results confirmed the correlation between CapG expression and response to GEM treatment observed in the generated protein expression profiles.

Overexpression of CapG has been reported in various types of malignancies [22–27]. In addition, *in vitro* experiments using breast and pancreatic cancer cell lines demonstrated that CapG plays a key role in metastasis and invasion [22,24,28]. We used immunohistochemistry to examine CapG expression in an additional set of 196 cholangiocarcinoma cases that did not receive GEM treatment alone and that were not included in the proteomic study. In 123 EHCC cases, but not 73 IHCC cases, CapG-positive and CapG-negative tumors had significantly different macroscopic type, histological type, lymphatic invasion status and surgical resection procedure in univariate analysis (Supplementary Table 1). Because CapG expression was correlated with established prognostic parameters, such as lymphatic invasion [29,30], in the EHCC cases (Supplemental Table 1), we further investigated the prognostic value of CapG expression. The Kaplan–Meier survival curve showed that patients with CapG-positive cholangiocarcinoma had significantly worse prognosis than those with CapG-negative one in terms of overall survival rate (EHCC, $p=0.047$; IHCC, $p=0.021$) (Fig. 5). Univariate and multivariate analyses revealed that CapG was an independent prognostic factor for overall survival (EHCC: HR, 1.89; 95% CI, 1.11–3.20; $p=0.018$, IHCC: HR, 2.26; 95% CI, 1.23–4.14; $p=0.008$), along with other established clinicopathological parameters such as the macroscopic type, degree of differentiation, venous involvement, and lymph node metastasis (Table 3).

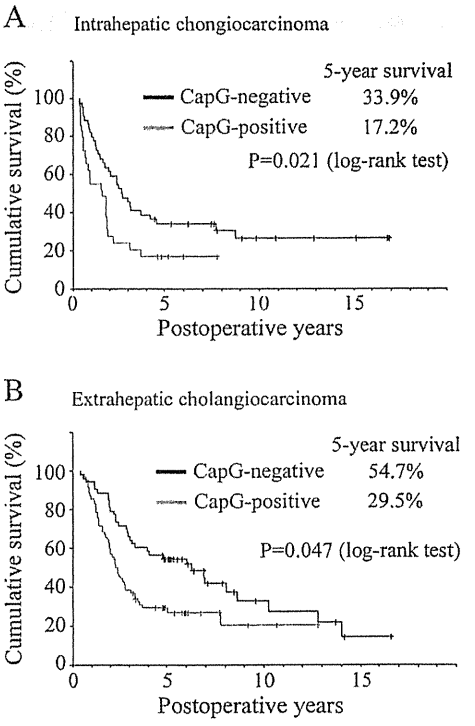

Fig. 5 – Survival curves stratified by CapG expression in (A) intrahepatic and (B) extrahepatic cholangiocarcinoma (Kaplan–Meier method). The outcome for the CapG-positive cases was significantly worse than that for the CapG-negative cases in both intrahepatic ($P=0.021$) and extrahepatic cholangiocarcinoma ($P=0.047$) (by log-rank test).

4. Discussions

GEM has been used in the treatment of various types of malignancies [31–34]. However, since only a limited number of patients has benefited from GEM treatment, novel biomarkers are required to predict the response to treatment and hence to optimize the therapeutic strategy.

Previous global studies and studies on individual genes for GEM resistance revealed that the expression levels of human equilibrative nucleoside transporter-1 (hENT1), deoxycytidine kinase (dCK), ribonucleotide reductase M1 and M2 (RRM1 and RRM2) [35], and heat shock protein 27 (Hsp27) in pancreatic cancer cells [36], correlated with gemcitabine-resistance, and that the expression levels of ribonucleotide reductase M1 [37], activation of checkpoint kinases, Chk2 and Chk1, extracellular signal-regulated kinase (ERK)1/2 [38], eukaryotic initiation factor 4E [39], micro-RNAs [40] and melanoma antigen family H 1 (MAGEH1) [16] were also associated with gemcitabine resistance in cholangiocarcinoma cells. In contrast, although the use of a proteomic approach has been proven to be effective for biomarker development [41], only two proteomic studies have examined the molecular backgrounds of the different response to GEM treatment [36,42], and there is no report on CapG expression in relation to GEM treatment in cholangiocarcinoma.

CapG controls actin-based motility by capping the bared ends of actin filaments [43]. CapG overexpression has been previously detected in a range of malignancies [23–26] probably having a role in the control of cell mobility, invasiveness, and metastasis in cancer cells [28,44]. However, the association between CapG expression and response to GEM treatment in cholangiocarcinoma has not been examined to date.

We found that CapG expression was significantly associated with histologic evidence of lymphatic invasion status, one of the dominant prognostic factors in EHCC [29]. We subsequently examined the relation of CapG expression with overall survival and found that patients with CapG-positive cholangiocarcinoma had significantly shorter survival than those with CapG-negative tumors irrespective of tumor location. Multivariate analysis revealed that CapG expression was an independent prognostic factor for survival of IHCC and EHCC patients. Although we did not identify the clinicopathological prognostic parameters associated with CapG expression in IHCC, our results show that CapG expression is a biomarker that has prognostic value and is possibly predictive of the response to GEM treatment in cholangiocarcinoma.

The three experiment model types used in this study have unique advantages for cancer research. Cell line and xenograft models provide preclinical experimental platforms, where the effects of drug treatment on cell phenotypes and target molecules can be repeatedly and easily assessed. Cell line models, albeit artificial, are easy to use and suitable for pharmacokinetics and pharmacodynamics studies, while xenograft models simulate human disease more accurately

Table 3 – Overall survival.

Survival		Adjusted HR	95% CI	p value
Total (73 IHCC cases)				
Macroscopic type	Non-mass forming	1.00		
	Mass forming	4.29	1.78, 10.36	0.001
Differentiation of adenocarcinoma	Well	1.00		
	Mod	1.05	0.46, 2.41	0.914
	Por	5.84	1.30, 26.24	0.021
Venous invasion	Negative	1.00		
	Positive	8.30	2.10, 32.81	0.003
CapG	Negative	1.00		
	Positive	2.68	1.52, 4.72	0.001
Total (123 EHCC cases)				
Differentiation of adenocarcinoma	Well	1.00		
	Mod	1.45	0.86, 2.44	0.165
	Por	4.34	2.10, 8.98	< 0.001
Venous invasion	Negative	1.00		
	Positive	4.20	1.54, 11.41	0.005
UICC pN	pN0	1.00		
	pN1	2.10	1.29, 3.40	0.003
Surgical resection procedure	PD	1.00		
	EHBR	1.13	0.40, 3.23	0.817
	HR+EHBR	1.94	1.10, 3.42	0.022
	HR	5.97	1.26, 28.29	0.024
	HPD	2.45	0.96, 6.25	0.061
CapG	Negative	1.00		
	Positive	1.74	1.06, 2.88	0.030

Abbreviation: HR, hazard ratio; CI, confidence interval; Well, well differentiated adenocarcinoma; Mod, moderately differentiated adenocarcinoma; Por, poorly differentiated adenocarcinoma; PD, pancreatoduodenectomy; EHBR, extrahepatic bile duct resection; HR, hepatic resection; HPD, hepatopancreatoduodenectomy.

[45]. The study of expression using primary tumor tissues provides data on the actual molecular events occurring in patients, however, experiments requiring living cells cannot be done using clinical materials. We identified CapG as a protein predictive of the response to gemcitabin treatment using all the aforementioned model types. Unique CapG isoforms were observed in each of the three experimental systems (Fig. 3B), and the functional difference of these three isoforms remains to be elucidated. The molecular backgrounds generating these isoforms are presently not clear. Each isoform may have its own functions, and certain common properties may associate with the malignant potentials examined in this study. In any case, as the association of the total amount of CapG with poor prognosis was proven in a large sample set (196 cases), further consideration of the clinical utility of CapG expression in personalized medicine may be warranted. The patients with CapG-positive tumor may have worse prognosis and exhibit resistance to GEM treatment. More intense treatments using presently available therapies, or development of novel drugs for such patients should be considered.

As CapG expression was correlated with both the sensitivity to GEM treatments and poor prognosis, it may be involved in the overall molecular mechanisms underlying the malignant potentials of cholangiocarcinoma cells. Previous studies suggested that CapG contributed to the cell motility in pancreatic cancer cells [24]. Thus, it is worthy challenging to explore the possibility of CapG as a therapeutic target.

5. Conclusions

We studied the proteomic profile of cholangiocarcinoma using three well-characterized sources of material. We identified CapG expression as a novel biomarker predictive of response to GEM treatment and as a prognostic indicator in cholangiocarcinoma. Although the number of cases in this study was still limited and the further validation studies should be needed before clinical applications, the inclusion of CapG expression in the diagnostic arsenal may lead the novel strategies for cholangiocarcinoma management. The cholangiocarcinoma patients who have CapG-positive primary tumor may need more intense therapy, other than that with GEM. The applications of CapG may be also worth challenged in the cholangiocarcinoma.

Supplementary materials related to this article can be found online at doi:10.1016/j.jprot.2011.11.030.

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Successful Control of Intractable Hypoglycemia Using Radiopharmaceutical Therapy with Strontium-89 in a Case with Malignant Insulinoma and Bone Metastases

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This report describes the case of a 57-year-old woman with liver and bone metastases from malignant insulinoma, who was afflicted with severe hypoglycemia. Treatment of the liver metastases using octreotide, diazoxide and transarterial embolization failed to raise her blood glucose level and she required constant glucose infusion (about 1000 kcal/day) and oral feeding (about 2200 kcal/day) to avoid a hypoglycemic attack. Subsequently, 110 MBq (2.0 MBq/kg) of strontium-89 were administered by intravenous injection. Three weeks after the strontium-89 injection, we could reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, the constant glucose infusion was discontinued. Although strontium-89 therapy is indicated for patients with multiple painful bone metastases, it was also useful as a means of inhibiting tumor activity and controlling hypoglycemia in this case. To our knowledge, this is the first report to provide evidence that strontium-89 can be useful in controlling intractable hypoglycemia in patients with malignant insulinoma with bone metastases.

Key words: strontium-89 – malignant insulinoma – bone metastases

INTRODUCTION

Insulinomas are rare tumors that arise from the pancreatic islet cells that produce insulin. Approximately 5–10% of the insulinomas are cancerous (1). It is often difficult to control inappropriate insulin secretion and hypoglycemia in patients with a malignant insulinoma. Although surgery is indicated for symptomatic or malignant insulinoma, only medical therapy is suggested for unresectable patients (2). Some cases suffer from intractable hypoglycemia as a result of the limited efficacy of medical therapy. We report here on the case of a 57-year-old woman with a malignant insulinoma and bone metastases in whom intractable hypoglycemia was successfully controlled by using radiopharmaceutical therapy with strontium (Sr)-89.

CASE REPORT

In March 2002, a 57-year-old woman experienced frequent hypoglycemic attacks and was diagnosed as having an insulinoma of the pancreas tail at a previous hospital. She

underwent surgery including a distal pancreatectomy and splenectomy at the previous hospital. The maximum diameter of the surgically removed tumor was 10 cm. The histopathological findings revealed a pancreas islet cell carcinoma. The tumor had directly invaded the spleen and protruded into the splenic vein and pancreatic duct. The surgical resection stump was negative.

In February 2005, multiple liver metastases were detected and the patient was referred to our hospital. Then, she received a partial hepatectomy for multiple liver metastases in our hospital. The histopathological findings of resected specimen showed a low-grade endocrine cell carcinoma. The immunohistochemical staining showed positive for chromogranin A and synaptophysin, but it showed negative for insulin. In July 2006, she underwent a second partial hepatectomy for recurrent multiple liver metastases. Histopathological examination of the liver metastases showed similar findings to the first liver segmental resection.

In December 2008, multiple liver metastases and multiple bone metastases including lumbar vertebrae and iliac bone were detected. In March 2009, she started zoledronic acid hydrate treatment for the bone metastases, but it was discontinued because of severe jaw pain suggesting the possibility of mandibular osteonecrosis. In November 2009, the patient experienced a hypoglycemic attack again. The patient was hospitalized to control her serum glucose level. The laboratory data obtained at admission are shown in Table 1. Regarding the serum hormonal level, the insulin level was slightly elevated but the glucagon level was not elevated. The level of neuron-specific enolase was slightly elevated. The patient underwent short-acting somatostatin analogs for 14 days to control the serum glucose level due to their antiproliferation effect. After having confirmed that there was no worsening of the hypoglycemia symptoms, we changed her treatment to a long-acting somatostatin analog (Sandostatin-LAR; Novartis Pharmaceuticals). However, hypoglycemia occurred frequently (Fig. 1) even after the initiation of octreotide therapy. The patient refused to continue the octreotide therapy because her hypoglycemic attacks had not improved. The hypoglycemia persisted after the discontinuation of octreotide. Next, diazoxide was administered with no effect but with the side effects of significant edema and weight gain. We decided to undertake transarterial embolization (TAE) to necrotize the liver metastases and

Table 1. Laboratory data upon the first admission after the experience of a hypoglycemic attack

	Actual level	Normal level		Actual level	Normal level
Hematology			Tumor markers		
Leukocyte (per mm^3)	10 200	(3900–6300)	CEA (ng/ml)	2.5	(<5)
Hemoglobin (g/dl)	11.9	(11.3–14.9)	CA19–9 (U/ml)	12	(<37)
Platelet (per mm^3)	39×10^4	($12.5–37.5 \times 10^4$)	NSE (ng/ml)	18.5 (H)	(<15)
Biochemistry			ProGRP (pg/ml)	37.7	(<46)
Total protein (g/dl)	8.0	(6.3–8.3)	Hormones		
Albumin (g/dl)	3.6 (L)	(3.7–5.2)	Insulin (mIU/ml)	12.9 (H)	(1.84–12.2)
Total bilirubin (mg/dl)	0.6	(0.3–1.2)	Gastrin (pg/ml)	82	(<200)
Fasting glucose (mg/dl)	70	(69–104)	Glucagon (pg/ml)	120	(50–150)
BUN (mg/dl)	14	(8–22)	Urine		
Creatine (mg/dl)	0.6	(0.4–0.7)	pH	6.0	(4.6–7.5)
Sodium (mEq/l)	138	(138–146)	Protein	(—)	
Potassium (mEq/l)	4.2	(3.6–4.9)	Sugar	(—)	
Chloride (mEq/l)	104	(99–109)	Blood	(—)	
Calcium (mg/dl)	9.0	(8.7–10.3)			
Amylase (IU/l)	64	(42–132)			
ALP (IU/l)	440 (H)	(115–359)			
AST (IU/l)	16	(13–33)			
ALT (IU/l)	9	(6–27)			
LDH (IU/l)	174	(119–229)			
γ-GTP (IU/l)	25	(10–47)			

BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NSE, neuron-specific enolase; Pro-GRP, pro-gastrin-releasing peptide; (H), high; (L), low.

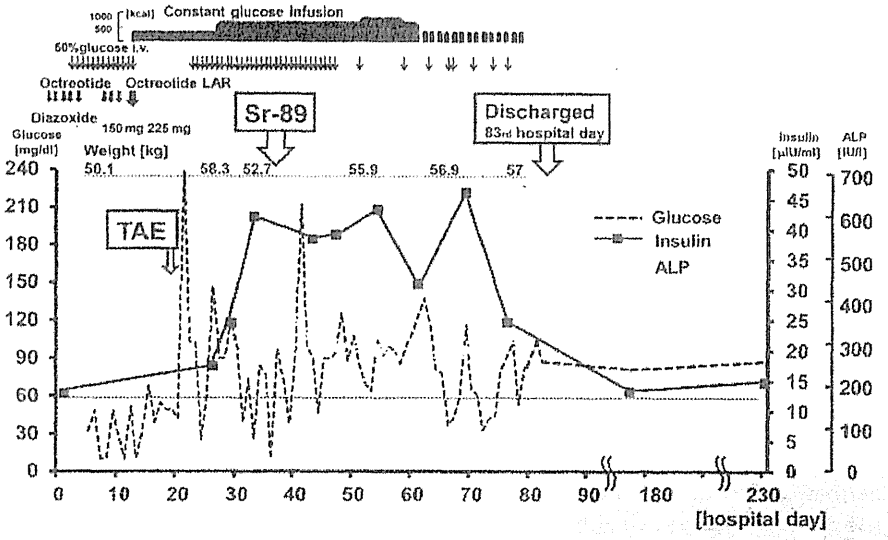

Figure 1. Clinical course. Three weeks after the strontium-89 injection, the patient was weaned from the constant glucose infusion while successfully maintaining euglycemia and lower circulating insulin levels. About 6 weeks after the injection, the constant glucose infusion was completely stopped, even though the previous treatment had failed.

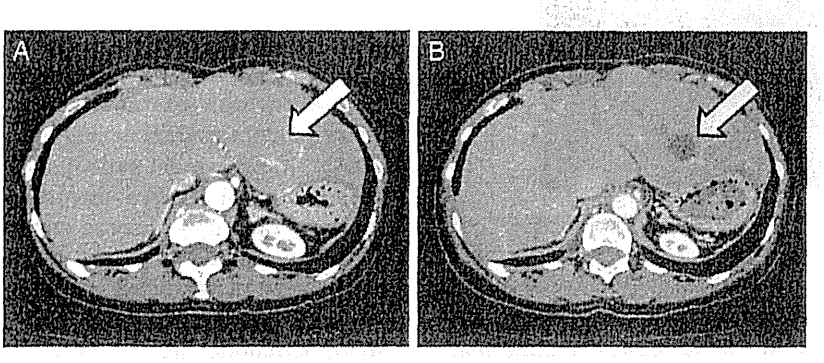

Figure 2. Liver metastases were observed using enhanced computed tomography (A and B, arrow). The liver metastases did not exhibit remarkable hypervascular staining in computed tomography before transarterial embolization (A, arrow), but successful necrotization was achieved using transarterial embolization, as shown in this enhanced computed tomographic imaging 1 week after the treatment (B, arrow). However, the treatment failed to increase the patient's blood glucose level.

prevent the hypoglycemia. TAE was performed on the 20th hospital day. We succeeded in necrotizing the metastases, as shown in Fig. 2. However the hypoglycemia persisted, and then the patient required constant glucose infusions and oral feeding to avoid a hypoglycemic attack (Fig. 1). As shown in Fig. 3A and B, bone scintigraphy revealed a worsening of the bone metastases, compared with images obtained 1 year previously.

^{89}Sr is a novel radiopharmaceutical agent used for the palliation of bone pain from multiple osseous metastases (3). The patient suffered from slight lumbago as a result of the bone metastases, so we attempted to use ^{89}Sr to alleviate her pain and to control her hypoglycemia. In the computed tomography (Fig. 4), the bone metastases showed osteoplastic findings that suggested high sensitivity to ^{89}Sr (4). A 110-MBq dose (2 MBq per kg) of ^{89}Sr was administered by intravenous injection on the 37th hospital day (Fig. 1). One week after the injection, the serum level of alkaline phosphatase was normalized. We were able to confirm the accumulation of ^{89}Sr in metastatic foci that corresponded to bone scintigraphy by using gamma camera (Fig. 3C). Three weeks after the ^{89}Sr injection, we were able to reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, she stopped constant glucose infusion and the bone pain was relieved (Fig. 1). The patient was discharged on the 83rd hospital day. Two months after the ^{89}Sr injection, she was hospitalized again for 3 weeks because of a transient liver dysfunction due to a hepatitis C virus infection. Liver dysfunction was improved using conservative treatment. In December 2010, no progression of bone metastases was seen on bone scintigraphy, and the hypoglycemic control was consistently good. The patient received a second ^{89}Sr treatment 1 year after the first ^{89}Sr treatment because of the recurrence of bone pain. After the ^{89}Sr treatment, the bone pain has remained improved until the time of writing. Local

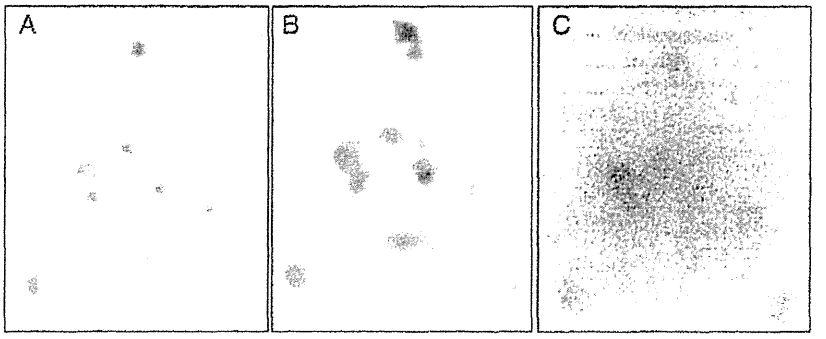

Figure 3. Compared with the results obtained 1 year earlier (A), technetium-99m bone scintigraphy revealed a worsening of the bone metastases (B). The accumulation of strontium-89 in a region corresponding to the observed uptake of sodium pertechnetate was confirmed 1 week after strontium-89 injection (C).

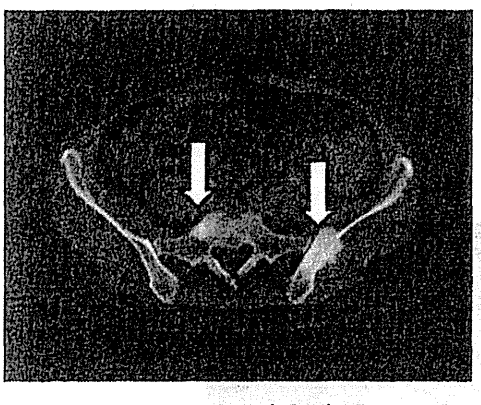

Figure 4. Bone metastases were revealed using computed tomography (arrow).

recurrences of the liver metastases were detected 18 months after TAE (May 2011). Although we proposed additional treatment by TAE or with anticancer agents, the patient refused any additional cancer treatment. At that time, the neuron-specific enolase level was normal (12.1 ng/ml). As of June 2011, the patient continued to be followed up as an outpatient, but she has not received any further treatment for hypoglycemia.

DISCUSSION

Although most patients with malignant insulinoma have lymph node or liver metastasis, there are very few reports in which malignant insulinoma metastasized to a bone (5–7). The prognosis of these patients is relatively poor with a median survival period of ~2 years (8,9).

Glycemic control is a key aspect of managing malignant insulinomas. Mild symptoms can sometimes be controlled by diet (10). Some reports have shown good control of blood glucose levels using a somatostatin analog (11–13). Somatostatin analogs such as octreotide may be helpful for the control of insulin release, but they can also suppress counter-regulatory hormones such as growth hormones, glucagons and catecholamines (10). In this situation, somatostatin analogs can lead to the worsening of hypoglycemia (14). However, octreotide had neither a good nor a bad influence on the hypoglycemia in the patient. Diazoxide, an anti-hypertensive agent known to increase the blood sugar level, inhibits the release of insulin in pancreatic beta cells by opening ATP-sensitive potassium channels (15,16). Its side effects include edema, weight gain, renal impairment and hirsutism (10). Although our patient exhibited edema and weight gain, her hypoglycemia did not improve (Fig. 1). Some authors reported that selective TAE for liver metastases may have the greatest benefit, next to diazoxide (17–22). However, in the present patient, TAE was not effective for glycemic control because unregulated secretion of insulin was mainly caused by the bone metastases.

Concerning other treatment options, De Jong et al. (23) reported that radiolabeled somatostatin analogs, such as [(90)Y-DOTA, Tyr(3)] octreotide and [(177)Lu-DOTA, Tyr(3)] octreotide, are promising treatment modalities for patients with neuroendocrine tumors. However, these radionuclide therapies are not available in Japan. Antiproliferative agents such as streptozotocin, sunitinib and everolimus are also good treatment options (24–26). However, these agents are not covered by the national health insurance in Japan.

^{89}Sr decays by beta emission, with a maximum beta energy of 1.46 MeV, an average soft-tissue penetration of 2.4 mm and a half-life of 50.6 days. After administration, ^{89}Sr is taken up into the mineral matrix of the bone and is selectively concentrated in areas of osteoblastic activity in disease-affected bone, with a biological behavior resembling that of calcium (27). The biodistribution of ^{89}Sr parallels technetium bone-scanning agents (28,29). Pain relief is often obtained 14–21 days after injection (30). Thrombocytopenia and neutropenia are the most common toxic effects, but these effects are generally mild and reversible. Because ^{89}Sr is eliminated mainly via the kidneys, patients are advised to carefully dispose of urine for the first 10 days after administration (27).

The biological mechanism by which ^{89}Sr mediates pain palliation remains unclear. In some basic studies, two possible mechanisms of pain palliation by ^{89}Sr have been proposed (31). One of these mechanisms is a direct radiotoxic effect on the cancer cells caused by the beta-ray emission

from ^{89}Sr. The second mechanism is an indirect action through prostaglandin E2 (PGE2) and interleukin-6 (IL-6) produced by cells in response to ^{89}Sr. PGE2 and IL-6 are known as potent biochemical modifiers of bone turnover. In the patient, the mechanism of improved hypoglycemia was thought to be a direct radiotoxic effect of ^{89}Sr on the cancer cells. The tumoricidal effect of ^{89}Sr on metastatic bone tumors has been reported previously. Dafermou et al. (32) reported that ^{89}Sr therapy resulted in the scintigraphic regression of bone metastases in patients with painful bone metastases from prostate cancer. In addition, Porter et al. (33) reported the reduction of tumor markers, including prostate specific antigen and alkaline phosphatase in the ^{89}Sr therapy of painful bone metastases from prostate cancer. Suzawa et al. (34) reported a case of the complete regression of multiple painful bone metastases from hepatocellular carcinoma after the administration of ^{89}Sr.

In our case, although obvious regression of bone metastases was not detected by the subsequent computed tomography image (Fig. 4), the alkaline phosphatase level decreased (Fig. 1). Because bone scintigraphy was not useful for strict response evaluation, we did not perform it immediately after the strontium-89 injection in this case. Successful pain relief was achieved. Although the intractable hypoglycemia was resistant to all other treatments, it was improved by ^{89}Sr therapy. Though ^{89}Sr therapy is generally indicated for patients with multiple painful bone metastases, in this case, it was also useful as a means of arresting tumor growth and inhibiting tumor activity. To our knowledge, this report is the first to provide evidence that ^{89}Sr can be useful in controlling intractable hypoglycemia in malignant insulinoma with bone metastases.

CONCLUSION

We experienced a case of malignant insulinoma and bone metastases in which intractable hypoglycemia was successfully controlled by using radiopharmaceutical therapy with ^{89}Sr.

Conflict of interest statement

Dr Chigusa Morizane received lecture fee from Novartis Pharma Co., Ltd.

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Japan Pancreatic Cancer Registry; 30th Year Anniversary

Japan Pancreas Society

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Objectives: Since 1981, the Japan Pancreas Society has been hosting a nationwide pancreatic cancer registry. To commemorate its 30th anniversary, we review its history and latest achievement.

Methods: During 3 decades, more than 350 leading institutions in Japan contributed voluntarily to register and periodic follow-up. The registry was modified to protect privacy by encrypting and hash algorithm.

Results: From 1981 to 2007, 32,619 cumulative records were analyzed. The overall survival of invasive cancer was improved significantly. More patients with earlier stage or with intraductal and cystic neoplasms underwent resection. The strongest prognostic factor of Union for International Cancer Control (UICC) stage IIA and IIB tubular adenocarcinoma in the pancreatic head was histological grade, followed by tumor size, extent of lymph node dissection, and postoperative chemotherapy. The 5-year survival rate of Union for International Cancer Control stage 0 reached 85%. The improvement of survival of patients with invasive cancer in Japan can be attributed to the introduction of effective chemotherapies, regionalization, and the earlier diagnosis and treatment. Simple definition of "early pancreatic cancer" is needed.

Conclusions: At the 30th year anniversary, the Japan Pancreas Society nationwide pancreatic cancer registry is more shining than ever for current perspectives and for future diagnostic and treatment tactics.

Key Words: pancreatic cancer, nationwide registry, early diagnosis, surgical treatment, adjuvant therapy, classification

(*Pancreas* 2012;00: 00–00)

The Japan Pancreas Society (JPS) has been conducting nationwide pancreatic cancer registry since 1981. This accomplished a magnificent and only-one database of not only pancreatic cancer but also other neoplastic disease including intraductal neoplasms, cystic neoplasms, neuroendocrine tumors (NETs), and others. Every record consists of more than 300 items regarding patients' background, diagnostic parameters, disease extension, treatment, and outcome. More than 350 leading institutions in Japan voluntarily contributed to its data collection and annual follow-ups. We have previously provided the progress and update[1,2] of our pancreatic cancer registry, and in this manuscript, we will review the history of pancreatic cancer registry in Japan and present its current accomplishment for the perspectives of diagnosis and treatment of pancreatic cancer.

HISTORY

After the establishment of JPS in 1969, the society grew rapidly, with clinicians and researchers exceeding 2000 in membership in 1981, when the nationwide pancreatic cancer registry was started. Before discussing the history of pancreatic cancer registry, we have to describe the history of pancreatic cancer classification in Japan and the world.

To make the registry successful, there has to be a rule for tumor classification. Otherwise, no scientific comparison is possible between the institutions, countries, and even with the historical controls. The TNM classification of cancer was developed in the late 1940s by Pierre Denoix at the Institute Gustave-Roussy.[3] The Union for International Cancer Control (UICC) first published TNM classification in 1953 and its first pocket book in 1968. The American Joint Committee on Cancer (AJCC) began publishing separate TNM classifications in the early 1980s, but AJCC and UICC classification was unified in 1987. As for pancreatic cancer, the TNM classification is currently in its seventh edition, which was not changed from the sixth edition revised in 2002.[4,5]

Partly owing to the difference of native language and partly owing to the difference of types of cancer-related death, the Japanese have developed their own tumor classifications. The first established Japanese tumor classification was for gastric cancer in 1963.[6] The JPS established the first version of rules for classification of pancreatic cancer in 1980. The rules had been periodically revised to the fourth edition, which resembles the UICC TNM classification in 1993. The first English version of the JPS classification was published based on this fourth edition in 1996.[7] The fourth JPS classification required grading description in every category, such as PV_0 (no infiltration to the portal venous system), PV_1 (suspicious infiltration), PV_2 (definite infiltration), and PV_3 (portal vein is stenotic by the invasion), which made the classification and registry complicated. In 2002, the JPS revised this grading simply to yes/no description in the JPS fifth version (English second version[8]) so that the classification can be as equal as the UICC/AJCC classifications. In the meantime, however, UICC had revised to its sixth version in 2002, which is the same with the current/seventh version. The JPS has published its seventh version in Japanese, and the third

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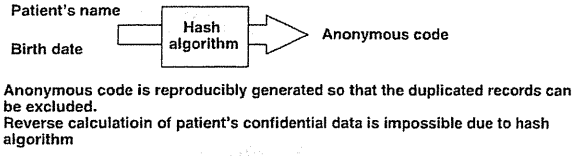

FIGURE 1. Anonymization by encrypting personal data using hash function. If a patient's name and birth date is perfectly the same, the anonymous code is the same. Same character in the anonymous code can be generated from multiple combination of name and birth date, making it impossible to recalculate the original name or birth date. The possibility of generating same anonymous code from different name is less than 1×10^{-20}. Each institution can identify individual patients easily.

English version will appear soon, but the concept of TNM is the same as its previous version in 2002 like UICC/AJCC.

From the beginning, the JPS conducted the pancreatic cancer registry, aiming at not only invasive cancer but also all neoplastic diseases including even benign adenomas, and the registry required the detailed description of the extent of the disease, so that the raw data were durable during several changes of the classification rules. For example, current JPS-T factor is as follows;

Tis: Noninvasive tumor (including mucinous cystic neoplasm, intraductal papillary mucinous neoplasm [IPMN], carcinoma in situ [CIS])
T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3: Tumor that has extended into any of the following: bile duct, duodenum, peripancreatic tissue (anterior, and posterior [RP])
T4: Tumor that has extended into any of the following: adjacent large vessels (portal venous system, PV; and arteries [A]), extrapancreatic nerve plexus (PL), other organs (OO).

If bile duct, duodenum, A, RP, PV, arterial venous system, PL, and OO factors have been registered, the resulting T factor can be recalculated according to the change of rules. The invasive site was also recorded, such as superior mesenteric vein, portal vein, splenic vein, together with its arterial and plexus details. Similarly, the stations of lymph node metastasis and site of distant metastasis were reported according to the rules. In the change of 2002, PV_0 was converted to PV(−); PV_1, PV_2, and PV_3 were converted to PV(+); and all the data were recalculated according to the latest rule.

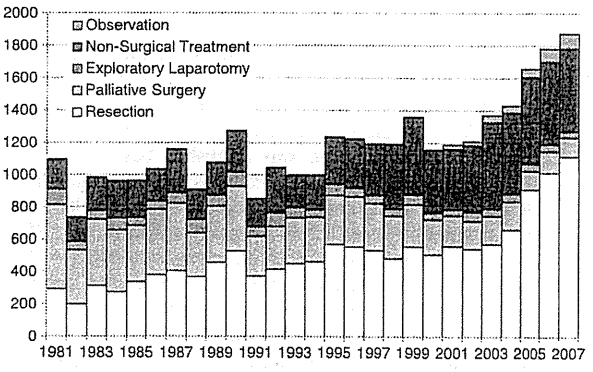

FIGURE 2. Trend of annual registry of all neoplasms. The number of patients treated and registered in each year. The number of patients who underwent pancreatectomy and nonsurgical treatment is increasing, whereas that with palliative surgery is decreasing.

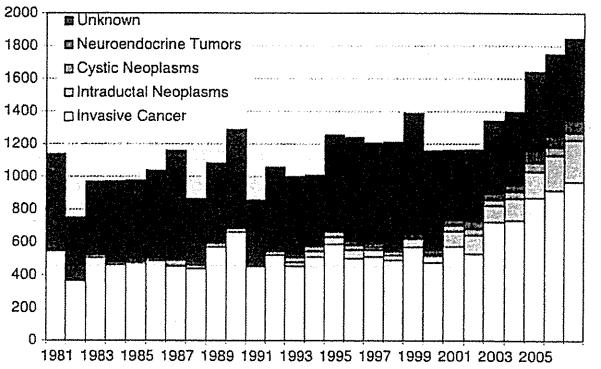

FIGURE 3. Trend of histological classification of all neoplasms. The number of patients with invasive cancer and INs is increasing, whereas that without histological confirmation is decreasing.

The pancreatic cancer registry was first conducted by Ryoichi Tsuchiya in Nagasaki University in 1981. The National Cancer Center jointly sponsored this registry because at that time, many other organizations and societies started their cancer registry. Because the registry required detailed recording on a data sheet and the rule should be widely spread, the manual of staging for the registration was published in 1986.[9] The annual report was published in Suizo in Japanese every year or every other year, and the retrospective review of surgical treatment was published in 1990.[10,11] Of the 7687 patients who were registered until 1990, 5826 cases (75.7%) underwent laparotomy, of whom 2311 (39.7%) underwent resection. At that time, the operative mortality rate was 4.5%. It should be noted that the rates for small carcinomas (>2 cm) were significantly higher than those for the tumors larger than 2 cm, and they insisted on early diagnosis. Then the registry was conducted by Yoichi Saito in Kobe University since 1989. Using the database, Satake et al[12] described the survival rate of patients with resected pancreatic cancer as much higher than that of patients with conservative treatment and emphasized the importance of early diagnosis of resectable pancreatic cancer, again. He offered the effectiveness of CA19-9 and elastase-1 as part of a screening program for early detection of cancer. Although the annual reporting in Suizo in Japanese continued,[13] the next English publication of pancreatic cancer registry appeared in

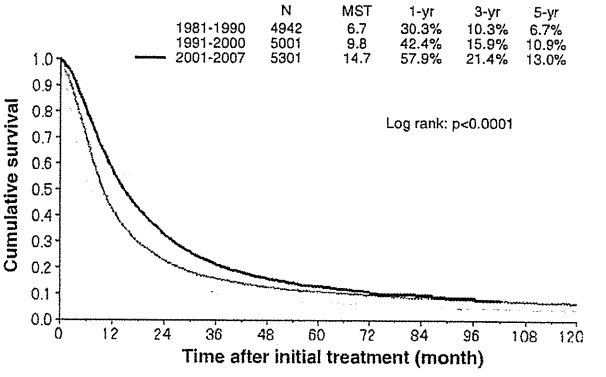

FIGURE 4. Survival of overall patients with invasive cancer. The overall survival significantly improved in the second and third decades.

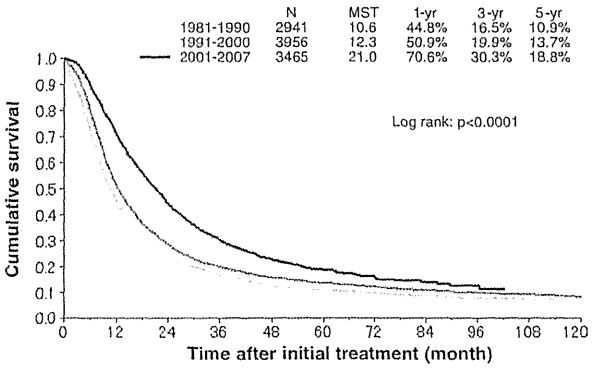

FIGURE 5. Survival of patients who underwent pancreatectomy for invasive cancer.

1998.[14] Using the data of 17,130 patients from 1981 through 1995, various aspects of diagnosis and treatment were reviewed. Ultrasonography and computed tomography have become increasingly important as the methods of detection. Tumor resection was performed in 36% of the patients, and the 5-year survival rate of the patients who underwent resection was 18.2%. They concluded that the rate of resection and results of surgical treatment had improved, which may be attributed to the increase in detection of resectable tumor and benefits of aggressive and extended surgery.

From 1998 to 2004, the registry was conducted by Seiki Matsuno in Tohoku University. Thanks to the development of computer, the data were integrated in a relational database in 1998, and the registration was first performed using electronic submission in 2003 after both UICC and JPS rule had been revised to their current form in 2002. Registry itself had a role in spreading the new rules of classification. The review was published periodically.[15,16] In 2004, "Pancreatic Cancer in Japan" was the special issue in *Pancreas*. The summarized data of 20 years of pancreatic cancer registry[1] and the clinicopathological characters of small pancreatic cancer[2] were included together with the achievements of Japanese pancreatologists. The cumulative number of records from 1981 to 2000 reached 23,302. In 2003, however, personal data protection law was enforced, and every kind of cancer registry faced the serious ethical problem of how to protect personal data and obtain a reliable data because the law requires the anonymization in clinical research if informed consent is not given. Actually, there is 2% to 5% of duplicated registry from multiple institutions in pancreatic cancer registry every year. There is an increasing

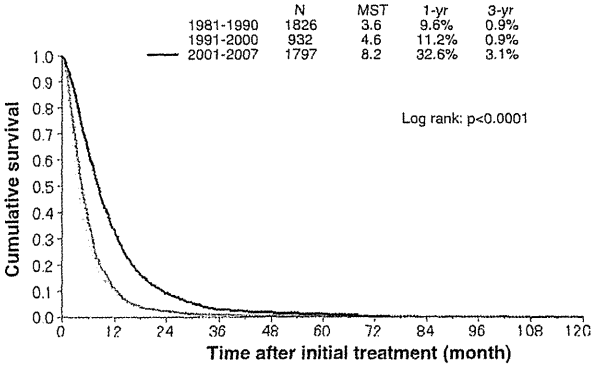

FIGURE 6. Survival of patients with unresectable invasive cancer.

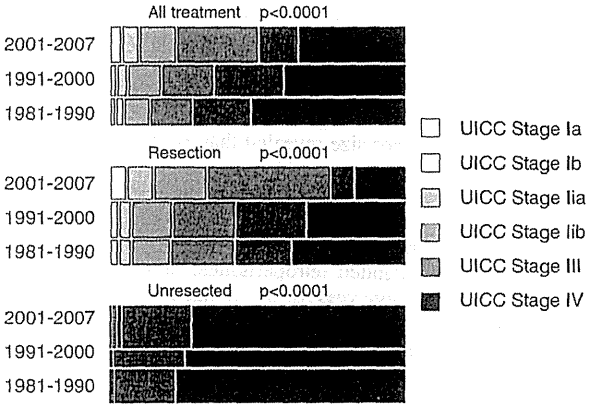

FIGURE 7. Union for International Cancer Control stage of patients in each treatment. In each decade, patients with earlier UICC stage disease underwent resection and nonsurgical treatment.

possibility that different institutions or different specialties treat the same patient and make the registration separately. Thus, without knowing the personal name or birth date, correct exclusion of duplicated data is required. We have originated encrypting technique using a hash function to generate a code to distinguish the records (Fig. 1). Since 2005 and on, the registry has been conducted by Masao Tanaka in Kyushu University. After legal solution with approval of the ethical committee in Kyushu University, the data collection of 2005–2007 was achieved using the anonymous code. Pancreatic cancer registry report 2007[17] was published online with English subtitles because the data consisted of a huge number of tables and figures, summarizing not only each item but also the trend of outcome in every decade. Currently, the data of 2008-2010 are being collected.

The Japan Surgical Society and other collaborative surgical societies have established the National Clinical Database (NCD) to collect the data of all surgeries in Japan and has been working since January 1, 2011. The NCD is going to incorporate cancer registry of not only surgical cases but also nonsurgical cases. Pancreatic cancer registry is moving forward to collaborate with NCD, aiming at the registry of wider population and to grasp the reality of pancreatic cancer diagnosis and treatment. Several issues should be improved, saving the efforts of every clinician by hiring medical record administrators, automatic extraction of medical information from electronic medical records, and standardization of description. However, pancreatic cancer registry should be continued because only by this registry can we compare the outcome between institutions, nations, and historical controls and obtain the future perspectives.

THE VISION

The most important vision and perspective of pancreatic cancer registry is the correction of patients' background, treatment, and follow-up of outcome. The leading 350 institutions are contributing more than 1200 records each year, but the annual death from pancreatic cancer in Japan exceeds 25,000, yielding less than 10% of the whole nation. Most of the patients are still diagnosed too late and are missing the chance of treatment. Widening of the registry is a suspended problem. Annual follow-up is another important vision. So far, continuous follow-up gives the most reliable outcome, survival; and these 30 years of experience will make it possible to define if our strategy is improving the patients benefit.

ACCOMPLISHMENTS

Periodical reports from the conductors and others described the on-time review of the diagnostic and treatment status.[8–10,12,13,17,18] Many spinouts focusing on specific issue were published using this database. Dividing the invasive cancer by tumor size revealed that as the tumor grows larger, the pathological grade and the vascular, lymphatic, or perineural infiltration are worsened, suggesting that pancreatic cancer gains its aggressiveness during the tumor development.[19] Many Japanese surgeons tried to cure the patients with pancreatic cancer by extended retroperitoneal dissection and combined resection of large vessels. In 628 patients with UICC stage IIA and UICC stage IIB disease, the PV, RP, and PL infiltrations had a significant impact on the accomplishment of R0 resection in univariate and multivariate analyses. There was no advantage of PV resection for both PV(−) and PV(+) disease among patients with UICC stage IIA or IIB, suggesting no benefit of prophylactic PV resection.[20] Acinar cell carcinoma is a rare histological type, and no single institution has the power to collect a hundred case series. Using the database, of 115 patients with acinar cell carcinoma, 76.5% underwent resection; and the 5-year survival rate was 43.9%. It was concluded that preoperative diagnosis of acinar cell carcinoma is difficult, but once resected, favorable outcome may be expected.[21] In the UICC classification,[4] pancreatic NETs are classified according to the rules for pancreatic cancer. The JPS classification deals with pancreatic NET from its beginning and collected a large series of 177 patients with NETs. Of the 177 patients, 100 patients had nonfunctioning tumor. The survival after treatment correlated well with JPS stage.[22,23] In addition, the tumor extent of 122 patients with invasive cancer derived from IPMN and 31 patients with invasive cancer concomitant with IPMN were significantly smaller, less invasive, and less extensive than ordinary invasive cancer. The median survival of patients with the 2 conditions was significantly longer than for those with ordinary invasive cancer, suggesting that these 2 categories have more favorable biological behaviors or are diagnosed earlier than ordinary pancreatic cancer.[24]

SUMMARY OF THE LATEST DATA

The cumulative number of records with pancreatic neoplasms from 1981 to 2007 was 35,903. Duplicated 1711 records and the 1573 records without prognostic information were excluded. Resulting 32,619 records were analyzed. The database is maintained in FileMaker Pro software (FileMaker Inc, Santa Clara, Calif), and the data were statistically processed by JMP software (SAS Inc, Cary, NC). Because the whole registry data are excessive to describe in one paper, representative summary of latest outcome is presented.

TREND OF REGISTRY

Figure 2 shows the trend of registry of all patients according to the treatment. The total registration is increasing owing to the increase in the number of patients who undergo pancreatectomy and who receive nonsurgical treatment. Additionally, the number of patients who are observed without any treatment mainly owing to a lesion, for example, branch type IPMN, is simply followed up. Figure 3 shows the trend of histological distribution. The improvement of endoscopic ultrasound-guided fine needle aspiration made a great advance in histological confirmation of cancer and other neoplastic diseases. The number of patients without histological diagnosis is decreasing.

TREND OF SURVIVAL OUTCOME OF INVASIVE PANCREATIC CANCER

As Figure 4 shows, the overall survival of patients with invasive pancreatic cancer is improving decade by decade. The survival curve is divided to that of patients who underwent pancreatectomy (Fig. 5) and those who had unresectable disease (Fig. 6). There was a significant increase of survival rate in the patients who underwent resection. The UICC stage distribution is shown in Figure 7. The number of patients with earlier UICC stage is increasing, but as shown in Figure 8, the survival of patients with UICC stages IIA, IIB, III, and IV disease is improving. In patients with UICC stages IA and IB in which the pancreatic cancer is confined to the pancreas, the survival rates among these 3 decades are not statistically different.

PROGNOSTIC FACTORS

Collecting detailed clinicopathological factors enables us to identify prognostic factors based on a large number of patients. For example, Table 1 shows the multivariate analysis of prognostic factors of 995 patients who underwent pancreatectomy

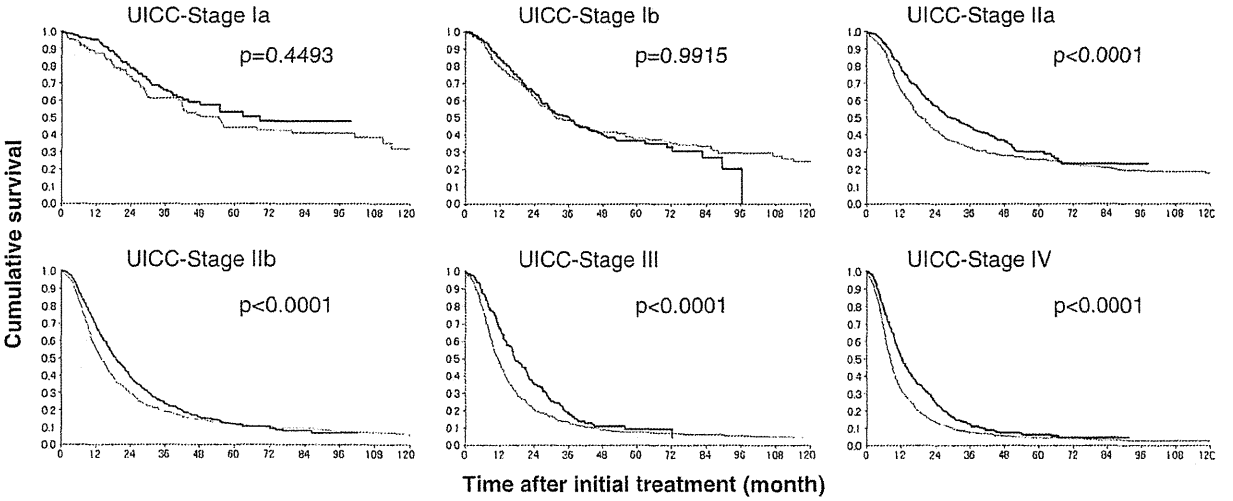

FIGURE 8. Survival of patients who underwent pancreatectomy by UICC stage. In UICC stages IA and IB, the outcome of surgery was not different statistically. In the advanced UICC stage, the survival was improved significantly.

TABLE 1. Multivariate Analysis of Prognostic Factors of Patients Who Underwent Pancreatectomy Within 2001–2007 for UICC Stage IIA and IIB Tubular Adenocarcinoma in the Pancreatic Head Using Cox Proportional Hazard Model (n = 995, censored 369)

Factor	Degree of Freedom	P (Prob > χ^2)	Hazard Ratio
Sex, M/F	1	0.0192	1.228:1
Histological Classification	2	<0.0001	
G1			1
G2			1.451
G3			2.301
Interstitial Abundance (Medullary/ Moderate/Scirrhous)	2	0.3112	
Interstitial Infiltration (INFα/β/γ)	2	0.1144	
Lymphatic Infiltration (0–3)	3	0.1570	
Venous Infiltration	3	0.0309	
v0			1
v1			1.048
v2			1.314
v3			1.479
Perineural Infiltration (1–3)	3	0.8102	
Tumor Size	3	0.0005	
TS1			1
TS2			1.265
TS3			1.899
TS4			2.898
Anterior Surface Invasion (No/Yes)	1	0.3156	
Bile Duct Invasion (No/Yes)	1	0.8046	
Duodenal Invasion (No/Yes)	1	0.6423	
Retroperitoneal Invasion (RP No/Yes)	1	0.5702	
Portal Vein Invasion (PV, No/Yes)	1	0.0819	
Arterial Invasion (No/Yes)	1	0.1805	
Plexus Invasion (PL, No/Yes)	1	0.1067	
Other Organ Invasion (No/Yes)	1	0.4408	
JPS-T (T1/T2/T3/T4)	3	0.3818	
JPS-N	2	0.0480	
N0			1.741
N1			1
N2			3.935
JPS Stage (I/II/III/IVa/IVb)	4	0.2232	
UICC-T (T1/T2/T3)	2	0.7594	
UICC-N (N0/N1)	1	0.0726	
Degree of Lymph Node Dissection	3	0.0086	
D1			1.490
D2			1.063
D3			1
Plexus Resection (No/Yes)	1	0.0933	
Portal Vein Resection (No/Yes)	1	0.1283	
Arterial Resection (No/Yes)	1	0.3536	
Preoperative Chemotherapy (No/Yes)	1	0.8566	
Postoperative Chemotherapy (No/Yes)	1	0.0146	
No			1.261
Yes			1
Preoperative Radiation (No/Yes)	1	0.9873	
Postoperative Radiation (No/Yes)	1	0.9362	

INF indicates interstitial infiltration.

from 2001 to 2007 for UICC stages IIA and IIB tubular adenocarcinoma in the pancreatic head using Cox proportional hazard model. Interestingly, the strongest factor was histological grade, followed by tumor size, the extent of lymph node dissection, postoperative chemotherapy, sex, venous infiltration, and JPS-N. Because UICC stages IIA and IIB are the most frequently encountered, these prognostic factors give us an insight not only about the biological aggressiveness of the tumor but also what we should do. In patients with UICC IIA and IIB diseases, the hazard ratio of male-to-female patients was 1.228. If the histology is G3, the hazard ratio is 2.3 times that of G1. Among various histological parameters of tubular adenocarcinoma, only venous infiltration had a statistically significant impact on survival at UICC stages IIA and IIB. If the tumor is larger than 6 cm, the hazard ratio is 2.898. It seems paradoxical that the hazard ratio of JPS-N0 is larger than that of JPS-N1, but JPS-N0 in the same UICC stage means that the tumor extent is more severe. The hazard ratio of JPS-N2 was highest at 3.935. Although, statistically, significance was not reached, the hazard ratio of UICC-N1 was 2.661 (data not shown). In what we did, the extent of lymph node dissection had a $P = 0.0086$. The hazard ratio of lymph node dissection (D)1 was significantly worse than D2 or D3. In the same cohort, the Kaplan-Meier method shows that the survival rate of patients who underwent D1 resection is significantly lower than that of patients with D2 and D3 resection (Fig. 9). In Japan, D2 resection is most frequently performed for UICC stage IIA and stage IIB disease. There was no statistically significant difference between the survival with D2 and D3 resection. Any of the combined resection of portal vein, artery, and extrapancreatic nerve plexus did not have significant positive or negative impact on survival at this stage. Postoperative adjuvant chemotherapy had lowered the hazard ratio significantly. However, the actual impact on survival seems to extend

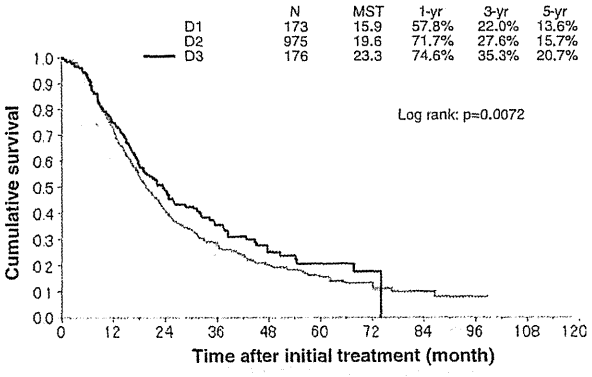

FIGURE 9. Survival of patients with UICC stages IIA and IIB tubular adenocarcinoma in the pancreatic head according to the extent of lymph node dissection. The 1374 records from 2001 to 2007 were analyzed. The survival rate between D1 and D2 was significantly different ($P = 0.0246$), whereas that between D2 and D3 was not statistically different ($P = 0.0887$).

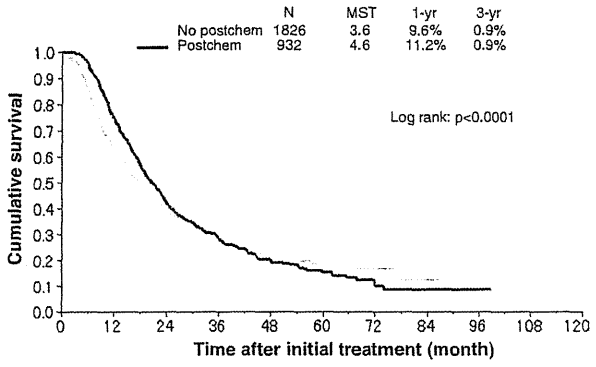

FIGURE 10. Survival of patients with UICC stages IIA and IIB tubular adenocarcinoma in the pancreatic head according to the postoperative chemotherapy. The patients without postoperative chemotherapy at the time of registration may receive chemotherapy after the recurrence was detected.

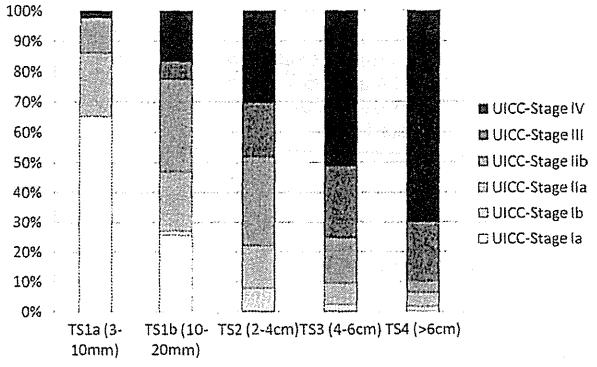

FIGURE 12. Union for International Cancer Control stage according to the size of invasive cancer. The frequency of advanced stage increased as the tumor grew.

the disease- free survival for a short period of time (3 months in median) because the curves become close as shown in Figure 10. The numbers of patients with preoperative chemotherapy, with preoperative radiotherapy, and with postoperative radiotherapy were too small (<10% of the cohort) to draw any conclusion.

EARLY PANCREATIC CANCER

Because pancreatic cancer is one of the deadliest diseases, the effort for the earlier detection has been continued. In the JPS registry, the statistics of pancreatic cancer starts by definition from invasive stage, and there has been no simple definition of early pancreatic cancer.[25] With the accumulation of knowledge about molecular carcinogenesis and biological behaviors of premalignant disease such as PanINs,[26,27] IPMNs[28] and mucinous cystic neoplasms,[29] together with their relationships with chronic inflammation,[30] the definition of early pancreatic cancer cannot be made with the data of invasive cancer alone. There should be a seamless transition between intraepithelial premalignant change, microinvasion, and invasive cancer.

To define early pancreatic cancer, we have to think about the size of the tumor and the depth of invasion. Figure 11 shows the survival of patients with invasive cancer according to the size of tumor. When the tumor is 10 mm or less (TS1a), the survival rate was significantly higher than that of patients with tumor larger than 10 mm (TS1b and more). The 5-year survival rate of patients with TS1a invasive cancer is more than 80%. Furthermore, as the tumor grows, the rate of advanced UICC stage increases (Fig. 12). In patients with TS1a tumor, 65% of them had UICC stage IA disease, whereas only 25% of the patients with TS1b had UICC stage IA disease. You may notice that none of the patients with invasive cancer has UICC stage 0 disease,

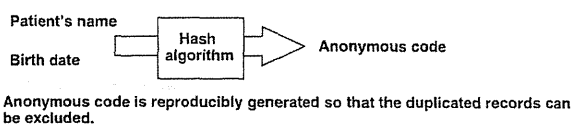

FIGURE 11. Survival of patients with invasive cancer according to tumor size. The actual tumor size is available from the records in 2000. The records that have contradiction between the actual size and TS rank were excluded from the analysis.

although the tumor is 10 mm or less. Thus, we should next take the depth of invasion into account to define early pancreatic cancer. Figure 13 shows the trend of UICC stage distributions of all patients including invasive cancer, intraductal neoplasms (INs), cystic neoplasms (CNs), and NETs (same patient cohort with Fig. 3). Increasing numbers of patients with UICC stage 0 (in situ), IA, and IB disease are registered. The overall survival rate of patients with INs, CNs, and invasive cancer is shown in Figure 14. Intraductal neoplasms includes IPMA, IPMC, PanIN1 to PanIN3, CIS with or without microinvasion, and their invasive counterparts. Cystic neoplasms include mucinous cystadenoma, mucinouscystadenocarcinoma, serous cystadenoma, and serous cystadenocarcinoma, with or without microinvasion, and their invasive counterparts. Invasive cancer includes papillary adenocarcinoma, tubular adenocarcinoma, adenosquamous carcinoma, anaplastic carcinoma, mucinous carcinoma, and undifferentiated carcinoma. The 5-year survival of patients with UICC stage 0 is 85.8%, followed by UICC stage IA of 68.7% and UICC stage IB of 59.7%.

DISCUSSION

The JPS nationwide pancreatic cancer registry is an original and unique database that gives us the perspective of current diagnostic and treatment measure based on 30 years of experience and insight to the future. Without the continuous understanding and cooperation from the whole country, it was not possible to obtain a large amount of data that is durable for

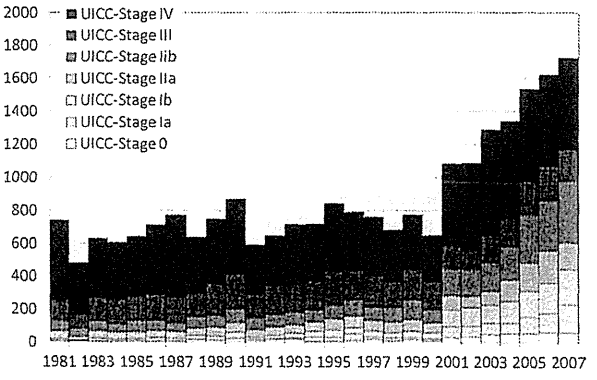

FIGURE 13. Trend of UICC stage of all neoplasms. Same patient cohort with Figure 3.

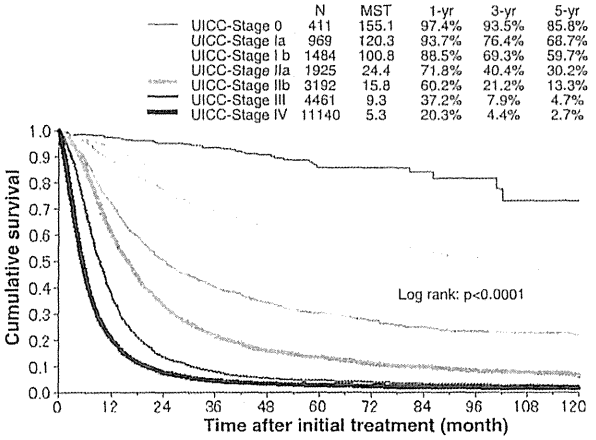

FIGURE 14. Survival of patients with INs, CNs, and invasive cancer according to UICC stage. Patients with NETs were excluded. Both adenomas and carcinomas are included.

detailed analysis. We appreciate the effort of former conductors and every physician, collaborator, and patient who had this intractable disease.

The improvement of survival of patients with invasive cancer may be attributed to mainly 3 reasons. First, gemcitabine (GEM) and S-1 (an oral 5-fluorouracil derivative consist of tegafur: 5-chloro-2,4-dihydroxypyridine: potassium oxonate at a 1: 0.4: 1 molar ratio) were approved for pancreatic cancer in Japan in 2001 and 2006, respectively. According to the several clinical trials,[31–33] postoperative adjuvant chemotherapy had become a standard treatment. Gemcitabine is currently the most used regimen, but several randomized trials are ongoing to test postoperative S-1 regimen or GEM/S-1 (GS) combination for an adjuvant therapy. This may have contributed to the improvement of survival in each UICC stage, as shown in Figure 8. A large-scale randomized phase 3 study performed in Japan and Taiwan that compared GS versus S-1 versus GEM in unresectable advanced pancreatic cancer (GEST study: American Society for Clinical Oncology 2011 abstract numbers 4007 and 9070) revealed that GEM and S-1 are equivalently effective in the treatment of advanced unresectable pancreatic cancer in overall survival. The combined GS therapy showed significantly longer progression-free survival than each monotherapy. Crossover usage of GEM and S-1 may have also contributed to the longer survival because nearly half of the patients had received second-line therapy in all arms, and this resulted in the median overall survival with GEM (8.8 M), S-1 (9.7M), and GS (10.1M), respectively. New therapies, such as GEM/erlotinib[34] or FOLFIRINOX,[35] that showed superior outcome than GEM will be introduced in Japan in the future.

The second reason is that the treatments are mainly performed and could be improved in the high-volume centers. In diagnostic process, ultrasound-guided fine needle aspiration is playing a more important role in the differential diagnosis, and recent clinical trials require histological confirmation before enrolling the patients. Evidence-based JPS clinical guidelines for pancreatic cancer 2009[36] indicate that the frequency of complications after pancreaticoduodenectomy is lower, and management of complication after pancreas resection is superior in high-volume centers. Because postoperative adjuvant chemotherapy had become a standard treatment and the combination of surgery and chemotherapy enhanced the regionalization too, patients are moving to large centers more frequently these days, sometimes to enter in a clinical trial and sometimes to obtain a second opinion.

Third, the pancreatic neoplasms are getting diagnosed earlier than before as shown in Figures 7 and 13. Pancreatic cancer registry requested to submit the real size of the tumor from the records in 2000 and the collected large number of records with detailed clinicopathological parameters. As the tumor size grows, the frequency of higher grade of histology increases. Accordingly, the frequency of lymphatic, vascular, and perineural infiltrations increases, resulting in advanced UICC stage of the disease as shown in Figure 12. If the tumor is 10 mm or less, most of the case is UICC stage IA, with favorable survival. However, as long as we start the definition of pancreatic cancer from invasive ones, it seems impossible to define an early pancreatic cancer. On the other hand, the JPS classification of INs include "intraductal" neoplasms with "microinvasion" and "invasive cancer derived from IPMN." PanINs are also included in Ins, although PanIN1 and PanIN2 are not regarded as tumors by themselves. PanIN3 is regarded as CIS with or without microinvasion. Thus, we should carefully correct the data of size and depth together with clinical outcome to define an early pancreatic cancer regardless of the histological classification. As shown in Figure 14, there seems to be an "early pancreatic cancer" with favorable long-term survival.

CONCLUSION

The JPS pancreatic cancer registry has fulfilled the vision and mission of its founding. This nationwide pancreatic cancer registry has been an indispensable tool in evaluating the progress of diagnosis and management of pancreatic cancer over 30 years of experience. It also provides a great database for comparative studies with other national databases. As the registry continues to expand to include other types and early stages of pancreatic cancer, it will undoubtedly improve the management strategy of pancreatic cancer and provide a much improved outcome in the near future.

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Gemcitabine-induced Pleuropericardial Effusion in a Patient with Pancreatic Cancer

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Pleuropericardial effusion is an extremely rare complication of gemcitabine chemotherapy. The patient was a 56-year-old woman administered systemic chemotherapy with gemcitabine for local recurrence of pancreatic cancer and lymph node metastasis developing 4 years after pancreaticoduodenectomy. Four months after the start of the chemotherapy, she presented with exertional dyspnea and edema in both her legs and face. Echocardiography and computed tomography revealed pericardial and bilateral pleural effusion. A pericardiocentesis was immediately performed to prevent the development of cardiac tamponade as well as to examine the cause of the pericardial effusion. As a result, the patient's exertional dyspnea and edema resolved. No metastases to the thorax or mediastinum were noted. A cytological study of the pericardial and pleural effusions revealed no malignant cells. Cultures for bacteria, mycobacteria and fungi were negative. Tests for autoantibodies indicating autoimmune disease were also negative, and hormonal assays for the detection of endocrine disease were normal. She was followed up after discontinuation of the gemcitabine treatment, and no further episodes of pericardial or pleural effusion occurred. Thus, it is speculated that the pericardial effusion and bilateral pleural effusion may have been caused by gemcitabine.

Key words: pericardial effusion – pleural effusion – chemotherapy – gemcitabine

INTRODUCTION

Pleuropericardial effusion can develop in patients with acute pericarditis or acute pleuritis, or in association with a variety of systemic disorders including drug adverse effects. Procainamide (1,2), hydralazine (3,4), isoniazid (5,6) and minoxidil (7) are well-known causative agents of pleuropericardial effusion. In addition, several reports have also described pleuropericardial effusion induced by anticancer drugs, such as dasatinib (8), imatinib (9) and docetaxel (11). However, drug-induced pleuropericardial effusion has seldom been reported with gemcitabine. Here, we report a patient who developed pleuropericardial effusion possibly caused by gemcitabine treatment. This is the first report of pleuropericardial effusion induced by treatment with gemcitabine alone.

CASE REPORT

The patient was a 56-year-old woman. Her past medical history included gastritis and insomnia, and she had been under treatment with ranitidine hydrochloride and alprazolam. She had no history of allergy. At the age of 51 years, she underwent a pancreaticoduodenectomy for the treatment of pancreatic cancer at another hospital. Gross examination of the resected specimen revealed a tumor (2 cm × 1.5 cm × 1.5 cm) arising from the head of the pancreas. Microscopic

examination revealed a moderately differentiated tubular adenocarcinoma with lymphatic and venous invasion. The edge of the resected specimen was negative. A regional lymph node metastasis was found in 1 out of 38 dissected lymph nodes. She underwent a laparotomy based on a diagnosis of ileus 2 years after the pancreaticoduodenectomy. Since recovering from the ileus, she had been followed up without any further anticancer treatment. Four years after the pancreaticoduodenectomy, a laboratory examination revealed an elevation of her serum carbohydrate antigen 19-9 (CA19-9) level to 101.8 ng/ml and she was referred to our hospital for the first time. A computed tomographic (CT) examination of the abdomen performed at our hospital revealed a local recurrence (15 mm in diameter) and also two abdominal lymph node metastases. The patient was asymptomatic, and her ECOG performance status was 0 at the time of detection of the recurrence. A blood examination showed no abnormalities, except for mild elevation of the serum amylase level (199 IU/l) and the serum CA19-9 level (49 ng/ml). Systemic chemotherapy using gemcitabine was started for the treatment of the recurrence. During the first 4 months of treatment, the only adverse effects of gemcitabine were mild nausea and mild fatigue. Oral intake was sufficient. However, at 4 months after the start of the chemotherapy, she presented with complaints of exertional dyspnea and edema in both her legs and face. The edema steadily worsened over the course of the following 2 months. CT examinations revealed pericardial and bilateral pleural effusion, and she was admitted to our hospital with the diagnosis of pleuropericardial effusion. Upon admission, her blood pressure was 142/90 mmHg, pulse rate was 110 min^{-1}, regular, and body temperature was 37.6°C. Her peripheral blood arterial oxygen saturation level was 94% under room air. Her ECOG performance status had worsened to 2 because of the exertional dyspnea. The first heart sound and second heart sound were distant; however, there was no audible murmur or pericardial friction rub. The breath sounds were normal vesicular, except for a decrease over the right lung areas, presumably on account of the pleural effusion. An electrocardiogram performed at admission revealed a sinus rhythm, low-voltage complexes and no ST elevations in any of the leads. Laboratory examination revealed slight anemia, proteinuria (2+) and hematuria (3+), which were not observed before the initiation of gemcitabine (Tables 1 and 2). The daily urinary protein excretion level was 1.92 g/day. The serum creatinine level was of normal value throughout the entire course of this episode (Table 1). The serum C-reactive protein level was 2.2 mg/dl. The thyroid hormone profile was normal. Complement-fixation tests were performed in paired serum specimens for antibodies against Coxsackie virus, adenovirus and echovirus, which are well-known causes of pleuropericardial effusion. At the time of admission, the antibody titers for all of these viruses were 1:32 or less. A paired sample taken 4 weeks later showed a less than 4-fold increase in the titers when compared with the titers recorded at the time of admission (Table 3). A rapid influenza diagnostic test yielded negative results for influenza A and B. Although the rheumatoid factor test was positive, the tests for other autoantibodies were normal (Table 2). The possibility of collagen vascular disease was ruled out by a rheumatologist based on the absence of the characteristic arthralgia, skin sclerosis or antinuclear antibody in the serum. An X-ray of the chest revealed cardiac enlargement (CTR, 60%) and increased pulmonary markings. A chest CT revealed pericardial effusion and bilateral pleural effusion; no evidence of metastatic tumors was

Table 1. The time course for changes in laboratory data

	Normal value	Initiation of GEM (May 2009)	Pericardial effusion occurred (Oct 2009)	Two months after the discontinuation of GEM (Dec 2009)
Leukocyte (μl^{-1})	3900–6300	5400	3700	5900
Hemoglobin (g/dl)	11.3–14.9	13.6	8.7	10.0
Hematocrit (%)	33.6–44.6	41.3	27.1	31.2
Platelet ($\times 10^4\ \mu l^{-1}$)	12.5–37.5	22.5	21.6	15.8
Albumin (g/dl)	3.7–5.2	4.7	3.5	3.9
Creatinine (mg/dl)	0.4–0.7	0.6	0.9	0.8
C-reactive protein (mg/l)	<0.1	0.32	0.09	0.42
CEA (ng/ml)	<5.0	0.8	0.8	4.3
CA19-92 (U/ml)	<37	49	80	2130
Protein (urine)	—	—	2+	2+
Occult blood (urine)	—	—	3+	3+

GEM, gemcitabine; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.