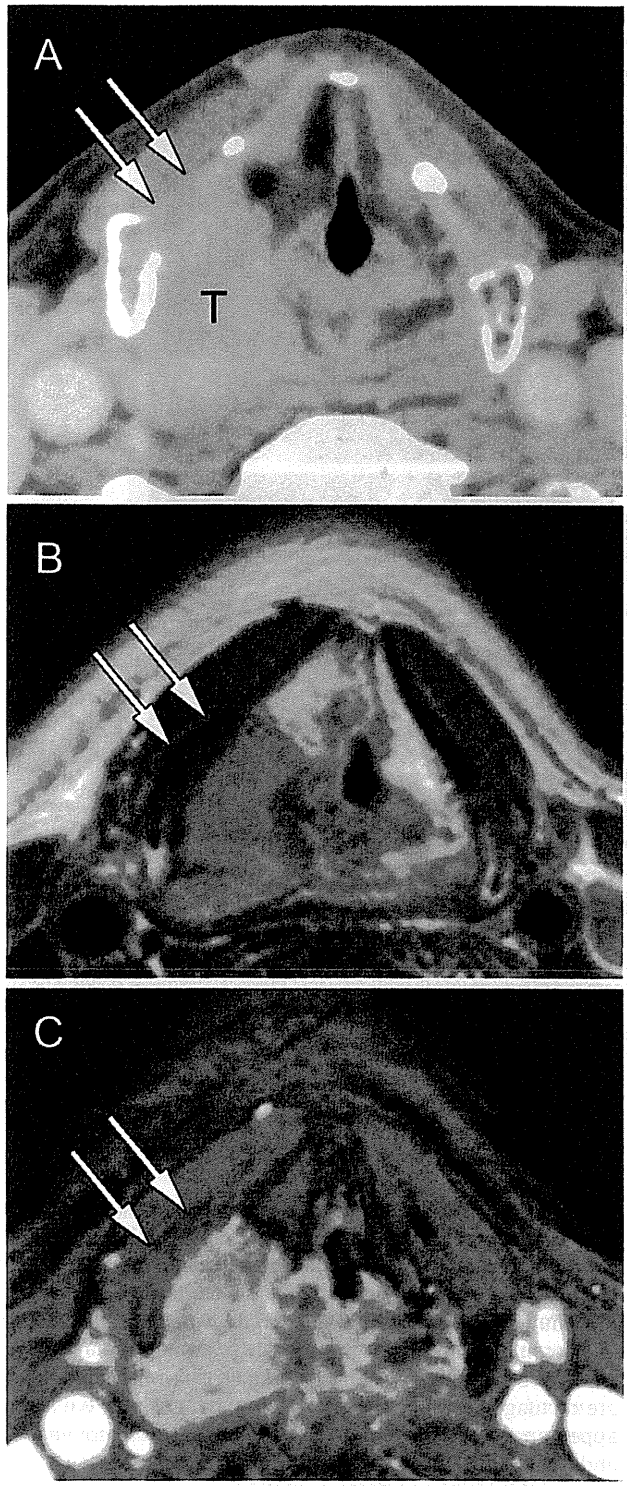

Fig. 4. True negative finding for thyroid cartilage invasion by MR imaging in a 69-year-old man with hypopharyngeal cancer. (A) Axial contrast-enhanced CT image at the level of the false vocal cords shows tumor mass (T) arising from the right piriform sinus. The tumor is located adjacent to non-ossified cartilage of the right thyroid lamina, and the tumor and cartilage show similar CT values, making them almost indistinguishable (arrows). (B) T2-weighted MR image obtained at the same level shows a right-sided piriform sinus tumor with intermediate signal intensity. The adjacent right thyroid lamina can be differentiated by its low signal intensity (arrows). (C) Fat-suppressed contrast-enhanced T1-weighted image shows contrast enhancement of the tumor mass and poor enhancement of the thyroid lamina (arrows) relative to the adjacent tumor mass. Pathological findings confirmed that there was no tumor cell infiltration into the cartilage.

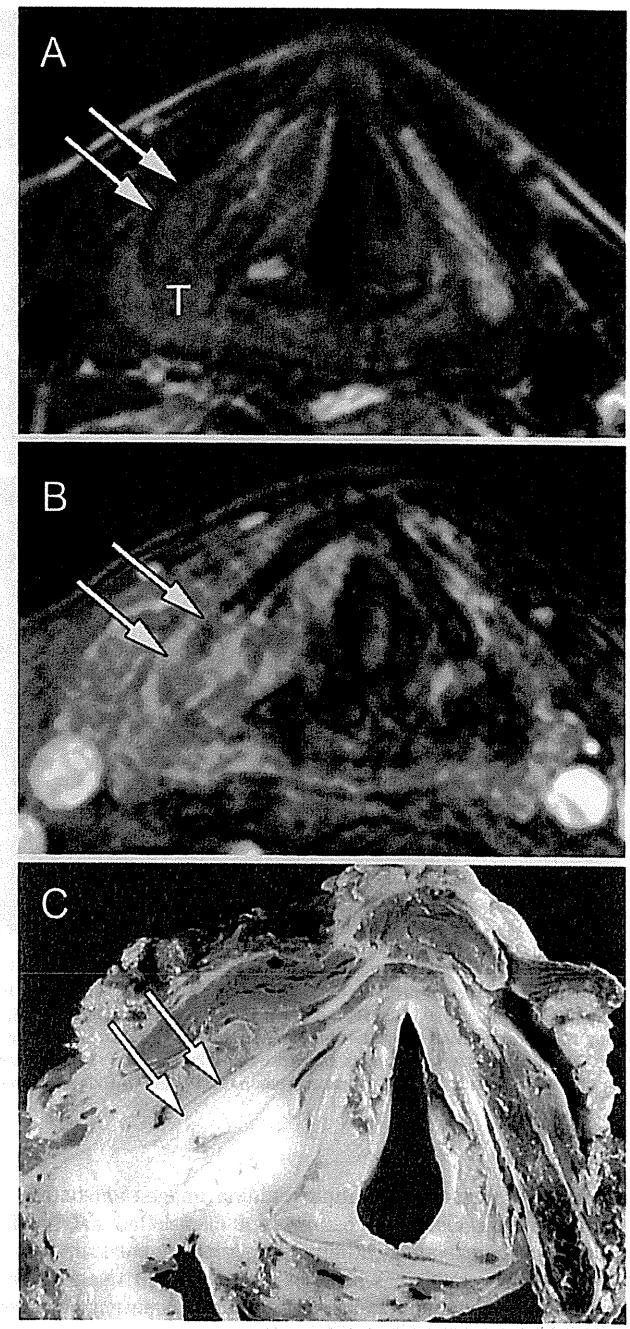

Fig. 5. Positive finding of thyroid cartilage invasion on MR imaging in a 69-year-old man with hypopharyngeal cancer. (A) Axial T2-weighted image at the level of the vocal cords shows a tumor mass (T) arising from the right piriform sinus with intermediate signal intensity. The adjacent right thyroid cartilage shows a similar signal intensity (arrows). (B) Fat-suppressed contrast-enhanced T1-weighted image shows enhancement of the tumor mass and similar enhancement of the adjacent thyroid lamina (arrows). (C) Corresponding axial slice from the surgical specimen at the same level confirms that the posterior thyroid cartilage has been invaded by the tumor cells (arrows).

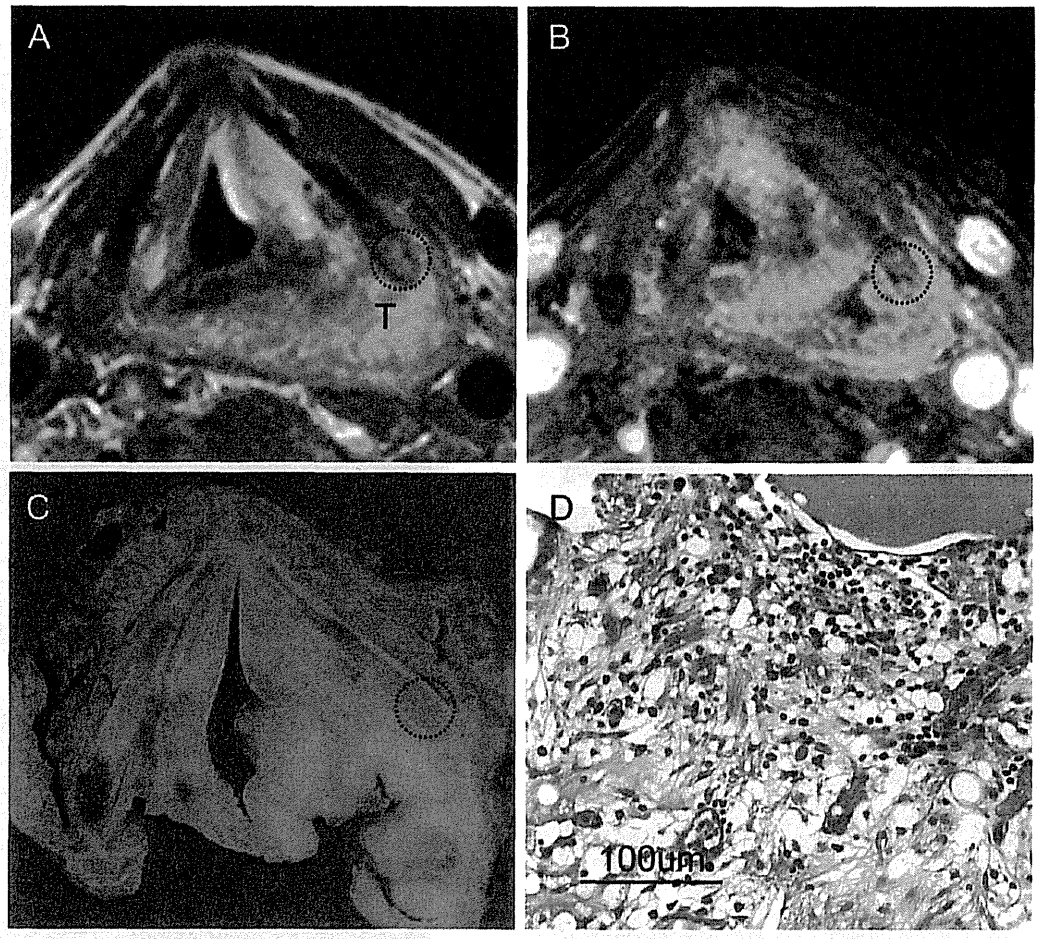

Fig. 6. False-positive findings for thyroid cartilage invasion by MR imaging in a 59-year-old man with hypopharyngeal cancer. (A) T2-weighted MR image at the glottic level shows a tumor mass (T) arising from the left piriform sinus with invasion of the paraglottic space and extension into the soft tissues of the neck. The tumor shows intermediate signal intensity, and the adjacent thyroid cartilage has similar signal intensity (circle). (B) Fat-suppressed contrast-enhanced T1-weighted image shows enhancement of the tumor mass and similar enhancement of the adjacent thyroid lamina (circle). (C) Corresponding axial slice from the surgical specimen at the same level shows that the left thyroid lamina has not been invaded by the tumor (circle). (D) Posterior part of the left thyroid lamina with enhancement (circle in B) shows the moderate infiltration of lymphocytes into the medullary space, accompanied with fibrosis and aggregation of macrophages. (Hematoxylin–eosin stain; original magnification 200×.).

Healthcare) is used to compute iodine images and virtual non-contrast images. The algorithm can be applied at the default parameters for extracting iodine since pharyngeal and laryngeal soft tissues and cartilages have CT values similar to hemorrhage and brain parenchyma. "Organ contour enhancement" and "resolution enhancement" are deselected to ensure quantitative analysis of the small cartilage structures. Finally, the iodine images and the virtual non-contrast or weighted average (WA) images can be linearly fused at a ratio of 0.5, creating iodine overlay (IO) images.

Reconstructed images can then be generated from the WA images and the IO images as frontal and coronal sections parallel and vertical to the vocal cords from 1 cm above the hyoid bone to the inferior margin of the cricoid cartilage (2-mm thickness and 16-cm field of view).

4. Clinical application of CT, MR imaging and dual-energy CT

4.1. Cartilage invasion

Both CT and MR imaging are routinely used for detection of subtle cartilage invasion, but there is still controversy about which modality can most accurately detect cartilage invasion, and both modalities have shortcomings [8,26,37,38]. Dual-energy CT may have the potential to overcome some of the shortcomings of conventional CT, due to the possibility of iodine contrast becoming distributed in tumor tissues but not in normal cartilage. Iodine enhancement can reveal the presence and shape of a tumor, and combined analysis of WA and IO images can be applied to evaluate cartilage invasion. In the next few paragraphs, we discuss the appearances of laryngeal cartilage invasion with conventional CT and MR imaging, as well as dual-energy CT, and explain the advantages and limitations of these modalities.

4.1.1. Conventional CT

Previous studies using single-slice spiral CT scanners have concluded that the CT criteria used for determining neoplastic invasion of the thyroid cartilage include erosion, lysis, and transmural extralaryngeal tumor spread [17,18,26,38,39]. These positive signs of invasion are defined according to the depth of invasion into cartilage, and careful evaluation of the shape and attenuation of the thyroid cartilage (Fig. 2A). In 1997, Becker et al. redefined the diagnostic criteria for single-slice CT and were able to reach an acceptable balance of 71% sensitivity versus 83% specificity by applying these criteria [26]. For evaluation of extralaryngeal spread