Case Report
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대한영상의학회지

Two Cases of Unresectable Cholangiocarcinoma Treated by Yttrium-90 Microspheres[1]

이트리움-90 미세구를 이용한 절제 불가능한 간내 담관암 치료 2예[1]

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Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy and many cases of ICCs are diagnosed in an unresectable state. Until now there has been no effective palliative treatment for these cases. Recently yttrium-90 (^{90}Y) radioembolization has been highlighted as a new palliative treatment for these cases. In Korea, there has been no reported case of unresectable ICC which was treated by ^{90}Y radioembolization up until now. We treated two cases of unresectable ICCs with ^{90}Y radioembolization and the ICCs were necrotized effectively without significant toxicity.

Index terms
Yttrium-90 Microspheres
Intrahepatic Cholangiocarcinoma

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INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is an epithelial cancer which arises from the intrahepatic bile duct. Surgical resection or liver transplantation is the only known curative treatment for ICC (1). However, most of the patients visit hospital too late due to asymptomatic progression of the tumor to be treated curatively. Because there is no established effective palliative treatment option for unresectable ICC, median survival duration of unresectable ICC is only 6-12 months (2).

For this reason, variable palliative treatments have been tried on patients with unresectable ICCs. Systemic chemotherapy with the combination of gemcitabine and cisplatin showed poor results in treating patients with unresectable ICC. The overall survival was still less than 1 year (2). Several trials on the effects of transarterial chemoembolization (TACE) also showed a wide range of the relatively short median survival from 12.2-15 months (3-5). Recently, chemoembolization with drug-eluting beads-TACE was investigated, but the median overall survival was also short - 11.7 months (6). Despite the development of stereotactic body radiotherapy, median survival of patients receiving external beam radiation therapy for unresectable ICC was 10.6 months and patients experienced some complications such as biliary stenosis or liver failure (7).

Herein, yttrium-90 (^{90}Y) radioembolization is highlighted as an effective palliative treatment in patients with unresectable ICC without significant adverse effects. ^{90}Y-bearing microspheres are the point radiation-source which release pure high-energy β-ray localized in the intratumoral arterial vasculature. Mean penetrating length is 2.5 mm and maximum penetrating length is 11 mm in soft tissue (8). ^{90}Y-bearing microspheres can necrotize the tumor only, without extensive hepatic parenchymal damage when implanted in the tumor supplying artery.

We performed transarterial ^{90}Y radioembolization treatment on two patients with unresectable ICCs and the malignant lesions were necrotized effectively by this new treatment without significant toxicity. This is the first report of transarterial ^{90}Y radioembolization treatment of ICCs as a palliative option in Korea.

CASE REPORT

Case 1

A 38-year-old man presented with a 2-week history of severe fatigue. His medical history was not unusual except for a 5-year history of diabetes mellitus. Liver function tests were in the normal range. An abdominal CT scan showed an 18 cm mass occupying most of the right hepatic lobe and segment 4 (Fig. 1A). We did sonography-guided biopsy for this lesion and it revealed ICC. At the time of the diagnosis, ICC was in an unresectable state, stage 4, due to its huge size although there was no evidence of distant metastasis. There were no significant abnormalities in hepatic and renal functions and total bilirubin was measured at 1.36 mg/dL. We planned transarterial ^{90}Y radioembolization treatment as a palliative treatment. Before ^{90}Y bead implantation, we did a Technetium 99m macroaggregated albumin (^{99m}Tc-MAA) scan for evaluation of the hepatopulmonary (HP) shunt and tumor-to-normal (T/N) ratio (Fig. 1B). Results of the examination showed that the HP shunt rate was 5.87% (Table 1). We determined that the maximum radiation dose for the tumor within the limitation of that HP shunt did not exceed 20% and the normal liver dose did not exceed 100 Gy. First, we did hepatic arteriography (Fig. 1C). After that, we implanted 2.94 GBq and 0.84 GBq of resin ^{90}Y microsphere (Sirspheres@, Sirtex, Sydney, Australia) into the right and left hepatic arteries, respectively.

After 18-months of ^{90}Y radioembolization, the follow-up contrast enhanced CT scan at the arterial phase showed that the size of the lesion was reduced (18 cm to 15 cm) and the internal necrotic portion of the tumor had increased (Fig. 1D). Also the follow-up positron emission tomography (PET)-CT scan showed total disappearance of the previously noted hot-uptake lesion (Fig. 1E), and there was no new hot-uptake lesion in the liver (Fig. 1F). So we believed that the tumor was necrotized effectively. The patient did not complain of any symptoms and did not show significant toxicities above grade 3 (Table 2).

Case 2

A 74-year-old man presented with weight loss of 5 kg in one

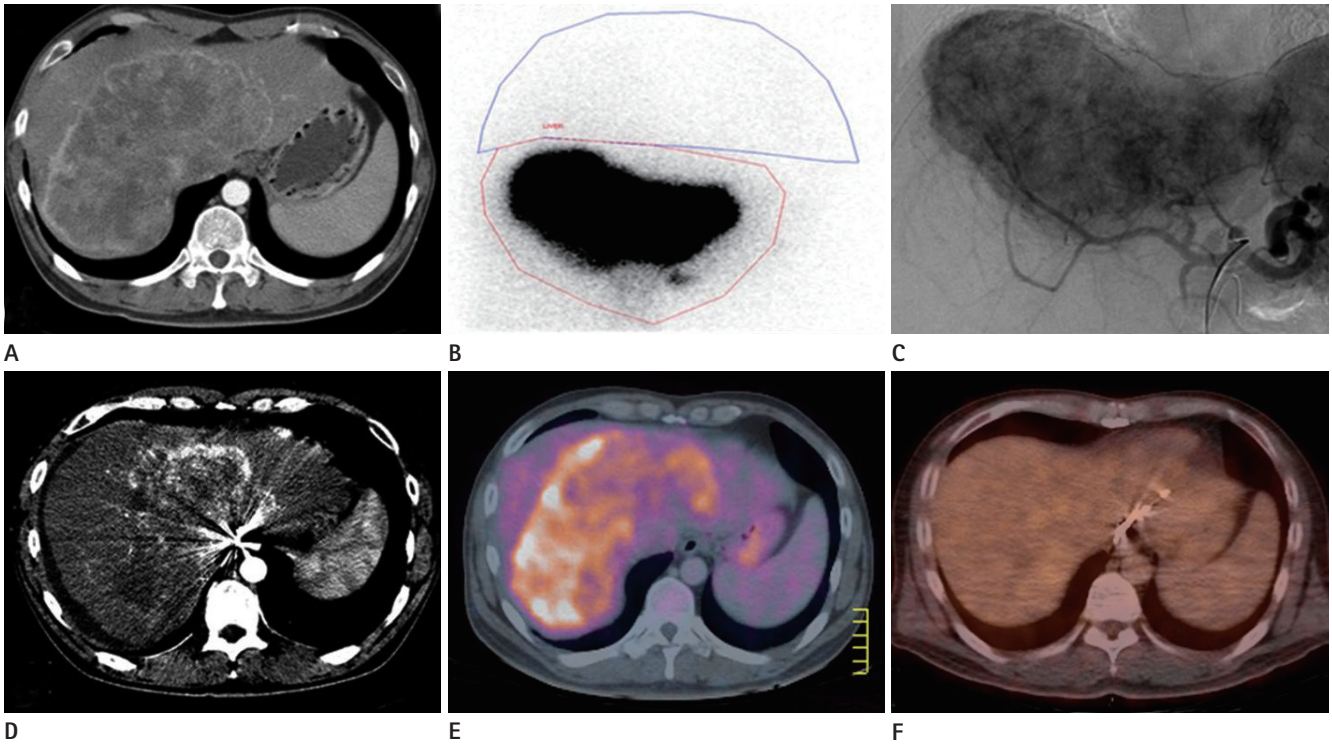

Fig. 1. A 38-year-old man with unresectable intrahepatic cholangiocarcinoma.
A. Initial abdominal CT scan (arterial phase) shows 18 cm sized huge mass lesion with peripheral arterial enhancement in both hepatic lobes.
B. Technetium 99m macroaggregated albumin scan shows low hepatopulmonary shunt rate (5.87%) and high tumor-to-normal ratio (7.89).
C. Celiac arteriography shows hypervascular tumor in both hepatic lobes.
D–F. At the 18-month after treatment, size of lesion is reduced (15 cm) and internal necrotic portion is increased. At the 18-month after treatment, previously noted hot-uptake lesion **(E)** is no more detected in positron emission tomography-CT scan **(F)**.

Table 1. Patient Characteristics

Variables	Case 1	Case 2
Age	38	75
Sex	M	M
Performance status (ECOG)	0	0
Morphologic tumor type	Peripheral	Peripheral
Extrahepatic metastasis	None	None
Prior treatment	None	None
Baseline evaluation of biochemical status		
AST (IU/L)	19	19
ALT (IU/L)	29	24
ALP (IU/L)	156	-
Albumin (g/dL)	4.3	4.5
Bilirubin, total (mg/dL)	1.36	0.3
PLT (10^3/μL)	113	238
Cr (mg/dL)	0.8	0.8
AFP (ng/mL)	4.2	2.6
PIVKA (mAV/mL)	33	-
CA 19-9 (IU/mL)	9.8	25.1
Baseline evaluation of abdominal CT		
Hepatic tumor distribution	Bilobar	Bilobar
Tumor size (cm)	18	5.5
Portal vein thrombosis	None	None
Baseline status of arteriography and ^{99m}Tc-MAA		
Hepatopulmonary shunt (%)	5.87	4.12
T/N ratio	7.89	8.08
Delivered ^{90}Y dose and received radiation dose		
^{90}Y dose (GBq)	3.78	1.20
Received dose of tumor (Gy)	120.00	565.80
Received dose of normal liver (Gy)	15.21	70.00
Received dose of normal lung (Gy)	11.28	2.31

Note.—ECOG = Eastern Cooperation Oncology Group, PIVKA = protein induced by vitamin K antagonism, T/N ratio = tumor-to-normal uptake ratio, ^{99m}Tc-MAA = Technetium 99m macroaggregated albumin, ^{90}Y = yttrium-90

Table 2. Responses and Toxicities of ^{90}Y Radioembolization Therapy in Two Cases

Variable	Case 1	Case 2
Follow-up duration (month)	18	25
Response		
Baseline tumor size (cm)	18	5.5
Tumor size after treatment (cm)	15	3.0
RECIST criteria	16.7% decrease, stable disease	45.5% decrease, partial response
Hot uptake lesion of the liver after treatment in PET-CT	None	None
Toxicity		
Clinical toxicity*	None	None
Biochemical toxicity†	None	Grade 1

Note.—*Containing fatigue, abdominal pain, nausea and vomiting.
†According to National Cancer Institute's Common Toxicity Criteria for adverse event (version 3).
PET-CT = positron emission tomography-CT, RECIST = Response Evaluation Criteria in Solid Tumors, ^{90}Y = yttrium-90

year. His medical history was not unusual except for well controlled hypertension. Liver function tests were in the normal range. Contrast enhanced abdominal CT scan showed a 5.5 cm sized homogeneously well enhanced lesion in S1, S7 and S8 (Fig. 2A). We did sonography-guided biopsy for this lesion and it revealed ICC. At the time of the diagnosis, ICC was in an unresectable state. There were no significant abnormalities in hepatic and renal functions and total bilirubin was measured at 0.3 mg/dL. We planned transarterial ^{90}Y radioembolization treatment as a palliative treatment. Before the ^{90}Y bead implantation, we did a ^{99m}Tc-MAA scan (Fig. 2B). Results of the examination showed that the HP shunt rate was 4.12%, so we could do the treatment without a radiation dose reduction (Table 1). After we superselected the supplying artery of the tumor in S1 and the right hepatic artery (Fig. 2C), we implanted 0.5 GBq and 0.7 GBq of the resin ^{90}Y microspheres (Sirspheres@, Sirtex, Sydney, Australia), respectively.

After 25-month ^{90}Y radioembolization, a follow-up contrast enhanced CT scan at the arterial phase showed that the size of the lesion was reduced (5.5 cm to 3 cm) and most of the tumor had necrotized (Fig. 2D). Also, the follow-up PET-CT showed total disappearance of the previously noted hot-uptake lesion (Fig. 2E, F). So we thought that the tumor had necrotized effectively. The patient did not complain of any symptoms and did not show significant toxicities over grade 3 (Table 2).

DISCUSSION

In the USA, the prevalence of cholangiocarcinoma is 0.32 cases per 100000 people in 1975-1979, and it has increased rapidly to 0.85 cases per 100000 people in 1995-1999 (9). In Korea, in 1999, already the prevalence of the cholangiocarcinoma was already 3.6 cases per 100000 people because of the high infection rate with Clonorchis sinensis due to the high rate of ingestion of freshwater fish in Korea (10). In addition, the prevalence of cholangiocarcinoma in Korea has shown rapid growth trends, so in 2005, 5.2 people per 100000 were reported as having cholangiocarcinoma (10).

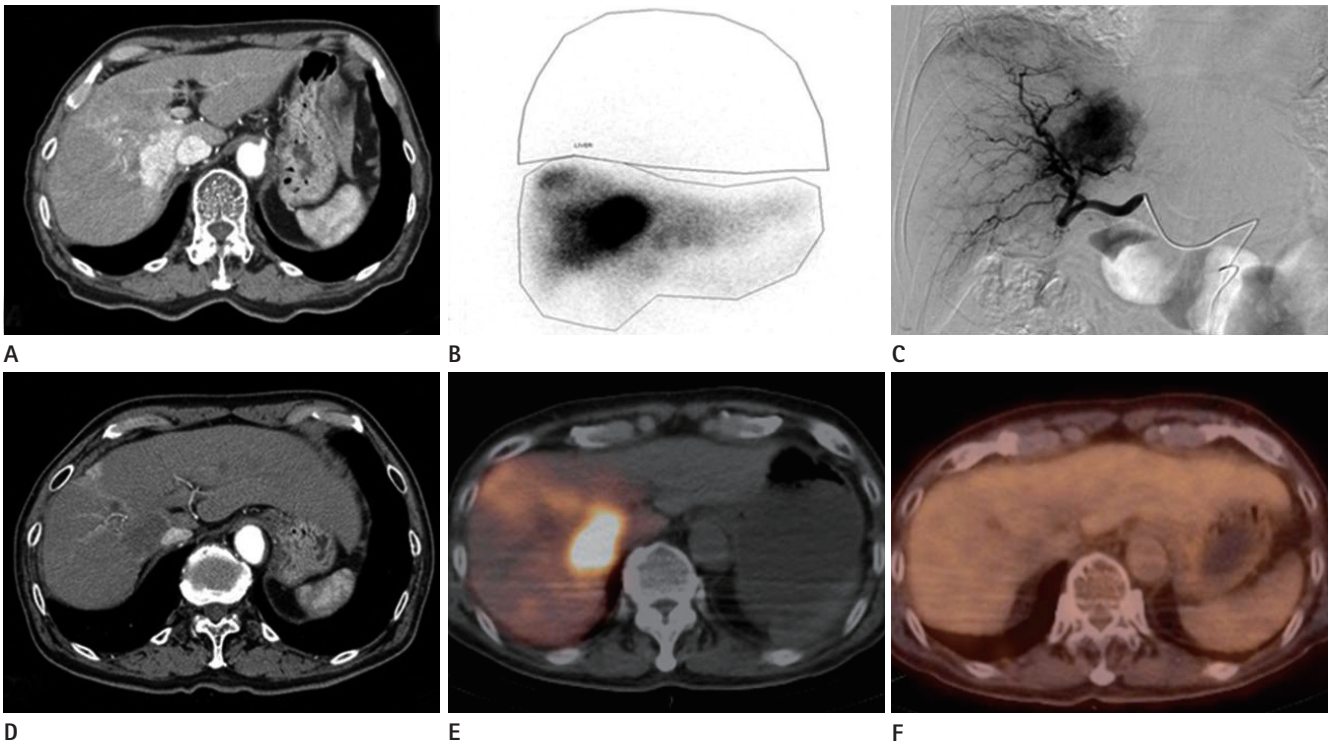

Fig. 2. A 74-year-old man with unresectable cholangiocarcinoma.
A. Contrast enhanced CT scan at arterial phase shows 5.5 cm sized intrahepatic cholangiocarcinoma in S1, S7 and S8 before treatment.
B. Technetium 99m macroaggregated albumin scan shows low hepatopulmonary shunt rate (4.12%) and high tumor-to-normal ratio (8.08).
C. Celiac arteriography shows hypervascular tumor.
D–F. At the 25-month after treatment, size of lesion is reduced (3.0 cm) and internal necrosis is noted. At the 25-month after treatment, previously noted hot-uptake lesion **(E)** is no more detected in positron emission tomography-CT scan **(F)**.

Recently ^{90}Y radioembolization has been highlighted as effective palliative treatment in patients with unresectable ICC without significant adverse effects. US FDA permitted ^{90}Y radioembolization treatment in unresectable primary hepatic cellular carcinoma and metastatic hepatic carcinoma from colon cancer, and several clinical studies have shown good results. Three small group studies were conducted on the effects of ^{90}Y radioembolization treatment on unresectable ICCs in 2008, 2010 and 2011. Those studies showed mean survival duration of 14.9, 9.3 and 10 months, respectively, without significant toxicities (11-13).

Before ^{90}Y radioembolization, a ^{99m}Tc-MAA scan should be done for radiation dose selection. The ^{99m}Tc-MAA scan shows the rate of flow in the HP shunt and the T/N uptake ratio of the ^{90}Y microspheres. First, the rate of the shunt between hepatic artery and pulmonary vessel should be under the 20% because of radiation pneumonitis caused by refluxed ^{90}Y microspheres. Second, the selective delivery of radiation to the tumor with sparing of non-tumorous liver parenchyma depends on the T/N uptake ratio of the ^{90}Y microspheres (14). In general, we determine the maximum radiation dose for the tumor within the limitation of that HP shunt is not exceed 20% and the normal liver dose should not exceed 100 Gy.

Until now, several adverse effects after treatment have been reported. Most of these are caused by unwanted implantation of ^{90}Y microspheres by reflux or the shunt. Gastroduodenal ulceration can develop when there is reflux of ^{90}Y microspheres into the gastroduodenal artery, and radiation pneumonitis can develop if the microspheres become implanted in the lung through the HP shunt. To avoid these toxic effects, coiling of the gastroduodenal artery and exact evaluation of the HP shunt should be done.

In general, the Response Evaluation Criteria in Solid Tumors criteria (15) is used in systemic chemotherapy or general radiation therapy. However it has limitations in evaluating the effects of ^{90}Y radioembolization. Because the main mechanism of treatment is micro-infarction and embolization, ^{90}Y radioembolization induces necrosis with or without change in tumor size. For this reason, PET-CT is a more useful modality to evaluate the treatment response after ^{90}Y radioembolization because it shows metabolic activities. A tumor that has been treated effectively does not show hot-uptake, although it does not show decrease in size (8). In our case (case 1), there was no considerable decrease in size, but the follow-up PET-CT showed total disappearance of the hot-uptake portion.

^{90}Y radioembolization treatment for unresectable cholangiocarcinoma is still in the experimental stage, but several studies including our study showed promising results. If this palliative treatment is performed on appropriate patients with thorough pre-assessment, we can obtain good results without specific toxicity. In the future, if the problem of the high cost can be resolved, ^{90}Y radioembolization treatment can be the most effective palliative treatment modality in unresectable intrahepatic cholangiocarcinoma.

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이트리움-90 미세구를 이용한 절제 불가능한 간내 담관암 치료 2예[1]

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간내 담관암은 담관 상피세포에 발생하는 드문 암으로 수술이 불가능한 진행된 상태에서 발견되는 경우가 많은 것으로 알려져 있다. 그럼에도 불구하고 현재까지 이런 증례들에 대한 효과적인 고식적 치료법은 정립된 바가 없다. 최근 이트리움-90 미세구를 이용한 방사선색전술이 이러한 증례들에서 효과적인 고식적 치료법으로 주목을 받고 있다. 그러나 현재까지 국내에서는 절제 불가능한 간내 담관암에 이트리움을 이용한 방사선색전술을 적용하여 보고한 예가 없었다. 이에 본 저자들은 이트리움 방사선색전술을 이용해 절제 불가능한 간내 담관암 2예를 독성 없이 성공적으로 괴사시킨 바 이에 대해 보고하는 바이다.

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