Recent advances on Hepato-biliary-pancreatic Cancer

Aichi Cancer Center International Symposium III

International Conference Hall
Aichi Cancer Center
Nagoya, Japan

December 13-14, 1996
Aichi Cancer Center International Symposium III

Recent advances on Hepato-biliary-pancreatic Cancer

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Friday, December 13, 1996

10:30 am - 10:40 am
Welcome and Opening Remarks: Makoto Ogawa (President, Aichi Cancer Center)

10:40 am - 0:15 pm
Session 1: Hepatocellular Carcinoma
Chairperson: Masae Tatematsu (Aichi Cancer Center)
1. Masamichi Kojiro (Kurume University): Pathology of Early Hepatocellular Carcinoma - From the view point of pathology
2. Masao Omata (Tokyo University): Chronic Hepatitis and Hepatocellular Carcinoma: How to Tackle with Those

0:15 pm - 1:30 pm Lunch

1:30 pm - 3:05 pm
Session 2: Metastatic Liver Cancer
Chairperson: Makoto Ogawa (President, Aichi Cancer Center)
1. Hayao Nakanishi (Aichi Cancer Center): Basic Approaches to the Diagnosis and Treatment of Micrometastases
2. Kenzo Yasui (Aichi Cancer Center): A Prognostic Significance of the new Macroscopic Classification of Liver Metastases from Colorectal Cancer

3:05 pm - 3:25 pm Coffee Break

3:25 pm - 4:10 pm
3. Yasuaki Arai (Aichi Cancer Center): Techniques and Therapeutic Effects of Hepatic Arterial Infusion Chemotherapy for Liver Metastases
Saturday, December 14, 1996

9:30 am - 11:20 am  
**Session 3: Pancreatic Cancer**  
Chairperson: Kazuhiko Ohhashi (Aichi Cancer Center)  
1. B.Kremer (Kier University): Surgical Treatment of Pancreatic Cancer  
2. Yo Kato (Cancer Institute):  

11:20 am - 11:30 am  
**Coffee Break**  

11:30 am - 1:00 pm  
3. John S. MacDonald (Temple University): Systemic Therapy for Pancreatic Cancer  
4. Takeshi Morimoto (Aichi Cancer Center): Surgical Treatment with Intraoperative Radiation Therapy and Intraoperative Hyperthermia for Pancreatic Carcinoma  

1:00 pm - 2:00 pm  
**Lunch**  

2:00 pm - 3:35 pm  
**Session 4: Biliary Tract Cancer**  
Chairperson: Yuji Nimura (Nagoya University)  
1. Inui Kazuo (Fujita Health University School of Medicine): Diagnosis of Early Gallbladder Carcinoma  
2. Hiroya Saito (Asahikwa Kosei General Hospital): Expandable Metallic Stens for Treatment of Malignant Billary Obstruction  

3:35 pm - 3:50 pm  
**Coffee Break**  

3:50 pm - 5:35 pm  
3. Yuji Nimura (Nagoya University): Surgical Treatment of Hilar Cholangiocarcinoma  
4. Bernard Launols (Hospital de Pontchaillou): Proximal Bile Duct Cancer: High Resectability Rate and 5 Year Survival  

5:35 pm - 5:40 pm  
Closing Remarks: Kouzou Morita (Director, Aichi Cancer Center)
PATHOLOGY OF EARLY HEPATOCELLULAR CARCINOMA
- From the view point of pathology -

Masamichi Kojiro, M.D.

Kurume University, School of Medicine
67 Asahi-machi, Kurume 830, Japan

Based on the pathomorphologic studies of resected small hepatocellular carcinoma (HCC) and biopsy materials from minute HCCs of the early stage, it has been clarified that the majority, of minute HCC of the early stage are uniformly, composed of well-differentiated cancerous tissues. Those minute HCC in the early stage are nodular but have indistinct margins and retain the portal tracts within a tumor. When tumors grow over around 2-3 cm in diameter, about one-third of them display various combinations of more than two cancerous tissues of different histologic grades. In those HCCs, the areas of less differentiated cancerous tissues are almost always surrounded by well-differentiated ones, and some of them show "nodule in nodule" appearance. The area of Well-differentiated cancerous tissues diminish in size along with the increase of tumor size. And then are completely replaced by moderately to poorly differentiated cancerous tissues.

We established two distinct HCC cell lines of well-differentiated and poorly, differentiated from, the resected small HCC with "nodule in nodule" appearance in which the inner nodule was composed of poorly, differentiated cancerous tissue and the outer nodule was of well-differentiated. The doubling time of poorly differentiated HCC cells is about one-third of that of the well-differentiated one. Although poorly HCC cells were easily xenografted into nude mice, well-differentiated cells could not be xenografted. Despite of distinct morphologic difference in both cell lines, the evidences of 2 identical chromosome abnormalities and point mutation of p53 protein at Codon 242 in both cell lines strongly suggest a clonal origin of them; possible development of poorly differentiated cells from well-differentiated ones.
Taken together with above results, it is suggested that dedifferentiation is closely related to tumor proliferation in HCC.
The treatment for hepatitis B started approximately ten years ago in Japan and the trials were aimed to see the acute suppression of the hepatitis B virus by interferon. Now it appears the time to see the long-term effect of the anti-viral treatment on the natural course of chronic hepatitis B, namely, the possible prevention of the occurrence of the hepatocellular carcinoma. In my experience, however, so far there is no solid evidence that the anti-viral treatment certainly reduced the occurrence of the hepatocellular carcinoma related to the hepatitis B virus infection. Therefore, the effect of the interferon on the suppression of hepatitis B virus was limited and we may need better way of treating these patients. In contrast, the treatment of hepatitis C virus infection by interferon is more encouraging. We have treated not only chronic hepatitis patients but also patients in acute phase as well as patients with liver cirrhosis. The treatment effect seems depending upon pre-treatment virus amount, genotypes and the stages of the diseases. The complete eradication could be expected in 90% of those with acute hepatitis, approximately 30-40% of those with chronic hepatitis and somewhere between 10-20% of those with cirrhosis. Long-term effect was also studied in these patients treated by interferon. Not only eradication of the virus but histological resolution of liver diseases were also noted. Therefore, the treatment for hepatitis C is fairly encouraging, but we may need to improve eradication rates by modifying the treatment protocols. In our country, approximately over 90% of patients with hepatocellular carcinoma were infected by either one of the two viruses. Of 205 cases, 11% were currently infected by HBV and 83% by HCV, indicating practically the most (94%) being infected. In our unit at University of Tokyo, the most common disease is now hepatocellular carcinoma, and approximately 300 patients are admitted every year for the treatment of the tumor. 80% of those are treated by...
ethanol injection regardless of the size and the number of tumor. Five-year survival of 518 patients so far treated are currently 34%. The biggest problem of these patients is recurrence of tumor which may exceed sometimes 15 to 20% per year. Therefore, how to prevent the multicentric recurrence is the utmost important to prolong these patients' life. That can be accomplished may be by treating background liver diseases by anti-viral treatment. Therefore, it may be concluded that we need comprehensive strategies against virus induced liver diseases in our country.
Hepatic metastasis is one of the most major causes of mortality of colorectal cancer patients after curative surgery. Metastatic recurrence is considered to result from free tumor cells or micrometastases which are already present in secondary sites when the primary neoplasms are removed. To improve the survival rate of cancer patients, diagnostic and therapeutic approaches for micrometastasis are essential. At present, however, diagnosis is still difficult and the biological properties of the micrometastases including their sensitivity to various treatments remains unclear. The present talk introduces our approaches to treatment and diagnosis of micrometastases;

1. Approaches to the treatment of micrometastases

We have developed a novel micrometastasis model using lacZ gene-tagged mouse Lewis lung carcinoma cells and investigated the sensitivity of micrometastases to various treatments. The use of a tumor cell line transfected with the lacZ gene facilitates detection of micrometastases at the single cell level. We have demonstrated that the initial stage of micrometastasis formation is highly, sensitive to an anti-cancer agent (5-FU derivative) and can be effectively eliminated by oral administration of a low dose of the drug. On the other hand, advanced metastases which are resistant to chemotherapeutic agents could be definitely diminished by enzyme/prodrug gene therapy (herpes simplex virus thymidine-kinase/ganciclovir). In the latter case, a bystander effect via gap junctional communication was found to be involved in overcoming drug resistance. Anti-cancer agents or gene therapy capable of killing tumor cells, however, fail to reduce metastasis formation at the step of attachment to the endothelium or subendothelial matrix. We have developed a novel anti-adhesive heparin analogue, which effectively reduces metastasis formation, probably by interfering with the tumor cell-subendothelium at matrix interaction. Combination
therapy featuring both anti-adhesive and chemotherapeutic agents proved to be more effective than either treatment alone in a mouse model.

2. Approaches to diagnosis of micrometastases

Assays for carcinoembryonic antigen (CEA), ultrasonography and computed tomography (CT) allow an improvement in the number of liver metastases which can be detected, but they are still not sufficiently sensitive for reliable detection of hepatic micrometastases. Circulating tumor cells in the blood are a prerequisite for development of distant metastasis. Therefore, we have developed a highly sensitive method using RT-PCR for cytokeratin 19 (CK19) mRNA to assay for small numbers of tumor cells in the peripheral blood. The aim is to supplement tumor markers and select groups at high risk of micrometastasis to the liver. The colorectal carcinoma cell lines examined were all positive for CK19 expression, irrespective of their differentiation degree. CK19 RT-PCR proved capable of detection of 50 carcinoma cells in $1 \times 10^7$ peripheral blood mononuclear cells (PBMN). 24 of 48 patients with colorectal cancers (50%) had CK19 mRNA in their blood. On the other hand, only 3 of 33 RNA samples prepared from the peripheral blood of healthy controls were positive for CK19 transcripts (false positive rate, 9%). No significant correlation between the presence of tumor cells in blood and tumor stage was noted, suggesting that carcinoma cells may be released into the blood circulation from primary tumors at an early stage of tumor development. Although the clinical utility of the CK19 RT-PCR method awaits years of clinical study, this may be a useful prognostic marker for hepatic metastasis from colorectal cancers.
A PROGNOSTIC SIGNIFICANCE OF THE NEW MACROSCOPIC CLASSIFICATION OF LIVER METASTASES FROM COLORECTAL CANCER

Kenzo Yasui, M.D.
Aichi Cancer Center
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan

A retrospective study of our experience with hepatectomy for colorectal liver metastases was performed to elucidate the independent prognostic factor representing biologic behavior.

Surgical procedures
Anatomic hepatectomy with regional lymphadenectomy was performed in 73 of the 81 patients in the study. Of these, 61 patients (83.6%) underwent extended resection of two or more hepatic segments.

Patients
Between April 1983 and March 1995, hepatectomies were performed for 101 patients with colorectal liver metastases. Extrahepatic metastatic lesions coexisted in 12 cases. Advanced primary cancers of other organs were present in 3 cases. Another 3 cases had received intraarterial chemotherapy for extensive liver metastases before surgery. These 18 cases, as well as 2 postoperative deaths, were excluded from the study. The data from the remaining 81 cases form the basis of this report.

Assessment of liver metastases
Gross findings of the liver metastases were classified into two types as follows; the simple nodular type (SN): a smooth, distinct border and medullary structure with or without necrotic foci, the confluent nodular type (CN): an irregular contour and a cut surface consisting of multiple nodules. Meticulous macroscopic examination of the specimen was made in search of invasive factors such as vessel or ductal infiltration, minute satellite lesions, direct invasion into the adjacent viscera, or regional lymph node metastases.

Statistical analysis
Cumulative survival rates were calculated by the Kaplan-Meier method. The Logrank test was used to evaluate the differences between the survival curves. For comparisons between the SN and CN groups, the chi-squared test was applied. Several clinicopathologic factors, including those found to be associated with patient survival by univariate analysis, were subjected to multivariate analysis using Cox's proportional hazards model. A p<0.05 was considered statistically significant.

**Results**

There were 39 SN lesions and 42 CN lesions. No statistically significant differences were observed between the two types regarding sex, age (both mean and median), clinical stage of the primary lesion, histopathologic type of the primary and metastatic lesions, number of metastatic lesions, or the ratio of synchronous metastatic lesions to metachronous lesions. The cumulative 3- and 5-year survival rates for the SN type (72.6% and 41.7%, respectively) were significantly higher (p=0.0307) than those for the CN type (39.5% and 23.1%, respectively). Invasive factors were positive in 7 out of 39 patients (17.9%) with the SN type lesions, and 25 of 42 patients (59.5%) with the CN type lesions (p=0.0001). Of the invasive factors, vessel infiltration was observed in 19 of the CN type lesions (45.2%), and only 4 of the SN type lesions (10.3%) (p=0.0005).

Multivariate analysis using Cox's proportional hazards model revealed that the macroscopic type (p=0.023), the tumor diameter (p=0.0001), and the presence of lymph node metastases (p=0.0016) were statistically significant independent prognostic factors.

**Conclusion**

Invasive and progressive characteristics of the metastatic lesions are thus reflected well in this novel classification of the macroscopic type. In conclusion, the new macroscopic classification may be valuable as a prognostic factor reflecting the biologic behavior of liver metastases.
TECHNIQUES AND THERAPEUTIC EFFECTS OF HEPATIC ARTERIAL INFUSION CHEMOTHERAPY FOR LIVER METASTASES

Yasuaki Arai, M.D.,Ph.D.
Aichi Cancer Center
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan

Thechniques
Arterial redistribution to make multiple hepatic arteries one
In cases with two or more hepatic arteries, to gain the entire drug distribution by an indwelling catheter, hepatic arteries remaining one must be embolized by steel coils. By this procedure, infused drug via remaining hepatic artery can reach to entire liver through intrahepatic arterial anastomoses. In 51 cases, the successful rate of this procedure was 100% without major complications.

2. Right gastric arterial embolization
To prevent drug induced gastric ulcers, the right gastric artery must be embolized. In 89 cases, the successful rate of this procedure was 89% without major complications.

3. Percutaneous catheter placement
The advantage of percutaneous catheter placement is remarkably limited invasion compared with that by laparotomy. In 489 cases, the successful rate of percutaneous catheter placement was 95% under local anesthesia within 1.5 hour in average.

4. Fixation of the distal end of indwelling catheter.
The biggest problem in percutaneous catheterization was its high incidence of hepatic arterial occlusion (20-25%). Side-holed catheter with fixation method was developed to prevent hepatic arterial occlusion. In 103 cases, the successful rate of this procedure was 99%, and the incidence of hepatic arterial occlusion significantly decreased to 5%.

5. Embolization of collateral arteries
In the long term hepatic infusion, sometimes collateral blood supply to the liver
occur. In such cases, embolization of collateral arteries must be performed to correct drug distribution. In 26 cases, the successful rate of this procedures using liquid embolic material was 81% without major complications.

Therapeutic effects
1. Colorectal cancer
1000mg/sqm of 5FU was given by 5 hr continuous infusion every week. In 30 patients without extra-hepatic lesions, the response rate, the median survival and the prevention rate of hepatic death was 83%, 26 months and 69%, respectively.
2. Gastric cancer
330mg/sqm of 5FU in every week, 2.7mg/sqm of MMC in every 2 weeks and 30mg/sqm of EPIR or 20mg/sqm of ADM in every 4 weeks was given by bolus injection (FEM/FAM regimen). In 40 patients, the response rate, the median survival and the prevention rate of hepatic death was 72%, 17 months and 72%, respectively.
3. Breast cancer
Using FEM or FAM regimen, in 56 cases, the response rate, the median survival and the prevention rate of hepatic death was 81%, 12 months and 70%, respectively.

Conclusion
Hepatic arterial infusion chemotherapy has much potential for good management of patients with unresectable liver metastases, and interventional procedures are the most important keys to start and continue good hepatic arterial infusion chemotherapy under minimal invasion and complications.
High risk state and early change of the pancreatic carcinoma

Department of Pathology, Cancer Institute, Tokyo

Y.KATO and A. YANAGISAWA

Since long, there have been a lot of discussions on high risk states and precursor lesions for the common type pancreatic carcinoma, i.e. ductal pancreatic carcinoma. As for the former, duct cell hyperplasia, particularly, atypical hyperplasia is the most famous candidate and, as to the latter, what is called 'in situ carcinoma' can be a suspected lesion. Here, we would like first to stress a significance of atypical epithelia, what we call G3 and G4, in the process of pancreatic carcinogenesis, then refer to an unexpectedly high incidence of Ki-ras oncogene mutation in mucous cell hyperplasia', and finally show changes found in cases of 'in situ carcinoma'.

1) High risk state for pancreatic cancer development.

Using 14 resected carcinomas (13 of head and one of body ) sectioned completely stepwise, duct epithelial changes occurring in main and branch pancreatic ducts were investigated according to our Group Classification (G1: normal epithelium., G2: regenerative or hyperplastic change, G3: adenoma and atypical hyperplasia or dysplasia, G4: changes strongly suggestive of carcinoma, and G5: overt carcinoma) and compared with those in 8 cases with a carcinoma of papilla Vateri. When G3 and G4 were focused on, they appeared in 7 (50%) and 4 (29%) out of 14 cases respectively either within the tumor area or in the area adjacent to the tumor. However, no such change was detected in cases with a carcinoma of papilla Vateri. Further, the change G3 was associated with G4, and G4 with G5, Thus, G3 can be a change at high risk for pancreatic cancer development and a sequence of G3-G4-G5 is considered to be a rather common pathway of pancreatic carcinogenesis.

2) Frequent Ki-ras mutation in mucous cell hyperplasia and its significance in pancreatic carcinogenesis.

It is well known that Ki-ras oncogene mutation is very common in pancreatic tumors and has been reported recently that it is also frequent even in
musous cell hyperplasia of the duct epithlum. In this line, we investigated the mutation in multiple foci with mucous cell hyperplasia found in the same pancreas suffered only from pancreatitis. All four pancreases examined showed high frequencies (75-100%) of the mutation for mucous cell hyperplasia and a tendency to have higher incidences of the mutations such as GGT(Gly) to GAT(Asp) and GGT(Gly) to GTT(Val), as found in obvious invasive carcinomas of the pancreas in the Japanese. This indicates that the pancreatic carcinoma develops from mucous cell hyperplasia. However, this change may be a quite early event in the process of tumorigenesis and how frequently and how long later the tumors take place in such conditions remain to be clarified.

3) Early changes of the pancreatic carcinoma.

Although mucinous cystic tumors associated with a focus or foci of carcinoma were sometimes encountered, it is very rare to meet cases of what is called 'in situ carcinoma', which is considered to be a precursor lesion for most of common type pancreatic carcinomas. According to Classification of the Pancreatic Carcinoma compiled by Japanese Research Society for Pancreatic Carcinoma, it is defined as a carcinoma limited to the ducts and composed of rather flat or low papillary epithelium. Therefore, carcinomas found in intraductal papillary adenoma or intraductal papillary carcinomas should be excluded from the category. Using two cases of 'in situ carcinoma', changes occurring in the ducts will be shown and associated lesions be again discussed.
Adenocarcinoma of the pancreas is the fifth leading cause of cancer death in the United States. Although surgery and radiation therapy may improve diagnosis in patients with localized and resectable tumors, cure of this disease is rare. Patients with pancreatic cancer very commonly have locally advanced disease and frequently developed disseminated metastatic disease. Such patients would be good candidates for therapy with effective systemic anti-neoplastic treatments.

Single cytotoxic agent chemotherapy, with the possible exception of Gemcitabine, has been of relatively little value in patients with advanced pancreatic cancers. Fluorinated pyrimidine based regimens have only uncommonly produced clinically valuable responses. The main role for fluorinated pyrimidines in the treatment of pancreatic cancer is in combination with radiation, a situation in which these drugs function as radiation sensitizers. Combination chemotherapy has also of little value. FAM (5-fluorouracil, adriamycin, mytomycin-C) type regimens and SMF (streptozotocin/mitomycin-C/ fluorouracil) regimens have produced objective responses in pancreatic cancer but impact upon survival has been nil.

Newer agents are of some interest in pancreatic cancer. Gemcitabine, a fluorine substituted cytarabine analog, not only induces objective anti-tumor responses with very acceptable toxicity but also has a positive effect on quality of life by improving pain control and nutrition. The taxanes (paclitaxel and docetaxel) have been evaluated to some extent in this disease. Paclitaxel in combination with G-CSF was generally not effective in patients with advanced pancreatic cancer. Of 35 eligible patients in a Southwest Oncology Group study, stable disease was observed in some cases and there was one response documented. Docetaxel has been reported in a study of 28 patients to produce a 17% objective response rate with a median duration of response of three months. Further evaluation of taxanes and taxane combination would seem warranted. A new non-fluorinated pyrimidine thymidylate synthase inhibitor, Tomudex, will
need to be evaluated in pancreatic cancer as it has some activity in colorectal cancer and is generally well tolerated. Topoisomerase-1 inhibitors such as CPT-11 and topotecan also have not been broadly evaluated in pancreatic cancer and need such evaluations. Modulation of 5-FU continue to be pursued in pancreatic cancer. One of the more interesting approaches is the use of DPD inhibitors with oral 5-FU. The Southwest Oncology Group is initiating a phase II trial of this approach in pancreatic cancer.

There are approaches to the management of pancreatic cancer that are exploring therapies other than cytotoxic chemotherapy. Biologic therapies are being tested. Somatostain analogue is being evaluated in a large trial in the United States versus 5-FU given as a single agent. This is an ongoing study. The monoclonal antibody 17-1A which is of interest because of some apparent benefit in colorectal cancer has been tested in pancreatic cancer. In a study of 25 evaluable patients, one CR was noted.

There has been some interest in a new ribonuclease with promising in vitro activity. This is the drug onconase which is also called P-30 protein. This drug was originally isolated from the ova of the leopard frog. The drug has been demonstrated to produce cell differentiation and induce apoptosis in tumors in vitro. In a phase I trial in case with stage IV pancreatic cancer, 1 CR was produced along with a stable disease in approximately 15% of pretreated cases. Two multicenter studies are currently underway with onconase to assess its activity in previously untreated patients.

Molecular genetics of adenocarcinoma of the pancreas is of interest since >90% of cases have mutated K-ras oncogenes. Khleif and co-workers at the National Cancer Institute have developed an interesting study in which PCR techniques are used to amplify mutated K-ras. The mutated gene product is then used as an antigen which is given with a non-specific immunoadjuvant to "vaccinate" patients. This approach has shown that it is possible to develop specific immune responses to the mutated ras protein in pancreatic cancer patients. Whether this will result in clinical benefit in such patients is still unknown.

It should be clear that systemic therapy for pancreatic cancer is still at an early and less than optimally successful stage. Newer cytotoxic agents and biologic approaches along with molecular genetic approaches do hold out hope for a brighter future.
SURGICAL TREATMENT WITH INTRAOPERATIVE RADIATION THERAPY AND INTRAOPERATIVE HYPERThERMIA FOR PANCREATIC CARCINOMA

Takeshi Morimoto, M.D.
Aichi Cancer Center
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan

The cure rate for patients with pancreatic carcinoma remains low. In our previous study, radical resection with conventional intraoperative radiation therapy (IORT) for pancreatic carcinoma has been shown to improve survival a little. The survival rate of the patients of radical resection with IORT for pancreatic carcinoma (n=30) in our hospital are one year: 44.2%, 3 years: 27.1% and 5 years: 27.1%. This result is relatively good compared with the survival rate of resected cases registered to the Pancreas Registration Committee of Japan Pancreas Society (n=1,121) one year 49.8%, 3 years: 16.8%, 5 years: 9.6%. But it remains unsatisfactory and not very effective in our prior experience with patients having locally advanced pancreatic carcinoma, we initially treated these patients with simultaneous intraoperative interstitial hyperthermia (IOHT) and IORT as a pilot study to potentially improve local control. This simultaneous IOHT-IORT was initiated in February 1992 for patients with pancreatic carcinoma diagnosed histologically. Six patients were treated, four were not resected and two were resected after simultaneous IOHT-IORT. Interstitial hyperthermia treatment is delivered by a MINERVE hyperthermia system (Odam Co. Ltd, France). After surgical exposure, three to four pairs of metal catheters are implanted into the pancreatic carcinoma for IOHT. Then the patient is moved under the linear accelerator beside the MINERVE system. At the midpoint in time during 30 minutes of steady state temperature at 43°C, 25Gy of IORT is delivered using high-energy electrons (12-16 MeV). After completion of IORT and IOHT, for resectable cases pancreaticoduodenectomy with regional lymphnodes dissection is performed. Then for unresected patients, fibrin glue is sprayed on the sutured field and
gastrojejunostomy and/or hepaticoduodenostomy are performed. Six patients underwent the simultaneous IOHT-IORT treatment. Two were resected and four were unresected cases. In resected cases, the purpose of this therapy prior to resection is to prevent intraportal dissemination to the liver during manipulation of pancreas resection. The advantage of this method is simultaneous use of two effective modalities for local tumor control. The thermal enhancement ratios for tumors were higher after simultaneous treatment than when heat and radiation were given in immediate succession. In our clinical trial 43.0°C 30 min heat and 25 Gy radiation were applied at exactly the same time. Evaluation of local control was attempted with CT scanning at 3-4 weeks and three months. In two unresected cases, the presence of a CT-documented decrease in the size of the primary tumor mass was noted. Two resected cases given IOHT-IORT before resection have lived for 4 years and 2 months, and lived for 3 years and 8 months. In four unresected cases, patients were survived 6, 6, 4, and 2 months, respectively. In the six cases under study, there were no critical side effects or complications such as bleeding or pancreas fistula after surgery. This pilot study has been proven that simultaneous IOHT and IORT are safe and clinically feasible forms of treatment.
DIAGNOSIS OF EARLY GALLBLADDER CARCINOMA

Kazuo Inui, M.D.

Second Teaching Hospital, Fujita Health University
3-6-10, Otoubashi, Nakagawa-ku, Nagoya, Japan

We treated 133 patients with gallbladder carcinoma in our hospital from 1979 to 1996. According to the TNM classification, 32 of 133 patients (24.1%) were T1 (so called early gallbladder carcinoma), tumor invades to mucosa or muscular layer, 36 were T2, tumor invades to perimuscular connective tissue with no extension beyond serosa or into liver, 28 were T3, tumor invades beyond serosa and/or into adjacent organ with extension into liver of 2cm or less, 37 were T4, tumor extends more than 2cm into liver and/or into two or more adjacent organs.

The findings of ultrasonography (US) in early gallbladder carcinoma were polypoid lesion, gallstone and dilatation of the common bile duct. 24 of 32 patients (75%) were detected as polypoid lesion, but 7 of 32 (29.2%) were not detected because of gallstone.

A T1 carcinoma was correctly diagnosed with Endoscopic ultrasonography (EUS) in 19 of 22 patients (86.4%). A T2 carcinoma was diagnosed correctly with EUS in 10 of 12 patients (83.3%). Over all accuracy for depth of tumor invasion was 85.3%. Non-metastatic lymph nodes were correctly diagnosed with EUS all 23 patients (100%). Lymph node metastasis was correctly diagnosed with EUS in 9 of 12 patients (75%). Over all accuracy of EUS for regional lymph node metastasis was 91.4%.

EUS is very useful for differential diagnosis of gallbladder polypoid lesions and detection of abnormal connection of pancreato-biliary duct, which is thought as a cause of gallbladder carcinoma.

We performed percutaneous transhepatic cholecystoscopy (PTCCS) in 8 patients with early gallbladder carcinoma. All of them (100%) were diagnosed correctly.

Accuracy rates of the recent diagnostic modalities were as follows, US
was 62.5\%, EUS 85\%, ERCP (endoscopic retrograde cholangio-
pancreatography) 65.0\%, CT (computed tomography) 64.7\%, angiography
72.7\% and percutaneous transhepatic cholecystoscopy 100\%.
The first step of early diagnosis of gallbladder carcinoma is ultrasonography. EUS is recommended for the important examination of gallbladder polypoid lesions followed after the routine ultrasonography, and percutaneous transhepatic cholecystoscopy is useful for differential diagnosis between benign and malignant tumors of the gallbladder.
EXPANDABLE METALLIC STENS FOR TREATMENT OF MALIGNANT BILIARY OBSTRUCTION

Hiroya Saito, M.D.
Asahikawa Kosei General Hospital
24-111 1Jo-dori, Asahikawa 078, Japan

Metallic stents have been widely used to relieve biliary obstructions as an alternative to plastic endoprostheses and conventional drainages. In this study, I evaluate the efficacy of the metallic stents in the management of malignant biliary obstruction.

Between August 1989 and September 1996, 310 patients with inoperable malignant biliary obstruction were received internal drainages in my hospital. One hundred and eighty-five patients were treated with metallic stents via a transhepatic approach. The remains of the patients were treated with tube stents via a transhepatic approach or an endoscopic approach. In the patients treated with metallic stents, one hundred and forty-nine patients were combined with anticancer therapy prior to stenting, and 36 patients were without combined therapy. Most of the patients treated with tube stents were without anticancer therapy.

We used Gianturco "Zig-Zag" stents in 79 cases, Wallstent in 64, Strecker stent in 4, and Accuflex stent in 27 cases. Furthermore, 11 patients received modified Gianturco Z stents covered with Gore-Tex. We employed the PTCS before and after stent placement and at reobstruction.

If cancerous tissue was present in the bile duct, the stents embedded in the tumor and the caliber of the bile duct was smaller than that of the stents. Metallic stents are indicated in case with less tumor in the bile duct. If bulky tumor exists in the bile duct, adequate combination therapy to reduce the volume of the tumor should be required before EMS placement. In the cases of inefficient therapy (example pancreatic carcinoma), plastic endoprosthesis or covered stents should be chosen for long-term patency.
MEMO
SURGICAL TREATMENT OF HILAR CHOLANGIOCARCINOMA

Yuji Nimura, M.D.
Nagoya University
65 Tsurumai-chou, Shouwa-ku, Nagoya 466, Japan

Introduction
Recent advances of diagnostic and surgical procedures have led an increased number of surgically curable biliary cancers and improved the surgical results. In this report, my surgical approach to hilar cholangiocarcinoma is described.

Materials and Method
From April 1971 to December 1995, 154 patients with hilar cholangiocarcinoma were treated in the 1st Department of Surgery, Nagoya University Hospital. Percutaneous transhepatic biliary drainage (PTBD) was performed in 145 patients out of the 154, and 114 patients underwent resective operation after unilateral or bilateral multiple PTBD. Hepatectomy was carried out in 109 patients and bile duct resection in 13 patients out of the all 122 resected patients. Fifteen kinds of curative hepatectomy was possible in 93 cases out of the 100 curative resection. Combined portal vein resection was performed in 39 patients out of the 122 resected patients, and pancreatoduodenectomy was also carried out in 18 patients. Since 1989, percutaneous transhepatic portal vein embolization (PTPE) has been carried out to increase the safety of major hepatectomy for biliary cancer patients. And 18 patients with hilar cholangiocarcinoma underwent preoperative portal vein embolization: Right trisegment portal vein embolization in 3 patients, right portal vein embolization in 8, and the left trisegment portal vein was embolized in 6 patients.

Results
Some kinds of complication were encountered in 28(19%) patients after
PTBD, but there has been no fatal complication. Several kinds of postoperative morbidity were experienced in 62 (50.8%) patients out of the 122 resected patients, and 8 patients died in the hospital after 100 curative surgery.

The 5-year and 10-year survival rates for 100 patients with curative resection and 83 resected patients without portal vein resection were 24%, 18%, 23%, respectively. Only 1 patient (5.8%) survived after combined liver and portal vein resection. There are statistically significant differences in survival times between the 3 groups: curative resection, palliative resection and non-surgical treatment, respectively.

Conclusions

It is recommended that rational hepato-biliary resection should be applied after careful preoperative managements with precise diagnosis to prolong and improve the quality of survival for patients with hilar cholangiocarcinoma.
PROXIMAL BILE DUCT CANCER: HIGH RESECTABILITY RATE AND 5 YEAR SURVIVAL

B. Launois

Hospital de Pontchaillou
Rue henri Le Guilloux-35033, Rennes, France

From January 1968 to January 1993, 40 of the 94 patients seen at our institution and submitted to surgery for proximal bile duct carcinoma underwent resection of the lesion with or without liver resection. The aim of this paper is to update the Rennes results with resectional surgery and to evaluate the role of hepatectomy associated with bile duct resection in the management of proximal bile duct cancer of the 40 patients undergoing resection. 23 were men and 17 women ranging in age from 34 to 81 years (mean 60.4 years). According to Bismuth classification, there were 5 type I, 4 type II, 25 type III and 6 type IV. 11 patients underwent a tumor resection without hepatectomy, 18 patients underwent a tumor resection with hepatectomy, right hepatectomy in three, right hepatectomy extended to segment IV in four, right hepatectomy extended to segment IV and I in one, bisegmentectomy II and III in one, left hepatectomy in four, left hepatectomy extended to segment I in three resection of segment IV in two patients. Seven patients had liver resection with regional vascular resection. In 3 patients venous allografts were used to reconstruct the portal vein and its main branches. The bile duct and portal vein resection was combined with a left hepatectomy extended to segment I plus resection and reconstruction of the right hepatic artery in one patient, segmentectomy I, IV and V plus the resection of the right hepatic artery in one patient with the remaining patient undergoing a left hepatectomy. Two other patients had a left hepatectomy extended to segment I; one had ligation of the right hepatic artery and the other reconstruction of the right hepatic artery. The other 2 patients had an end-to-end approximation of the portal vein, one with a left hepatectomy and the other with a right hepatectomy extended to segment IV. Four patients had a liver transplantation which was combined in two patients with an organ Cluster-type resection. Of the 40 patients who had tumor resection, 5 died within 30 days of operation giving an
operative mortality of 12.5%. There were no operative death following bile duct resection alone or after the more extensive hepatectomy and vascular resection. The resectability rate was 49.4%. The type of surgery is closely related to tumor location, tumor size and TNM classification. Actual survival of the overall group of 40 patients at 1,3,5 years was 82.5%, 30% and 12.5%. Following tumor resection alone, the actual survival at 1, 3 and 5 years was 91.1%, 45.5% and 27.3% respectively. Following tumor resection and hepatectomy without vascular resection, 1, 3 and 5 years survival rates were 77.8%, 16.7% and 5.6%. With vascular resection the survival is similar, 80%, 20% and 4%. In conclusion, if tumor location is type I or II, if primary tumor is T in situ or T1 stage 0 or stage I tumor resection alone is sufficient. If tumor location is type III or IV, if primary tumor is T2 or T3, stage II, III or IV, hepatectomy is necessary. An higher resectability rate released to hepatectomy rate improves the chances of survival.
Addresses of Speakers

Kazuo Inui, M.D.  
Assistant Professor  
Department of Internal Medicine  
Fujita Health University School of Medicine. Second Teaching Hospital  
3-6-10, Otoubashi, Nagoya 454, Japan  
Phone: 052-321-8171  
Fax: 052-323-9886

John S. Macdonald, M.D.  
Professor  
Division of Medical Oncology  
Temple University  
3322 North Broad Street. Philadelphia, PA 19140, USA  
Phone: 215-707-8030  
Fax: 215-707-1669

Bemard Latinois  
Professor  
Clinique Chirurgicale  
Hospital de Pontchaillou  
Rue henri Le Guilloux-35033. Rennes, France  
Phone: 99-28-43-21  
Fax: 99-28-41-29

Takeshi Morimoto, M.D.  
Vice Director  
Department of Gastroenterological Surgery  
Aichi Cancer Center  
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan  
Phone: 052-762-6111  
Fax: 052-763-5233

Hayao Nakanishi, M.D.  
Section Head  
Laboratory of Pathology  
Aichi Cancert Center Research Institute  
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan  
Phone: 052-762-6111  
Fax: 052-763-5233

Masao Omata, M.D.  
Professor and Chairman  
Second Department of Internal Medicine  
University of Tokyo  
7-3-1 Hongo, Bunkyou-ku, Tokyo 113, Japan  
Phone: 03-3815-5411  
Fax: 03-3814-0021
Kenzo Yasui, M.D.  
Vice Director  
Department of Gastroenterological Surgery  
Aichi Cancer Center  
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan  
Phone: 052-762-6111  
Fax: 052-763-5233

Masamichi Kojiro, M.D.  
Professor and Chairman  
First Department of Pathology  
Kurume University School of Medicine  
67 Asahi-machi, Kurume 830, Japan  
Phone: 0942-35-3311  
Fax: 0942-32-0905

Hiroya Saito, M.D.  
Director  
Department of Radiology  
Asahikawa Kosei General Hospital  
24-111 1Jo-dori, Asahikawa 078, Japan  
Phone: 0166-33-7171  
Fax: 0166-33-6075

Yasuaki Arai, M.D., Ph.D.  
Vice Director  
Department of Diagnostic Radiology  
Aichi Cancer Center  
1-1 Kanokoden, Chikusa-ku, Nagoya 464, Japan  
Phone: 052-762-6111  
Fax: 052-763-5233

Yuji Nimura, M.D.  
Professor and Chairman  
Department of Surgery  
Nagoya University  
65 Tsurumai-chou, Shouwa-ku, Nagoya 466, Japan  
Phone: 052-744-2217  
Fax: 052-744-2230

B. Kremer, M.D.  
Professor and Chairman  
Department of General and Thoracic Surgery  
University of Kiel  
Arnold-Heller-Str. 7., D-24105, Kiel, Germany  
Phone: 49-431-5974304  
Fax: 49-431-5974586

Yo Kato, M.D.  
Chief  
Department of Pathology  
Cancer Institute  
1-37-1 Kamiikebukuro, Toshima-ku, Tokyo 170, Japan  
Phone: 03-3918-0111  
Fax: 03-5394-3923