

# Hepatobiliary and Pancreatic Surgery

## Introduction

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

## Routine Activities

In hepatobiliary and pancreatic oncology, systemic chemotherapy regimens remain unsatisfactory and insufficient. We utilize systemic chemotherapy protocols in clinical trials or as standard treatments in patients with distant metastases or locally advanced disease. We have been using gemcitabine to treat pancreatic cancer patients with unresectable lesions since its approval by the Ministry of Health, Labour and Welfare in 2001. However, the therapeutic effects remain unsatisfactory. Hence, we have been performing clinical trials investigational new regimens. For hepatocellular carcinoma (HCC) and biliary tract cancer, many patients require systemic chemotherapy, but a standard regimen of systemic chemotherapy has not been established. We initiated clinical trials for these patients in 2004.

Percutaneous ablation therapy, including ethanol injection (PEI) or radiofrequency ablation (RFA), is indicated as a standard treatment for HCC in patients with no more than 3 tumors, each with a diameter of less than 3 cm. RFA has been the treatment of first choice for small HCCs since 2000 because a wide necrotic area can be obtained by a single course of treatment and a shorter hospital stay is required, compared to that after PEI. We have also been using RFA combined with simultaneous PEI since 2002 in an attempt to treat an even wider area by a single course of treatment. Transcatheter arterial chemoembolization (TACE) is routinely used to treat advanced or recurrent HCC, in cases where a hepatectomy or percutaneous ablation therapy is not indicated. Hepatic arterial infusion (HAI) chemotherapy with epirubicin has been used to treat very advanced HCC, for which TACE is not indicated. In July 2004, cisplatin was approved as a new HAI agent for the treatment of HCC by the Ministry of Health, Labour and Welfare. We have since applied cisplatin as the first-choice treatment for very advanced HCC.

Radiotherapy is also utilized for the treatment of hepatobiliary and pancreatic cancer. We completed a phase

II study of proton beam radiotherapy for HCC in June 2001 and now utilize this highly sophisticated medical technology. We also use radiotherapy to treat localized and larger unresectable HCCs: proton beam radiotherapy is utilized where possible and conventional photon radiotherapy is used in cases where proton beam radiotherapy is not indicated, such as when the lesion is adjacent to the intestine. Patients with unresectable advanced bile duct cancer have been treated using radiation therapy consisting of external beam radiation therapy (EBRT) and intraluminal brachytherapy using Ir192 in a phase II study since 1999.

Percutaneous transhepatic biliary drainage (PTBD), cholangiography, and cholangioscopy are performed in patients with obstructive jaundice to improve jaundice symptom and determine the cause of the bile duct obstruction. Metallic stents are utilized in patients with obstructive jaundice to improve their quality of life. In addition, PTBD tubes can be removed if a stent is used to further improve the patient's quality of life.

Abdominal ultrasonography plays a very important role in both screening for malignancies and thorough examinations, especially in patients with suspected hepatobiliary or pancreatic cancers. Abdominal ultrasonography is used during interventional treatments, such as ablation therapies for liver cancer and percutaneous drainage for obstructive jaundice or abscess. A total of 5,180 patients were examined using ultrasonography in 2004. We use color Doppler ultrasound and/or contrast-enhanced ultrasound to evaluate tumor vascularity, aiding the diagnosis of hepatic tumors that are difficult to diagnose differentially using conventional ultrasound examinations.

## New Developments

### 1. Systemic chemotherapy for advanced HCC

A phase I study of BAY 43-9006, a new molecular target agent, was initiated as a single-center trial in April 2004. This agent is a potent inhibitor of Raf kinase and VEGFR2 signaling. The endpoints of the study are to assess the pharmacological kinetics and toxicities and to determine the optimal dose. A phase I/II study of UFT+mitoxantron has been ongoing in our division since March 2004.

### 2. SM11355 for unresectable HCC

A multi-center late phase II study of SM11355 (liposoluble platinum complex) transcatheter hepatic arterial infusion chemotherapy for unresectable HCC was completed in 2004, and the results are now being analyzed.

### 3. Systemic chemotherapy for biliary tract cancer

A multi-center late phase II study of systemic chemotherapy with S-1 for biliary tract cancer with distant metastases has been completed and the results are now being analyzed. We have also completed an early phase II study of UFT plus doxorubicin as part of a multi-center study. The response rate was over 10% and the toxicities were mild. A further trial evaluating this regimen in a larger number of patients is warranted, so a late phase II study will start in early 2005.

### 4. Systemic chemotherapy for unresectable advanced pancreatic cancer

We completed two phase I studies of a combination of S-1 fixed-dose rate and gemcitabine and at the National

Cancer Center Hospital and Hospital East in 2004. Both regimens are expected to be more effective than the standard gemcitabine regimen. A phase II study of gemcitabine+S-1 in patients with metastatic disease was initiated as a multi-center trial on October 2004.

### 5. Chemoradiotherapy for locally advanced pancreatic cancer

To establish a more effective and efficient method of chemoradiotherapy for locally advanced pancreatic cancer, we initiated a phase I trial of S-1 and concurrent radiotherapy at the National Cancer Center Hospital and Hospital East in 2004.

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Number of inpatients for the past 10 years

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
<b>Total</b>	270	317	352	420	444	432	430	426	531	596
HCC	175	210	245	290	331	283	254	269	284	338
Biliary tract	39	47	48	50	47	64	74	40	74	81
Pancreas	23	21	34	54	43	59	84	97	152	159
Others	33	39	25	24	23	26	18	20	21	18
<b>New referrals</b>	127	135	123	164	177	184	174	140	246	285
HCC	63	75	66	81	102	85	70	50	91	116
Biliary tract	19	25	20	28	26	32	26	24	43	49
Pancreas	18	10	22	35	29	44	56	60	91	103
Others	27	25	15	20	20	23	22	6	21	17

Treatment methods and number of the patients as the first line in 2004

	HCC	Biliary tract	Pancreas
<b>Percutaneous ablation therapy</b>	31	0	0
PEI	5	0	0
RFA+PEI	26	0	0
<b>Transcatheter treatment</b>	42	0	0
TACE	23	0	0
HAI	19	0	0
<b>Radiation therapy</b>	6	3	3
Photon	2	0	0
Proton	3	1	0
Photon+RALS	0	2	0
RT+chemotherapy	0	0	3
Other	1	0	0
<b>Systemic chemotherapy</b>	17	39	90
<b>Best supportive care</b>	20	7	10
<b>Total</b>	<b>116</b>	<b>49</b>	<b>103</b>

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