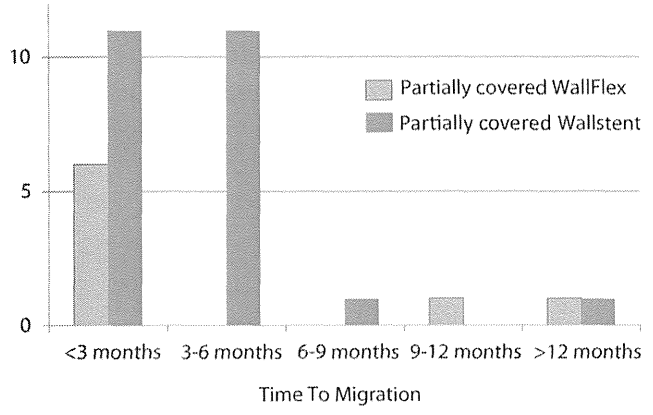

Figure 4. Distribution of time to migrations in partially covered WallFlex stents and partially covered Wallstents: most stent migration occurred within 6 months in both groups.

days in the partially covered WallFlex stent group (P = .250). The rate of recurrent biliary obstruction did not differ between WallFlex and Wallstent groups (33% vs 38%; P = .385), but the rate of stent migration was lower (8% vs 17%; P = .019), and time to recurrent biliary obstruction was significantly longer (373 vs 285 days; P = .007) in the WallFlex group compared with the Wallstent group (Fig. 2). The Cox proportional hazards model confirmed that the use of a partially covered WallFlex stent was associated with longer time to recurrent biliary obstruction (HR 0.47; 95% confidence interval [CI], 0.29-0.78; P = .003). Prior drainage was not associated with recurrent biliary obstruction (HR 0.70; 95% CI, 0.42-1.21; P = .192) in our study. There was no significant difference in time to migration in both groups (Fig. 4). The rate of cholangitis without stent occlusion had a low tendency in the WallFlex stent group compared with the Wallstent group (6% vs 11%; P = .131). The rates of pancreatitis and cholecystitis were similar between WallFlex stent and Wallstent groups (6% vs 4%; P = .572 and 10% vs 7%; P = .385, respectively).

DISCUSSION

In this multicenter, prospective study, partially covered WallFlex stents demonstrated a low stent occlusion rate without tumor ingrowth. The two major features of partially covered WallFlex stents that differ from partially covered Wallstents are flared ends and low axial force with nitinol wire. As a result, less stent migration in partially covered WallFlex stents led to a longer time to recurrent biliary obstruction than that of a historical cohort with partially covered Wallstents, showing the efficacy of its anti-migration system and low axial force profile.

CSEMSs were developed to prevent tumor ingrowth with their covering membrane, the major cause of stent occlusion with SEMSs.[5-7] The occlusion rate of partially covered WallFlex stents was 26% without tumor ingrowth, which was similar to 21% with partially covered Wallstents. The silicone cover of the partially covered WallFlex stents or partially covered Wallstents was shown to be effective to prevent tumor ingrowth. On the other hand, CSEMSs are prone to stent migration because they are not embedded in the bile duct. The anti-migration systems such as the fin structure of Viabil stents (W.L. Gore & Assoc, Flagstaff, Ariz)[17] and flared ends of covered WallFlex stents have been developed to prevent migration in CSEMSs. With flared ends, less stent migration was observed in partially covered WallFlex stents than in partially covered Wallstents (8% vs 17%; P = .019). Most stent migration occurred within the first 6 months of stent placement in both groups.

Axial force, which is the recovery force that leads to a SEMS straightening after being bent, is one of the important characteristics of SEMSs. We encountered a high incidence of stent-related complications including stent migration or the bile duct kinking with partially covered Wallstents, possibly caused by its high axial force.[10] ComVi stents (Taewoong Medical Inc, Seoul, Korea), with low axial force, were shown to have a low stent-related complication rate compared with partially covered Wallstents.[18] The Diamond stent, another stent with low axial force, also was associated with less common bile duct kinking than was the Wallstent.[19] The axial force of partially covered WallFlex stents with nitinol wire is lower than that of partially covered Wallstents with Elgiloy wire. The incidence of cholangitis without stent occlusion decreased with partially covered WallFlex stents, probably because of low axial force. Thus, both the anti-migration system and low axial force of partially covered WallFlex stents worked efficiently and achieved a longer time to recurrent biliary obstruction, with less migration.

Two recent randomized, controlled trials[13,20] failed to demonstrate the superiority of CSEMSs to uncovered SEMSs because of a high incidence of tumor ingrowth or stent migration. Although CSEMSs were developed to prevent ingrowth, incidences of tumor ingrowth varied from 0% to 6%.[6,8-10,13,20] In this study, the silicone cover of partially covered WallFlex stents and partially covered Wallstents prevented tumor ingrowth successfully. Costamagna et al[21] also reported no tumor ingrowth with partially covered WallFlex stents. Nitinol stents have low axial force, and stent migration was reported to be less frequent in nitinol SEMSs.[18,21] This study showed similar results. So far, no randomized, controlled trial has demonstrated the superiority of commercially available CSEMSs to uncovered SEMSs, but CSEMSs with less tumor ingrowth and stent migration would show better patency than uncovered SEMSs. For further patency of CSEMSs, prevention of sludge formation is necessary because sludge was the main cause of stent occlusion in our study.

Removability is one of the characteristics of CSEMSs.[22,23] The removability of CSEMSs led to the potential role of CSEMSs for benign biliary strictures[24] or bile leakage.[25,26]

As the prognosis of pancreatobiliary cancer is improved by chemotherapy, the chance of reintervention for stent dysfunction has been increasing. In our study, survival was significantly longer, and the rate of stent dysfunction that needed reintervention was higher in patients receiving anti-cancer treatment, although not significantly higher. Thus, the importance of removability of CSEMSs is an important advantage, especially in patients receiving anti-cancer treatment. The anti-migration system potentially interferes with removability, but in our study, stent removal for reintervention was successful in all 27 attempts other than in one patient with worsening hemobilia during stent removal. However, one case with difficult stent removal because of hyperplasia in the uncovered proximal flared ends was reported with the partially covered WallFlex stent.[27] If flared ends of WallFlex stents can prevent migration, fully covered WallFlex stents would be easier to remove.

Cholecystitis has been considered as one complication related to CSEMS placement,[28] when the orifice of the cystic duct is covered. The incidence of cholecystitis in this study was 10%, which is similar to previous reports of 3% to 10% with CSEMSs.[8-12,28-30] Two studies showed that tumor involvement to the orifice of the cystic duct, but not CSEMSs, is a risk factor of cholecystitis after SEMS placement.[29,30] In this study, tumor involvement to the orifice of the cystic duct was evaluated by using CT, magnetic resonance imaging, EUS, or intraductal US[31] before stent placement. The incidence of cholecystitis was significantly higher in patients with tumor involvement to the orifice of the cystic duct than in patients without orifice of the cystic duct involvement (22% vs 7%; $P = .041$). Thus, assessment of tumor involvement is important, but prevention of cholecystitis is not established. The irrigation of the gallbladder was reported by Kahaleh et al,[9] but obviously in patients with orifice of the cystic duct involvement, this technique would be difficult. The incidence of cholecystitis with partially covered WallFlex stents in patients without orifice of the cystic duct involvement was higher than 0.5% to 4% in previous reports.[29,30] This might be because the flared ends or increased radial force of partially covered WallFlex stents causes strong compression of the orifice of the cystic duct by the stent.

The incidence of pancreatitis was 6% with partially covered WallFlex stents. Covering the orifice of the pancreatic duct can cause pancreatitis, but the use of a CSEMS was not a risk factor of pancreatitis after SEMS placement.[32] We performed endoscopic sphincterotomy (EST) in all patients, but could not prevent pancreatitis. The rate of pancreatitis was higher in patients with nonpancreatic cancer (14% vs 3%; $P = .029$), which was similar to the previous reports.[10,33] We speculate that in patients with pancreatic cancer, chronic obstruction of the pancreatic duct by cancer causes atrophy of pancreatic parenchyma and exocrine insufficiency, which reduces the risk of pancreatitis.

There are some limitations in this study. We compared two CSEMSs with different features, but this is not a randomized, controlled trial, and the participating institutions in the two groups are different. There also are significant differences in performance status and the rates of pathologic diagnosis between the two groups. Given these differences between the two groups, the comparison of outcomes between two stents should be cautiously interpreted. We could not deny the possibilities of bias between the two groups, rather than the stent itself, as a cause of better outcomes of partially covered WallFlex stents. Another limitation is the relatively short follow-up period. We analyzed data after 6 months from the last recruitment. Therefore, 53 patients (37%) in the partially covered WallFlex stent group were still alive at the time of analysis.

In conclusion, our study showed that the partially covered WallFlex stents with the anti-migration system and low axial force profile demonstrated longer time to recurrent biliary obstruction than the partially covered Wallstents in patients with distal malignant biliary obstruction. The results of randomized, controlled trials of covered and uncovered SEMSs are conflicting,[8,13,20,34,35] but multiple other studies have documented that CSEMSs prevent tumor ingrowth. Further randomized, controlled trials are needed to further evaluate the value of the modified WallFlex stent.

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Tumor seeding after endoscopic ultrasound-guided fine-needle aspiration of cancer in the body of the pancreas

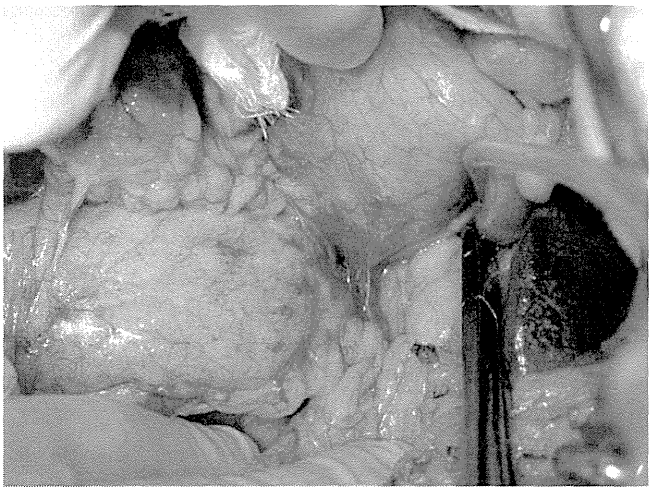

Fig. 1 Intraoperative findings. Bleeding and adhesion were observed at the puncture sites. Tumor resection was possible.

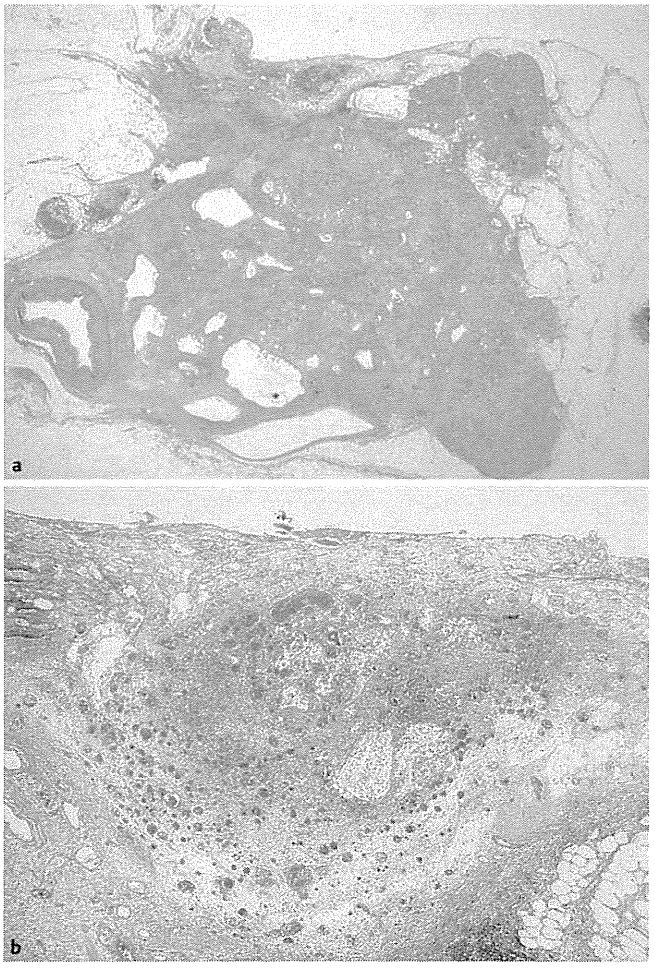

Fig. 2 **a, b** Histopathological findings from the resected specimen. Bleeding was observed at a site distal from the primary tumor, with tumor cells seen within lymphatic vessels in the sites of bleeding.

The use of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has been rapidly expanding as a useful examination technique which enables highly accurate histological diagnosis. Reports of tumor dissemination induced by EUS-FNA are rare [1–5]. We recently encountered a case in which tumor cells were observed in the puncture line in a surgically resected specimen after EUS-FNA, and in which dissemination in the posterior wall of the upper gastric body was later observed.

The patient was a 68-year-old woman. A computed tomography (CT) scan revealed a 2-cm mass in the pancreatic body, which was suspected to be pancreatic cancer. We scheduled distal pancreatectomy, and to obtain a definitive diagnosis the patient underwent preoperative EUS-FNA with a 22-gauge needle (Olympus Medical Systems, Tokyo, Japan) inserted four times, which yielded a diagnosis of adenocarcinoma. No clinical complications developed after EUS-FNA. Distal pancreatectomy was performed 20 days after the EUS-FNA and, intraoperatively, bleeding and adhesion were observed at the puncture sites (◉ **Fig. 1**). Histopathology of the surgically resected specimen confirmed adenocarcinoma (T2N0M0). A small number of tumor cells were found within the lymphatic vessels of the resected specimen, similar to the areas of bleeding and adhesion (◉ **Fig. 2**).

At 22 months after distal pancreatectomy, upper gastrointestinal endoscopy revealed a submucosal tumor-like mass in the posterior wall of the upper gastric body (◉ **Fig. 3a**), which was subsequently confirmed to be adenocarcinoma by biopsy (◉ **Fig. 3b**). An abdominal CT scan did not reveal any local recurrence at the resected site of the pancreas or lymph node metastasis around the stomach, but a tumor was observed on the posterior wall of the gastric body (◉ **Fig. 4**).

In the present case, bleeding was seen at the puncture sites and tumor cells were observed within the lymphatic vessels in these areas. As similar findings were absent in the areas which were free of bleeding or adhesion, we speculated that the punctures caused the bleeding and adhesion, and that subsequent reactive changes facilitated the survival of tumor cells within the lymphatic vessels. Moreover, it is possible that similar changes occurred in the gastric wall.

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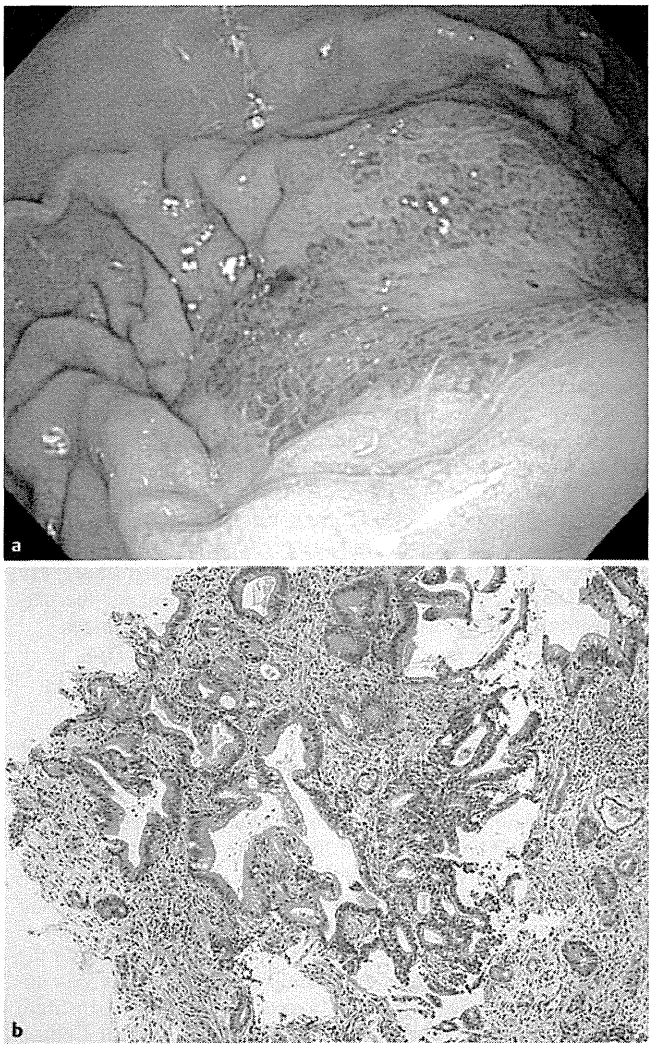

Fig. 3 **a** A tumor can be observed on the posterior wall of the upper gastric body. **b** Adenocarcinoma, as confirmed by biopsy.

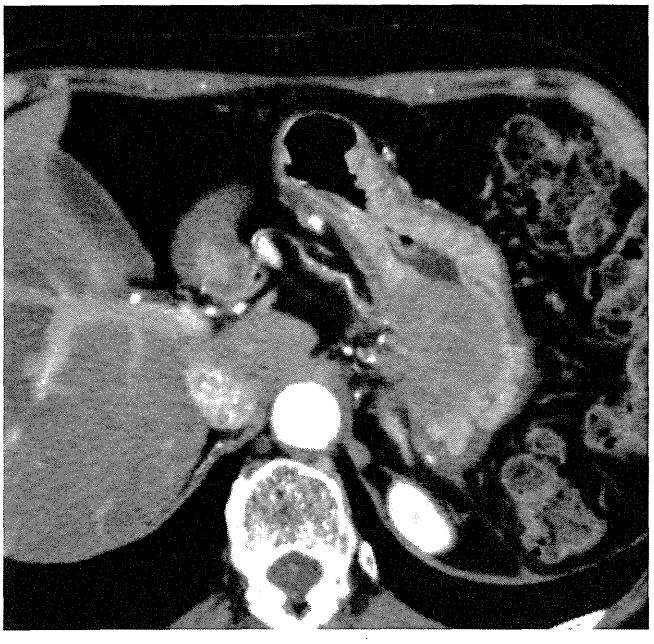

Fig. 4 Abdominal computed tomography scan revealed a tumorous lesion on the gastric wall, but did not show any signs of local recurrence.

Competing interests: Dr. Takao Itoi gives lectures for and is a consultant for Olympus Medical Systems. All other authors declare that they have no financialrelationships or other conflicts of interest relevant to this publication.

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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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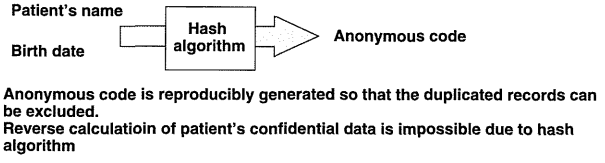


FIGURE 1. Anonymization by encrypting personal data using hash function. If a patient's name and birth date is perfectly the same, the anonymous code is the same. Same character in the anonymous code can be generated from multiple combination of name and birth date, making it impossible to recalculate 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.

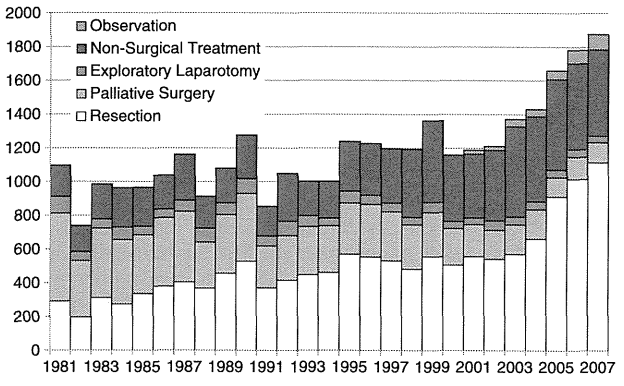


FIGURE 2. Trend of annual registry of all neoplasms. The number of patients treated and registered in each year. The number of patients who underwent pancreatectomy and nonsurgical treatment is increasing, whereas that with palliative surgery is decreasing.

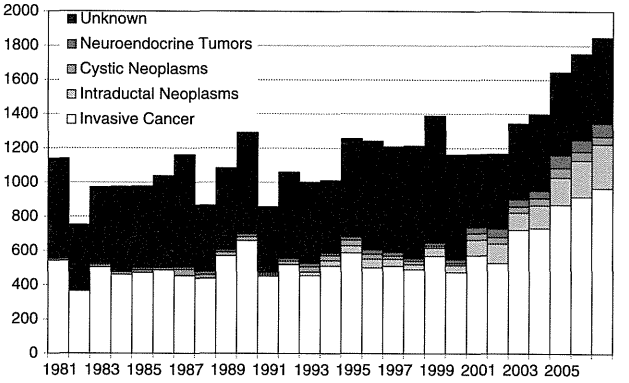


FIGURE 3. Trend of histological classification of all neoplasms. The number of patients with invasive cancer and INs is increasing, whereas that without histological confirmation is decreasing.

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

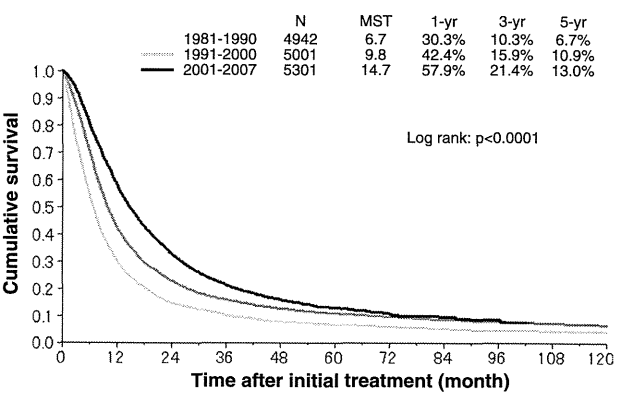


FIGURE 4. Survival of overall patients with invasive cancer. The overall survival significantly improved in the second and third decades.

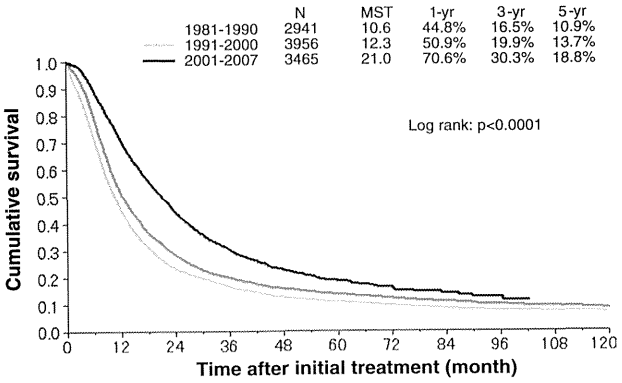


FIGURE 5. Survival of patients who underwent pancreatectomy for invasive cancer.

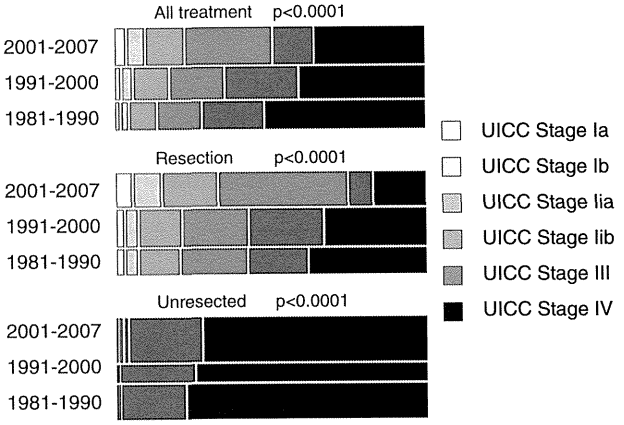


FIGURE 7. Union for International Cancer Control stage of patients in each treatment. In each decade, patients with earlier UICC stage disease underwent resection and nonsurgical treatment.

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 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.

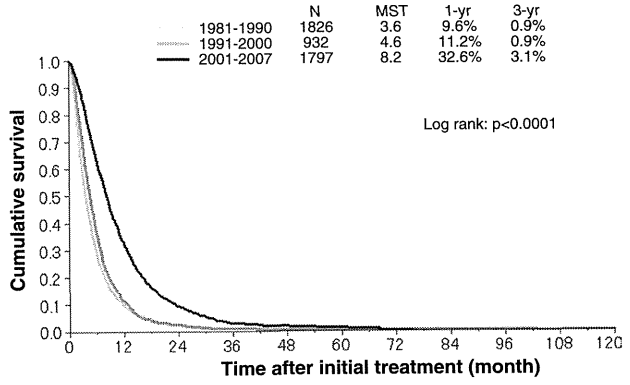


FIGURE 6. Survival of patients with unresectable invasive cancer.

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

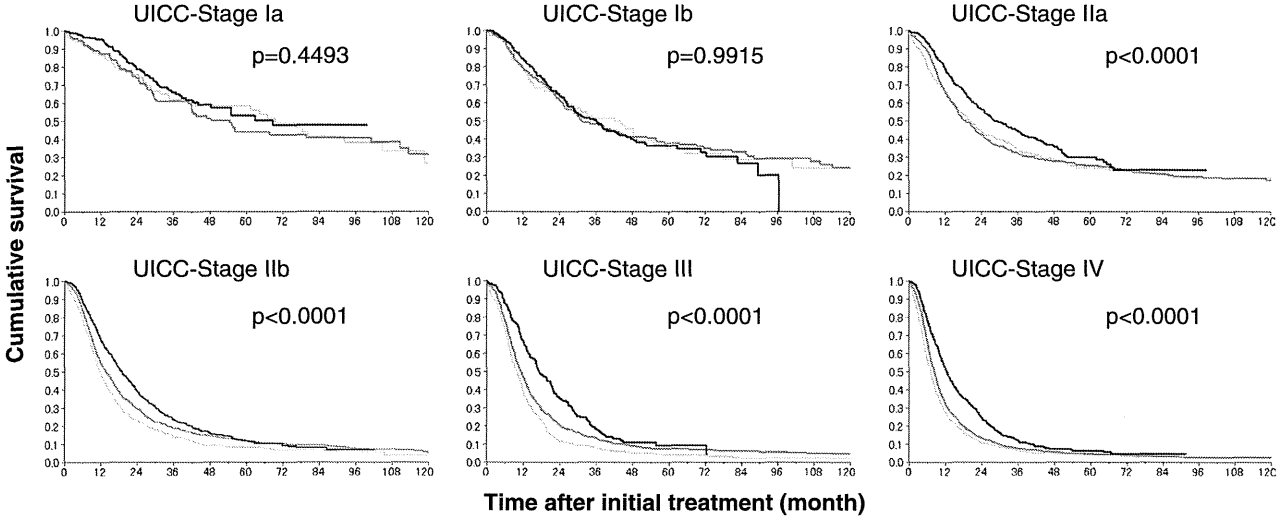


FIGURE 8. Survival of patients who underwent pancreatectomy by UICC stage. In UICC stages IA and IB, the outcome of surgery was not different statistically. In the advanced UICC stage, the survival was improved significantly.

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

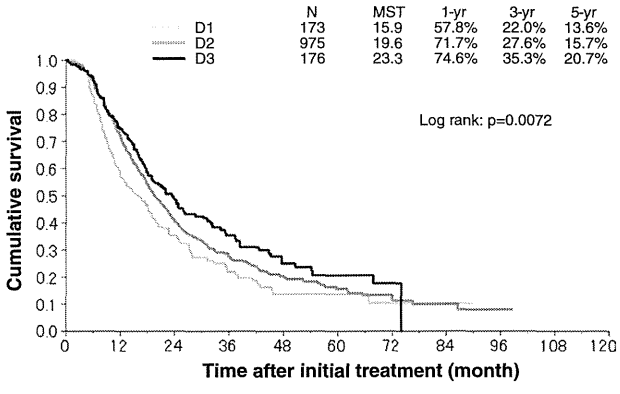


FIGURE 9. Survival of patients with UICC stages IIA and IIB tubular adenocarcinoma in the pancreatic head according to the extent of lymph node dissection. The 1374 records from 2001 to 2007 were analyzed. The survival rate between D1 and D2 was significantly different ($P = 0.0246$), whereas that between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

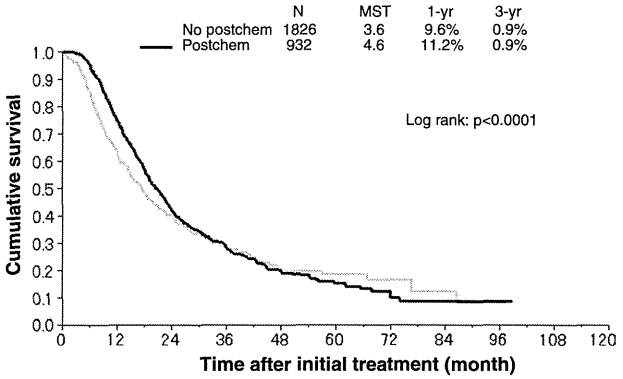


FIGURE 10. Survival of patients with UICC stages IIA and IIB tubular adenocarcinoma in the pancreatic head according to the postoperative chemotherapy. The patients without postoperative chemotherapy at the time of registration may receive chemotherapy after the recurrence was detected.

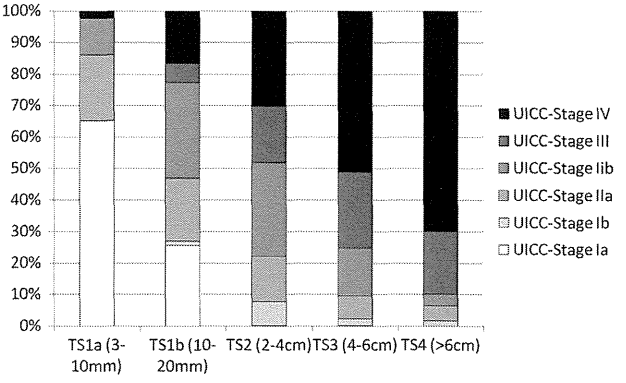


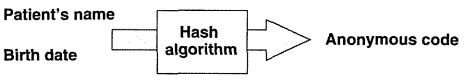
FIGURE 12. Union for International Cancer Control stage according to the size of invasive cancer. The frequency of advanced stage increased as the tumor grew.

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,



- **Anonymous code is reproducibly generated so that the duplicated records can be excluded.**
- **Reverse calculatioin of patient's confidential data is impossible due to hash algorithm**

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

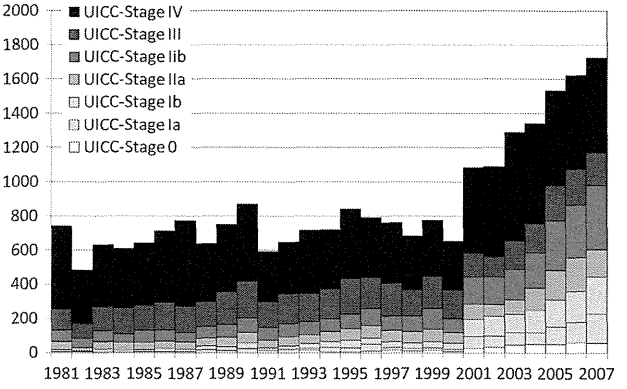


FIGURE 13. Trend of UICC stage of all neoplasms. Same patient cohort with Figure 3.

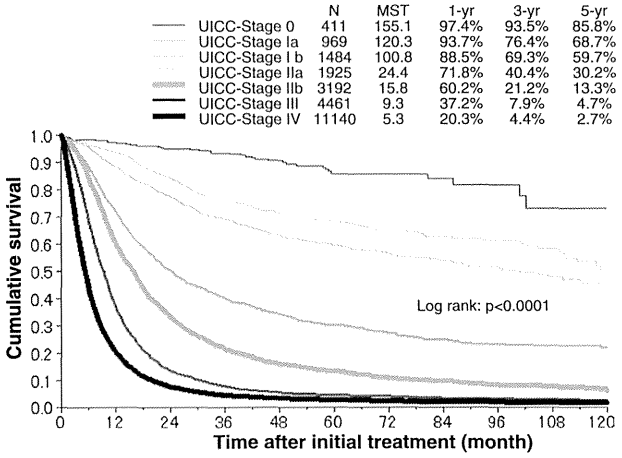


FIGURE 14. Survival of patients with INs, CNs, and invasive cancer according to UICC stage. Patients with NETs were excluded. Both adenomas and carcinomas are included.

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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ORIGINAL ARTICLE

RESULTS OF A JAPANESE MULTICENTER, RANDOMIZED TRIAL OF ENDOSCOPIC STENTING FOR NON-RESECTABLE PANCREATIC HEAD CANCER (JM-TEST): COVERED WALLSTENT VERSUS DOUBLELAYER STENT

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Background: No study has compared covered metallic stents with Tannenbaum stents. We evaluated the efficacy of the DoubleLayer stent (DLS) and Covered Wallstent (CWS) in patients with pancreatic head cancer (PHC).

Patients & Methods: This was a multicenter, prospective randomized study. Between October 2005 and December 2007, we enrolled 113 patients (58 DLS, 55 CWS) with unresectable PHC with distal biliary obstructions and observed them for at least 6 months.

Results: No significant difference in patient survival was found between groups, with a median survival of 231 and 248 days in the DLS and CWS groups, respectively. The cumulative stent patency was significantly higher ($P = 0.0072$) in the CWS group. The respective mean and median stent patency was 202 and 133 days in the DLS group and 285 and 419 days in the CWS group. The incidence of DLS occlusion (53.5%) was significantly higher than that of CWS (23.6%; $P = 0.0019$). The respective causes of occlusion were tumor overgrowth (0, 1), ingrowth (0, 2), sludge (24, 2), food impaction (3, 5), kinking bile duct (2, 0), and other (2, 3). Other complications were cholecystitis (0, 4), pancreatitis (0, 1), migration (1, 5), liver abscess (2, 0), and other (1, 2). No significant difference in the incidence of complications between groups was observed.

Conclusion: CWS had significantly longer patency than DLS for the management of PHC with obstructive jaundice. The incidence of complications other than stent occlusion was higher in CWS, but this difference did not reach significance.

Key words: biliary metallic stent, covered metallic stent, endoscopic treatment, obstructive jaundice, pancreas cancer.

INTRODUCTION

Endoscopic biliary stenting is a widely accepted palliative procedure for the management of unresectable malignant biliary obstruction.[1] The covered metallic stent (CMS) was developed to overcome tumor ingrowth through the stent mesh, which is a main cause of stent occlusion in uncovered metallic stents (UMS).[2–8] The covered Diamond stent was patent significantly longer than the uncovered stent in a randomized study.[9] Several studies have compared the CMS and UMS[9–11] and the UMS and plastic stent (PS),[12,13] and one study has compared CMS and PS.[14]

In a randomized study comparing CMS with a conventional PS, the CMS was patent significantly longer.[14] However, studies showed that the Tannenbaum type PS (TTPS) without side holes was patent longer than the conventional PS.[15,16] The DoubleLayer stent (DLS; Olympus Medical Systems, Tokyo, Japan) is a TTPS, and its patency was superior to that of the conventional PS in a prospective randomized study.[17]

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Migration was not reflected in the calculation of stent patency in the conventional analysis, although this complication impaired the quality of life. To estimate the real quality of life, we calculated the time to dysfunction between stent insertion and stent occlusion or migration.

Many biliary stent studies included various malignancies around the bile duct; however, different diseases may show different tumor behavior and prognoses.[9] Therefore, we need to determine the stent efficacy for a single causative disease. Consequently, we conducted a prospective randomized study of CMS *vs* TTPS in the management of unresectable pancreatic head cancer (PHC) with obstructive jaundice using the DLS and Covered Wallstent (CWS; Microvesive, Boston Scientific, Natick, MA, USA).

METHODS

Patients

Consecutive patients over 18 years of age undergoing a first diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP) were enrolled in the study on their initial diagnosis of non-resection pancreas head cancer (PHC) with distal biliary obstruction. Their International Union Against Cancer classification was limited to stages 2b, 3, and 4. Neoplasms were diagnosed based on a pathological examination or clinical and imaging findings.

Exclusion criteria were: (i) intraductal papillary mucinous neoplasm (IPMN); (ii) endoscopic approach impossible; (iii) performance status 4; and (iv) an American Society of Anesthesiologists Physical Status Classification System grade of 3 and over. Written informed consent was obtained from all patients before entering the study.

Study oversight

The trial was not sponsored by any company. No endoscopic equipment or stents were donated by manufacturers.

Study design

The study was a multicenter, prospective, open-labeled, randomized, controlled trial. The study protocol was approved by the ethics committees of each participating institute and was performed at 14 Japanese referral centers according to the guidelines described in the Declaration of Helsinki for biomedical research involving human subjects. The protocol appears on UMIN CTR (C000000388). Each of the participating endoscopists in this study had performed more than 200 ERCP examinations per year for more than 5 years.

Randomization

Patients were registered on the study website and subsequently assigned to one of two groups by computer-generated randomization: the CWS or DLS groups. The randomization procedure was a minimization method stratified on tumor stage and institution.

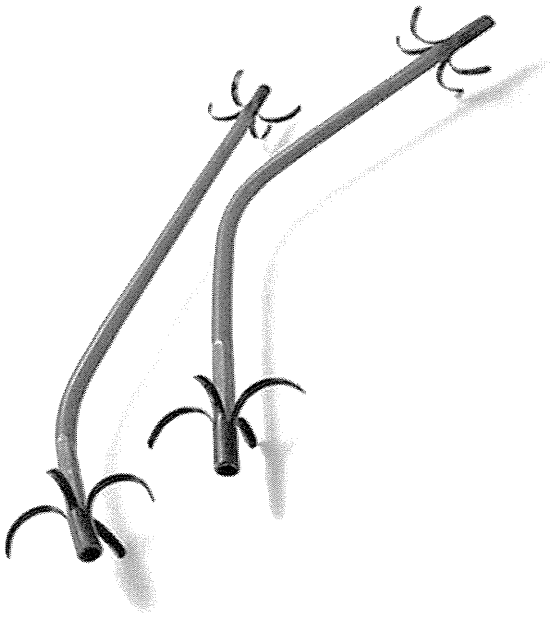

Fig. 1. DoubleLayer stent.

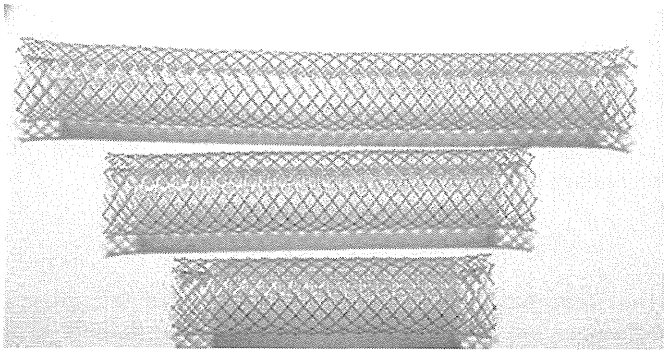

Fig. 2. Covered Wallstent.

Biliary stents

The plastic stent used in this study was a 10-Fr DLS duodenum bending type (Fig. 1). This stent is a Tannenbaum-type plastic stent constructed in three layers – the perfluoroalkoxy, wire mesh, and polyamide elastomer layers in order from the inner lumen – and has four distal and proximal flaps to prevent stent migration. The cost of each DLS was ¥45 000. A CWS with a partial silicone (Permalum) cover was used (Fig. 2), and its cost was ¥23 800. Both ends of this stent were uncovered for 5 mm. All stents were 10 mm in diameter. During the study, three lengths were available in the CWS (40, 60, and 80 mm) and DLS (50, 70, and 90 mm) groups.

Stent insertion

All endoprostheses were usually preceded by insertion of a 6-, 7-, or 8.5-Fr plastic tube stent or a nasobiliary drainage tube at the initial ERCP. After deciding that the tumor was

unresectable, the drainage tube was replaced with a 10-Fr DLS or CWS under fluoroscopic guidance using a therapeutic duodenal endoscope (JF-260V, TJF-200; Olympus, Tokyo, Japan). In patients who were deemed unresectable before the initial ERCP, either a DLS or CWS was inserted at the initial ERCP. An endoscopic sphincterotomy was performed and antibiotics given to all patients before either DLS or CWS insertion.

The length of the DLS was decided according to the stricture location from the papilla. The DLS tends to cause bile duct kinking because of its stiffness.[17] Therefore, we carefully selected the stent size to avoid bile duct kinking at the proximal stent end.

We selected the length of the CWS to be as long as possible to avoid stent occlusion by the tumor overgrowing beyond the stent end and to avoid bile duct kinking due to the strong axial force.[9,18,19] We placed the center of the CWS at the stricture to avoid stent misplacement due to a large shortening ratio.

Follow-up and definition of end-points

Blood biochemistry, clinical signs, and symptoms were monitored on an outpatient basis. Stent occlusion was diagnosed when patients presented with jaundice, cholangitis, or cholestasis. Palliative intervention involving either endoscopic or percutaneous drainage was performed as soon as possible, and the causes of stent obstruction were investigated endoscopically or cholangiographically. Most stents involving complications, either DLS or CWS, were removed, and the cause of occlusion was determined by examining the removed stents. The primary end-points of this study were stent obstruction or patient death with a patent stent. The secondary end-point was patient death.

Statistical methods

The stent patency period was calculated as the interval between stent insertion and its obstruction or patient death with a patent stent. We calculated the time to dysfunction (TTD) between stent insertion and stent dysfunction, including occlusion, cholangitis without stent occlusion, and migration. The cumulative patient survival, stent patency, and TTD were analyzed using the Kaplan–Meier method and the log–rank test for comparisons between two groups. The Mann–Whitney *U*-test was used to compare quantitative variables, and Fisher's exact test was used to analyze qualitative variables.

A previous study found an occlusion rate of 20% for the CWS,[4] which was about 25% less than that for the DLS (43%).[17] For a 5% type I error with 80% statistical power, the required number of patients in each group was estimated to be 60. All analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient enrollment and characteristics

We enrolled 120 patients between October 2005 and December 2007. Seven patients were excluded: one patient died from cancer progression before CWS placement, and the papilla could not be reached in the remaining six (two DLS and four CWS) due to duodenal obstruction. The remaining 113 patients were followed until June 2008, and the final data were fixed in May 2009. The clinical features were balanced between the two groups, as shown in Table 1. Pathological confirmation was made in 86.7% of the included cases. No patients were lost during the follow-up period.

Table 1. Patient characteristics

	DoubleLayer stent	Covered Wallstent	
Cases	58	55	
Sex (M/F)	30/28	33/22	NS
Mean age (range)	69.6 (44–86)	71.1 (53–86)	NS
Pathological confirmation	50	48	
Reason for non-resection			NS
Metastasis	23	27	
Locally advanced	26	20	
Advanced age	6	5	
Concomitant disease	1	2	
Patient request	1	1	

NS, not significant.

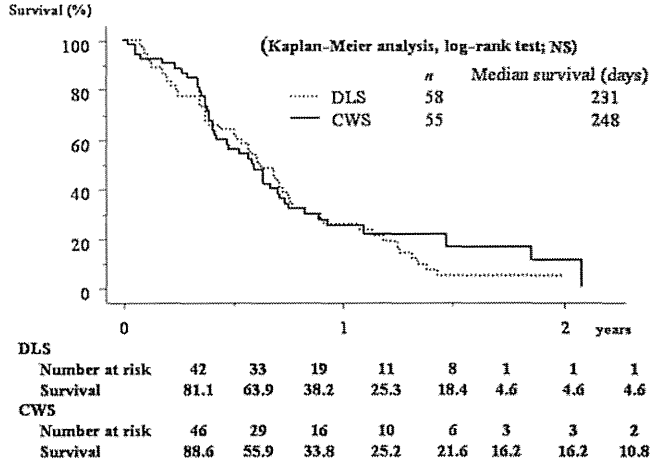

Fig. 3. Cumulative survival time calculated using the Kaplan–Meier method and log–rank test. No significant (NS) difference was found between the Covered Wallstent (CWS) group and the DoubleLayer stent (DLS) group.

Survival and stent patency

No significant difference in overall patient survival was found (Fig. 3), with a median survival of 231 days in the DLS group and 248 days in the CWS group. Twenty cases of duodenal tumor invasion occurred in each group, and the difference in stent patency did not differ significantly from the non-invasion cases. The cumulative stent patency according to the Kaplan–Meier method was significantly higher ($P = 0.0072$) in the CWS group than in the DLS group (Fig. 4). The respective mean and median stent patency was 202 and 133 days in the DLS group and 285 and 419 days in the CWS group.

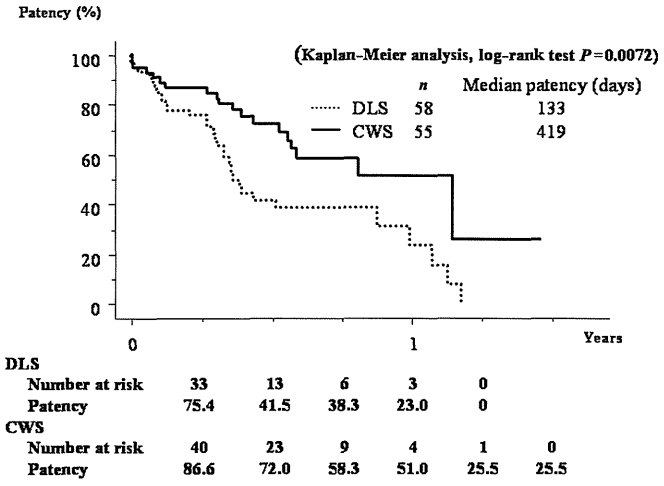

Fig. 4. Cumulative stent patency. The Covered Wallstent (CWS) was patent significantly longer than the DoubleLayer stent (DLS) ($P = 0.0072$).

Table 2. Details of biliary drainage and anti-cancer therapy

	DoubleLayer stent	Covered Wallstent	*P*-value
Cases	58	55	
Median survival (days)	231 (31–586)	248 (8–761)	
Stent patency (days)			
Mean	202 (0–429)	285 (2–536)	
Median	133	419	
Stent occlusion	31 (53.5%)	13 (23.6%)	0.0019
Patent period (days)	110 (0–429)	144 (2–419)	
Cause			
Tumor ingrowth	0	2	0.2347
Tumor overgrowth	0	1	0.2347
Sludge	24	2	< 0.0001
Food impaction	3	5	0.3552
Kinking	2	0	0.4959
Others	2	3	0.6736

Stent occlusion and other complications

Stent occlusion occurred in 31 (53.5%) cases after a median of 110 days in the DLS group and in 13 patients (23.6%) after a median of 144 days in the CWS group. The incidence of DLS occlusion was significantly higher than that of CWS ($P = 0.0019$). The causes of occlusion are summarized in Table 2, and the rate of stent occlusion due to sludge formation in the DLS group (24 cases) was significantly higher than in the CWS group (two cases) ($P < 0.001$). Two DLS were occluded by kinking of the bile duct at the proximal end of the stent, whereas this type of occlusion was not observed in the CWS group. No significant difference in stent occlusion by food impaction between the groups was observed.

The incidence of complications other than stent occlusion in the CWS group was higher than in the DLS group, but the difference did not reach significance (Table 3). No cholecystitis or pancreatitis was observed in the DLS group, but four cases (7.2%) and one case (1.8%) were seen in the CWS group, respectively.

Table 3. Complications

	DoubleLayer stent	Covered Wallstent	*P*-value
Cases	58	55	
Complications	4 (6.9%)	11 (20%)	0.0528
Cholecystitis	0	4 (7.3%)	0.0530
Pancreatitis	0	1 (1.8%)	0.4911
Migration	1	5 (9.1%)	0.1104
Liver abscess	2 (3.4%)	0	0.4959
Others	1	2	0.6117

Table 4. Stent dysfunction and time to dysfunction

	DoubleLayer stent	Covered Wallstent	*P*-value
Stent dysfunction	32 (55.2%)	18 (34.6%)	0.0228
Cause, TTD* (days)			
Stent occlusion			
Tumor ingrowth	0	2 (166, 419)	
Tumor overgrowth	0	1 (217)	
Sludge	24 (mean 154.0)	2 (193, 216)	
Kinking	2 (41, 1)	0	
Food impaction	3 (2, 36, 131)	5 (mean 57.6)	
Others	2	3	
Migration	1 (2)	5 (mean 146)	

TTD, time to dysfunction.

With stent-related complications, 33 DLS and 12 CWS were removed successfully. No complication related to stent removal and no failed case of removal occurred.

Stent dysfunction

Stent dysfunction occurred with stent occlusion or migration. Table 4 lists the causes of dysfunction in both groups and the period from stent insertion to stent dysfunction. The Kaplan–Meier analysis of the TTD, shown in Fig. 5, and median and range of TTD was 133 days (1–429) in the DLS group and 285 days (2–536) in the CWS group, respectively. Cumulative TTD of CWS was significantly longer than that of DLS ($P = 0.0209$), but the difference was shorter than the patency.

DISCUSSION

The CWS was patent significantly longer and had a longer TTD than the DLS for unresectable PHC with obstructive jaundice. Duodenal invasion did not affect the stent patency in either group. The TTD of the CWS was shorter than the patency due to migration.

Both covered metallic stents and plastic stents were able to prevent tumor ingrowth via the stent mesh and were mainly occluded by biliary sludge. In this study, the incidence of stent occlusion by sludge was significantly higher in the DLS group than in the CWS group. The large stent diameter may decrease the incidence of stent occlusion by sludge. Conversely, the large opening on the duodenal stent end may cause a high incidence of stent occlusion by impaction of food scraps. The TTPS may prevent this complication, and it

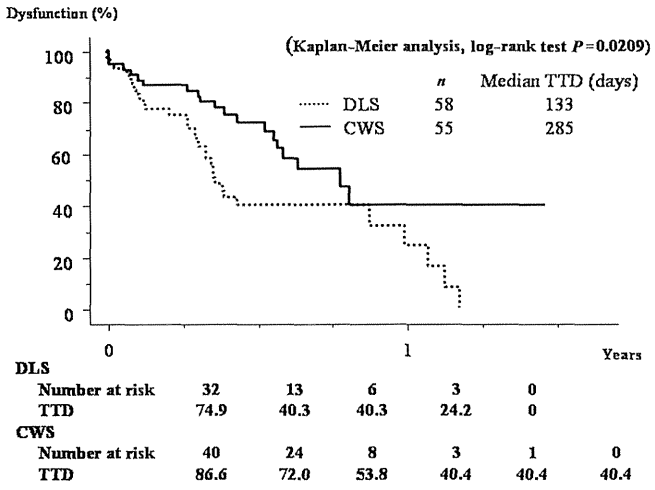

Fig. 5. Time to dysfunction (TTD) using the Kaplan–Meier method and log–rank test. The Covered Wallstent (CWS) had a significantly longer TTD than the DoubleLayer stent (DLS) ($P = 0.0209$).

has a longer reported patency than other types of PS.[15] However, the CWS was patent significantly longer than the DLS in this study.

This study enrolled only patients with PHC, whereas many reports on stenting for malignant biliary obstruction included various causative diseases. In a randomized study comparing covered and uncovered Diamond stents by the first author, differences were noted in the effectiveness of CMS according to the causative disease.[9] For PHC, the CMS was patent significantly longer than the UMS. Therefore, we think that the CMS is the first-line stent to choose for PHC with obstructive jaundice.

The removal of the CWS succeeded without any complications in all cases where it was required, although this stent has uncovered portions in both ends. A fully covered MS could be removed more easily and should be used for benign cases or resectable cases as a bridge to surgery.[3,20,21] For pancreatic cancer, new chemotherapeutic agents, such as gemcitabine, have prolonged survival times. Therefore, an exchangeable CMS may be suitable for the ongoing management of PHC.

The incidence of complications other than stent occlusion was higher in the CWS group. The prognosis of cholecystitis after CMS placement is affected by tumor involvement of the orifice of the cystic duct (OCD) and gallbladder stones.[22,23] In our study, of the four cholecystitis cases, OCD involvement was observed in one case, gallbladder stones in one case, and no data on the status of the OCD or gallbladder stones were available in two cases. Only one case developed pancreatitis in our series. Prior early stent thrombosis may reduce the incidence of pancreatitis compared with previous studies using the CMS.[4] Another problem with the CWS was the high migration rate (9.1%). The first author reported a lower incidence of migration with the ComVi stent, which has an outer uncovered layer as an anchor.[24] An anchoring system is needed for the CMS to prevent migration.

Migration is a serious complication that reduces the patient's quality of life. Migration was not recognized as stent occlusion, and was not reflected in the calculation of stent patency in many articles. We tried to estimate the TTD using Kaplan–Meier analysis. We think that this new method may surrogate real stent function.

The median patency of the DLS in this study (133 days) was higher than that of a conventional straight type PS (90–120 days). The previously reported median patency of the DLS (144 days) was similar to our result. We think that the DLS is superior to other types of PS based on our study, especially in PHC. Therefore, we consider that DLS should be selected for the patients with poor condition and expected prognosis of less than 3 months. The Tannenbaum plastic stent was reported to have a higher cost-effectiveness than the uncovered metallic stent.[25] In this study, the cost-effectiveness analysis was not performed, and we should clarify this issue in the near future. The disadvantage of the DLS was the bile duct kinking at the proximal stent end due to its stiffness. Two DLS were occluded because of bile duct kinking despite careful insertion to avoid this complication.

In conclusion, the CWS was patent significantly longer and had a longer TTD than the DLS in the management of PHC with obstructive jaundice. The incidence of complications other than stent occlusion was higher with the CWS, but the difference did not reach significance. Improvement in the design of the CWS is needed to prevent these complications.

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