

# Hepatobiliary and Pancreatic Oncology

## Introduction

The Division of Hepatobiliary and Pancreatic Oncology deals with cancers of the liver, the biliary system, and the pancreas. Various combination therapies are often required to treat cancers at these sites, and treatment strategies are carefully discussed by surgeons, radiologists, and our medical oncologists at our conferences. We are trying to establish new modalities of treatment for those cancers.

## Routine Activities

Abdominal ultrasonography is used for both to screen for malignancies and for thorough examinations. We have been performing contrast-enhanced ultrasound for the diagnosis of hepatic tumors and pancreatic tumors since clinical use of the contrast agent Levovist was approved in 1999. The contrast-enhanced method is useful for differentiating hepatocellular carcinoma (HCC), hemangioma, and focal nodular hyperplasia from other hepatic nodules. A total of 4794 patients were examined by ultrasonography in 2003.

Percutaneous ablation therapy, including ethanol injection (PEI) or radiofrequency ablation (RFA), is indicated as standard treatment for HCC when these are no more than 3 tumors and each tumor is less than 3 cm in diameter. RFA has been chosen as the treatment of first choice for small HCCs since 2000, because a wide necrotic area can be obtained during a single treatment session and the length of hospital stay is shorter than with PEI. We have also been using RFA combined with simultaneous PEI since 2002 in an attempt to treat a wider area during a single treatment session. Transcatheter arterial chemoembolization (TACE) is used to treat advanced or recurrent HCC, which is not suitable for hepatectomy or percutaneous ablation therapy in routine practice. Hepatic arterial infusion (HAI) chemotherapy with 5-FU or doxorubicin is used to treat far advanced HCC, to which TACE cannot be applied. We completed a phase II study of proton beam radiotherapy for HCC in June 2001, and we now perform it as highly advanced medical technology. We also use photon radiotherapy to treat localized and larger unresectable HCCs in which proton beam radiotherapy is not indicated, such as when a lesion is adjacent to the intestine.

We performed radiotherapy or chemotherapy to treat biliary tract cancer, including intra- and extra-hepatic cholangiocarcinoma (bile duct cancer), gall bladder cancer and papilla of Vater cancer according to the stage of the cancer. Patients with unresectable advanced bile duct

cancer have been treated by radiation therapy consisting of external beam radiation therapy (EBRT) and intraluminal brachytherapy using Ir192 in a phase II study since 1999. Chemotherapy is performed by hepatic arterial infusion (HAI) or systemic chemotherapy. 5-FU is used for HAI, and 5-FU HAI has been mainly used to treat unresectable intrahepatic cholangiocarcinoma. Systemic chemotherapy is performed in clinical trials or standard treatments in patients with biliary tract cancer with distant metastases.

Percutaneous transhepatic biliary drainage, cholangiography, and cholangioscopy are performed in patients with obstructive jaundice to improve the jaundice and determine the cause of the bile duct obstruction.

We have been treating pancreatic cancer patients with unresectable disease with gemcitabine as the key drug since its approval by the Ministry of Health, Labour and Welfare in 2001. Patients with locally advanced pancreatic cancer are treated with EBRT combined with sequential gemcitabine chemotherapy, because serious adverse effects have been reported, and full-dose gemcitabine could not be administered with concurrent chemoradiotherapy. Systemic chemotherapy has been performed in clinical trials or ordinary treatments for pancreatic cancer with distant metastases. Although gemcitabine has become the anticancer drug of first choice for pancreatic cancer, the outcome is still unsatisfactory. We are actively conducting clinical trials of systemic chemotherapy to establish more effective chemotherapy.

## New Developments

1. Hepatic arterial infusion chemotherapy for advanced HCC.

A phase I/II study of HAI with 5-FU alone in patients with far advanced HCC was begun in 2003. We use HAI with doxorubicin to treat patients who do not meet the criteria for enrolment in the study.

2. Randomized clinical trial of hepatectomy vs. ablation therapy for earlier stage HCC.

There has been controversy as to which treatment is better for earlier stage of HCC, hepatectomy or ablation therapy, such as by ethanol injection or radiofrequency therapy. This randomized clinical trial was begun as a multicenter trial in October 2002, but since most patients who were eligible for this study refused to be enrolled because they wanted to receive ablation therapy, we abandoned the study.

3. SM11355 for unresectable HCC

A late phase II study of SM11355 (liposoluble platinum complex) transcatheter hepatic arterial infusion chemotherapy

for unresectable HCC is still in progress.

#### 4. Chemotherapy for biliary tract cancer

A phase II study of systemic chemotherapy with gemcitabine for biliary tract cancer with distant metastases has been completed, and the results are being analyzed. We began a new phase II study of UFT plus doxorubicin in 2003.

#### 5. Chemoradiotherapy for locally advanced pancreatic cancer

In order to establish a more effective and efficient method of chemoradiotherapy for locally advanced pancreatic cancer, we have been conducting a phase I trial of hypofractionated radiotherapy followed by sequential chemotherapy with full-dose of gemcitabine for locally advanced PC since 2001. It is a dose-escalation study of radiotherapy from 45 Gy at 15 fractions to 40 Gy at 5 fractions. We have completed enrollment at both levels, and the results are being analyzed.

#### 6. Systemic chemotherapy for advanced pancreatic cancer

Gemcitabine has been used as the anticancer drug of first choice for pancreatic cancer since 2001. However, we conducted several phase I or II studies of systemic chemotherapy to establish more effective regimens.

A combination of gemcitabine and 5-FU was tested in a multi-center trial completed in 2003, and a phase II study of S-1 was started as a multi-center trial in 2003. We have cooperatively conducted some studies with National Cancer Center Hospital. NK-911 is a new anticancer drug that was developed based on a drug delivery system theory, and we are currently conducting a phase II study of NK-911. We also instituted two phase I studies of fixed-dose rate gemcitabine and a combination of gemcitabine and S-1 in 2003. Both regimens are expected to be more effective than the standard gemcitabine regimen.

● J. Furuse ●

	1992	93	94	95	96	97	98	99	2000	1	2	3
Total	68	196	227	270	317	352	420	444	432	430	426	531
HCC	33	86	129	175	210	245	290	331	283	254	269	284
Biliary tract	11	30	32	39	47	48	50	47	64	74	40	74
Pancreas	11	22	26	23	21	34	54	43	59	84	97	152
Others	13	58	40	33	39	25	24	23	26	18	20	21
New referrals	60	109	113	127	135	123	164	177	184	174	140	246
HCC	29	43	52	63	75	66	81	102	85	70	50	91
Biliary tract	8	10	18	19	25	20	28	26	32	26	24	43
Pancreas	11	12	11	18	10	22	35	29	44	56	60	91
Others	12	44	32	27	25	15	20	20	23	22	6	21

	HCC	Pancreas	Biliary tract
Percutaneous ablation therapy	26	0	0
PEI	20	0	0
RFA+PEI	6	0	0
Transcatheter treatment	44	2	0
TACE	26	0	0
HAI	18	2	0
Radiation therapy	11	7	4
Photon	4	6	0
Proton	7	0	0
Photon+RALS	0	1	0
RT+chemotherapy	0	0	4
Systemic chemotherapy	2	26	76
Best supportive care	8	8	11
Total	91	43	91

HCC: hepatocellular carcinoma, PEI: percutaneous ethanol injection, PMCT: percutaneous microwave coagulation therapy, RFA: radio-frequency ablation therapy, TACE: transcatheter arterial chemoembolization, HAI: hepatic arterial infusion of anti-cancer drug, RALS: remote after loading system using Ir192