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CLINICAL INVESTIGATION

Percutaneous Palliation of Pancreatic Head Cancer: Randomized Comparison of ePTFE/FEP–Covered Versus Uncovered Nitinol Biliary Stents

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Abstract The purpose of this study was to compare the clinical effectiveness of expanded polytetrafluoroethylene/fluorinated-ethylene-propylene (ePTFE/FEP)–covered stents with that of uncovered nitinol stents for the palliation of malignant jaundice caused by inoperable pancreatic head cancer. Eighty patients were enrolled in a prospective randomized study. Bare nitinol stents were used in half of the patients, and ePTFE/FEP–covered stents were used in the remaining patients. Patency, survival, complications, and mean cost were calculated in both groups. Mean patency was 166.0 ± 13.11 days for the bare-stent group and 234.0 ± 20.87 days for the covered-stent group ($p = 0.007$). Primary patency rates at 3, 6, and 12 months were 77.5, 69.8, and 69.8% for the bare-stent group and 97.5, 92.2, and 87.6% for the covered-stent group, respectively. Mean secondary patency was 123.7 ± 22.5 days for the bare-stent group and 130.3 ± 21.4 days for the covered-stent group. Tumour ingrowth occurred exclusively in the bare-stent group in 27.5% of cases ($p = 0.002$). Median survival was 203.2 ± 11.8 days for the bare-stent group and 247.0 ± 20 days for the covered-stent group ($p = 0.06$). Complications and mean cost were similar in both groups. Regarding primary patency and ingrowth rate, ePTFE/FEP–covered stents have shown to be significantly superior to bare nitinol stents for the palliation of malignant jaundice caused by inoperable pancreatic head cancer and pose comparable cost and complications. Use of a covered stent does not significantly influence overall survival rate; nevertheless, the covered endoprosthesis seems to offer result in fewer reinterventions and better quality of patient life.

Keywords Pancreatic cancer · Bile duct stent · Bile duct obstruction · Biliary drainage · Malignant jaundice · percutaneous interventions · covered metallic stents · ePTFE/FEP

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Introduction

Pancreatic cancer is the fifth most common cause of cancer-related death in the Western world [1, 2]. The most common histological type is ductal adenocarcinoma, which accounts for >80% of total cases. It has an extremely poor prognosis, and only 10–20% of the patients are eligible for a potential curative surgical resection. [3–5]. When it is located in the head of the organ (65% of cases), pancreatic adenocarcinoma frequently leads to biliary obstruction; therefore, treatment is limited to palliation of obstructive jaundice, which is followed by chemotherapy.

Palliation may be offered surgically or with stent placement (either endoscopic or percutaneous). Both methods offer similar overall survival rates, but the latter seems to be associated with lower early complication rate, procedure-related mortality, cost, and better quality of life [6–10].

In contrast, stents have the tendency to become obstructed, and reintervention might sometimes be necessary. Plastic stents do not seem to offer a valid and cost-effective long-term option for the palliation of malignant jaundice, and they have been replaced by bare metallic self-expandable stents [11], although they might still be used in some centers as an initial approach.

However, when a patient's survival is long enough, even metallic stents might become occluded [11] due to tumoural ingrowth through the mesh, leading patients to continuous readmissions and reinterventions, increasing discomfort, and procedural costs. In the effort to avoid tumour ingrowth, covered metallic stents were developed in the last 10 years, using various coverage materials [12–17]. Initial data on the efficacy of covered stents was controversial [12–14], but recent studies have shown more promising results [18]. In particular, the ePTFE/FEP–covered stents, because of the characteristics of their coverage material and their specific conformation, are likely to be safe and effective in the palliation of malignant biliary disease, efficient in the prevention of tumour ingrowth, and superior to bare stents for the palliation of malignant jaundice caused by extrahepatic cholangiocarcinoma in selected patients [19–23].

The purpose of this prospective randomized study was to compare the clinical results of covered ePTFE/FEP stents with nitinol bare stents for the palliation of malignant biliary disease secondary to unresectable adenocarcinoma of the pancreatic head.

Materials and Methods

Study Design and Patients

This two-centre study was designed to be prospective and randomized. The study hypothesis was that the use of ePTFE/FEP–covered endoprostheses in selected patients would improve the 6-month patency rate, thus leading to lower reintervention and complication rates without significant increase of the cost. The composite end point was defined as patient death or endoprosthesis occlusion. Considering the mean patency rate of covered (mean 222 days [SD 110]) and uncovered stents (mean 179 days [SD 82]) reported in previous publications, and to demonstrate a minimum difference of 43 days between the means of the two groups with a power of 80% (5% α error, 20% β error), the study was designed to include a minimum of 40 patients in each arm of the trial.

Two different medical centres were involved in the study under the same protocol. The study was approved by both local hospital ethical committees and adhered to the guidelines described in the Declaration of Helsinki for biomedical research involving human subjects. Participating physicians had considerable experience in performing percutaneous biliary interventions.

Inclusion criteria were obstructive jaundice caused by unresectable pancreatic head adenocarcinoma, which in turn caused occlusion of the biliary tree at the lower half of the common bile duct. Exclusion criteria were three of six of the following: total serum bilirubin level $\geq$15 mg/dl, leukocytosis $\geq 11 \times 10^9$/l, gamma glutamil transferase (γGT) > 165 IU/l, prothrombin ratio $\geq$1.4, C-reactive protein (CRP) $\geq$5 mg/dl, and serum carbohydrate antigen 19-9 (CA 19-9) level $\geq$10.000 IU/ml. The selection of the above-mentioned criteria is based on studies indicating factors that might influence survival in patients with pancreatic adenocarcinoma. For example, CRP, a marker of the acute-phase response that appears elevated in various conditions—such as infection, inflammation—has shown to be linked to cancer cachexia, and in previous studies it was detected as being increased in advanced cancer disease stage [15, 17, 29, 34]. The above mentioned inclusion criteria aimed to select a patient population which survival could possibly exceed three months. Nevertheless, these criteria do not represent a contraindication to bare-stent placement.

Absolute exclusion criteria were a performance status <3 on the Eastern Cooperative Oncology Group (ECOG) scale [28], presence of distal metastases to other than the adjacent lymph nodes, cirrhosis with portal hypertension, patients >80 years old, previous surgical or radiotherapeutic palliative treatment, and gastric outlet obstruction. The exclusion criteria are listed in Table 1. The presence of

Table 1 Study exclusion criteria

Criteria (three of six)	
Total serum bilirubin level (mg/dl)	≥15
Leukocytosis (WBC) ($\times 10^9$/l)	≥11
γGT (IU/l)	>165
Prothrombin ratio	≥1.4
CRP (mg/dl)	≥5
CA19-9 (IU/ml)	>10,000 IU/ml
Performance status (ECOG)	<3
Patient age (y)	>80
Distal metastases	
Previous surgical or radiotherapeutic palliative treatment	
Gastric outlet obstruction	
Cirrhosis with portal hypertension	

WBC = white blood cells

Table 2 Patient characteristics in the two groups

Characteristics	Uncovered group	Covered group
No. of patients	40	40
Sex (F/M)	4/36	23/17
Median (SD) age (y)	65 (SD 8.8)	63.5 (SD 9.8)
Histologic diagnosis	32/40	35/40
Average tumor size (cm)	1.6	1.9
Total median (SD) bilirubin before stenting (mg/dl)	8.3 (SD 1.1)	6.1 (SD 1.3)

ascites was not considered a contraindication, and a left-sided approach was used in these patients. Before the procedure, written informed consent was obtained from all patients.

Eighty patients were included in the study. They were 53 men and 27 women, who ranged in age from 41 to 79 years (mean 62.7, median 65). Bare nitinol stents (Luminexx nitinol biliary stent; Bard, Murray Hill, NJ) were used in half of the patients, whereas covered stent-grafts (Viabil biliary stent; Gore, Flagstaff, AZ) were used in the remaining patients. Patient characteristics of the two groups are listed in Table 2.

Randomization was performed using a randomization envelope containing 40 bare-stent and 40 covered-stent cards. The cards were randomly divided in the two centres involved in the study, and one card was drawn out after diagnostic percutaneous transhepatic cholangiography (PTC) proved that the patient fulfilled the study's inclusion criteria. Patient informed consent also involved the randomization process.

Pancreatic carcinoma diagnosis was based on histology after forceps or needle biopsy, computed tomography (CT), and/or magnetic resonance imaging (MRI) findings (mass in the head of the pancreas with delayed enhancement), plus laboratory and clinical findings (malignant jaundice with increased neoplastic markers, clinical signs of pancreatic cancer). In particular, contrast-enhanced CT using thin slices (3- to 5-mm) and image acquisition in arterial, portal, and late venous phase were used. Metastatic disease to the liver, peritoneum, and lung and infiltration of peripancreatic vessels were also detected. MR cholangiopancreatography (MRCP), if available, showed useful information in delineating the anatomy of the biliary tree and the pancreatic duct before stent placement.

Luminexx Nitinol Biliary Stent

The Bard Luminexx nitinol biliary stent is an electropolished, self-expanding, flexible, grid-like endoprosthesis dedicated to the treatment of malignant biliary stenosis. It is made of nitinol, which is a biocompatible nickel–titanium alloy that permits expansion to a preset diameter on exposure to body temperature. The stent has a segmental repeating pattern and open-cell geometry with flared ends to help prevent dislocation or migration. Partial cuts around the circumference of the stent provide enhanced flexibility and allow segment-by-segment expansion. Each end of the stent has four radiopaque tantalum markers to enhance visibility, thereby facilitating accurate stent placement. The stent is preloaded on a flexible delivery system that is compatible with a 6F introducer and accepts a 0.035" guidewire through the inner catheter lumen. The system also features a soft, rounded tip on the distal end of the outer catheter, which is tapered to fit with the guidewire for less traumatic introduction. It is available at a wide range of diameters (7- to 10-mm) and lengths (20- to 100-mm) but the 10 × 60-mm and 10 × 80-mm sizes are more frequently used. According to the manufacturer, safe deployment of Luminexx nitinol biliary stents requires that 5–10 mm of the stent extend beyond both ends of the stricture. This will allow adequate stent coverage and is likely to impede tumour overgrowth at the ends of the stent. In addition to this, the stent should be slightly larger in diameter (by approximately 1–2 mm) than the target duct. If overlapping is required, the same diameter is suggested for both stents, with the stents overlapping each other for at least 5 mm to include the flared ends. Finally, the Luminexx nitinol biliary stent is MRI safe and compatible.

Viabil Biliary Stent

The Viabil biliary stent (Gore) is a self-expanding covered stent with an ePTFE/FEP tubular lining that is externally supported by a helical nitinol stent with radiopaque markers at both ends. The coverage membrane is made of an ultrathin, low-porosity ePTFE/FEP material that is 0.010-mm thick. Multiple sections of the wires near both ends of the nitinol stent project outward and act as anchoring fins. These lateral anchoring fins decrease the risk of endoprosthesis migration. The delivery system consists of both 9F and 10F outer sheaths. Two different versions are available: one has transmural drainage side holes to avoid obstruction of the cystic duct, and the other does not. The Viabil biliary stent is available in diameters of 8 or 10 mm and lengths of 4, 6, 8, or 10 cm. According to the manufacturer, the Viabil biliary stent should extend at least 2 cm proximal and distal to the margins of the stricture. Because of the nitinol lining, total expansion is reached approximately 24 h after placement, whereas the endoprosthesis length is not subject to variation. There are not yet enough data to evaluate Viabil MRI compatibility.

Methods

PTC was performed with the patient under local anaesthesia (lidocaine 2%) and conscious sedation using 1–8 mg midazolam and 50–200 μg fentanyl. Antibiotic prophylaxis (750 mg cefuroxime) was administered before the procedure in all patients and was continued for up to 5 days after the drainage and stenting procedure. Right-side access was chosen in most patients, reserving left-side access for patients in whom there was a significant amount of ascites, thus precluding right-side puncture. Stent placement for both stents types was performed either as a one-step (primary stenting technique) or two-step (secondary stenting technique) procedure. The decision for primary or secondary stenting was physician related and was based on morphologic evaluation of the lesion at the moment of initial PTC. Particularly in patients in whom bleeding occurred during PTC, the stent was placed 3–4 days later to avoid obstruction from thrombus. When secondary stenting was performed, an 8F–10F locking biliary catheter (Flexima; Boston Scientific, Watertown, MA) was left in place for 2–6 days. In the case of tight strictures, dilatation was performed with a balloon catheter 6–8 mm in diameter (Opti-Plast XT; Bard) before stent insertion or drainage catheter placement. One or occasionally two stents were used to cover the whole extension of the lesion according to fluoroscopic image. Both covered and uncovered stents were advanced approximately 1 cm below the papilla to avoid occlusion caused by distal overgrowth. If the lesion protruded into the duodenum and infiltrated the enteric lumen, a duodenal stent (Wallstent; Boston Scientific) was placed after deployment of the biliary endoprosthesis. The duodenal endoprosthesis was usually placed in another session by way of transoesophageal access. Local anaesthesia (spray) and conscious sedation were administered. The lesion was crossed with the use of a 0.035" hydrophilic wire (Radiofocus; Terumo Europe, Leuven, Belgium), which was exchanged for an extra-stiff 0.035" Teflon-coated Amplatz Guidewire (Cook, Bloomington, IN), and a stent was deployed in the appropriate duodenal location. Regarding the proximal end of the covered stents, in the rare occasion (considering that we dealt with low common bile duct stricture) where the lesion was extending near the cystic duct junction, a stent with side holes was used to avoid obstruction of the cystic duct (Fig. 1). In total, we used 43 Luminexx nitinol biliary stents (6- to 9-cm long and 10-mm wide) and 41 Viabil biliary stents (4- to 8-cm long and 8- to 10-mm wide). Nine covered stents with side holes and 32 without side holes were used (Table 3). In two patients, a duodenal stent was placed. In both patients, the duodenum was eroded from the tumour without manifestation of gastric outlet syndrome. After stent placement, unless evident hemobilia occurred, a 5F catheter (with its distal end lying into the duodenum) was left in place as a "tutor" to perform cholangiogram 1–3 days after the procedure. The criteria for removal were satisfactory stent deployment, contrast runoff, and good patient clinical condition. For patients in whom macroscopic hemobilia occurred during the procedure, a larger (8F–10F) internal–external draining locking pigtail

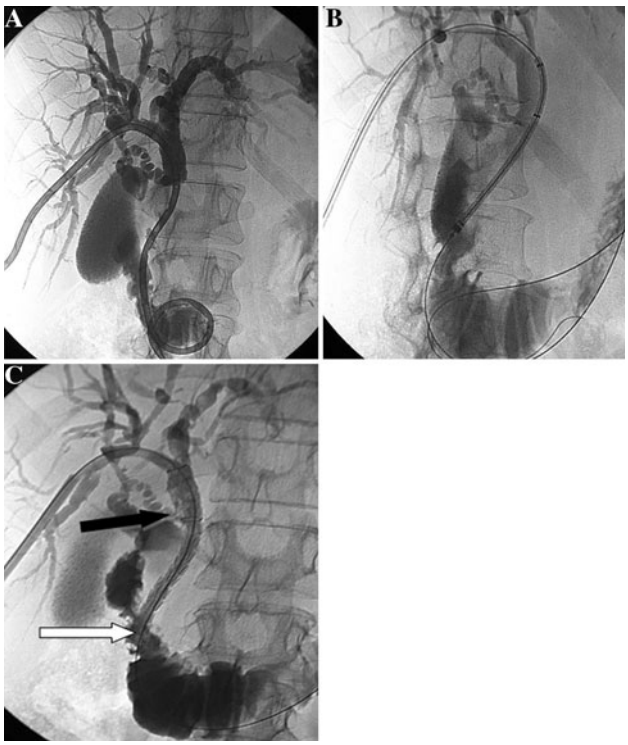

Fig. 1 **A** Percutaneous cholangiography through an 8F internal–external drainage catheter showing a low common bile duct stricture in a 62-year-old woman that extends to the orifice of the cystic duct. The pancreatic duct is not opacified. **B** An 8 × 80-mm Viabil biliary stent with side holes was advanced in the stenotic area. **C** The stent is satisfactorily deployed. Note the position of the stent, which protrudes 1–2 cm into the duodenum across the papilla (*white arrow*), while the side-hole region permits drainage of the cystic duct, thus avoiding cholecystitis (*black arrow*)

Table 3 Types of stents used in the two groups

Stent size (mm)	Uncovered group Luminexx	Covered group	
		Viabil with holes	Viabil no holes
4 × 80	0	0	2
8 × 80	0	0	2
10 × 60	18	6	19
10 × 80	22	3	10
10 × 90	3	0	0
Total	43	9	32

catheter (Flexima) was left in situ to tamponade the tract and evaluate the bleeding rate.

Follow-Up and Reintervention

Follow-up parameters consisted of blood laboratory examinations, clinical findings, and outpatient imaging results. When the patient presented with jaundice or cholangitis, stent occlusion was suspected. Imaging (US or CT) and clinical evaluation confirmed stent occlusion, and reintervention was followed by ERCP or PTC. ERCP was the initial approach, and PTC was performed when ERCP was not feasible.

To identify the cause of recurrent obstruction, a biopsy specimen was taken with a pair of flexible forceps. Dysfunction usually occurs due to the presence of sludge, stones, thrombus, and tumour ingrowth or overgrowth. Sludge accumulation or stone formation usually occurs due to biliary stasis in patients in whom the endoprosthesis is not fully deployed, is kinked, or is even fractured. Occlusion caused by thrombus is associated with the presence of haemobilia and a decrease in haematocrit. Tumour ingrowth occurs when there is neoplastic tissue growth between the stent's open cells or through the eroded coverage membrane in the case of covered stents. Tumour overgrowth takes place when occlusion is attributed to the growth of neoplastic tissue centrally (proximal overgrowth) or distally (distal overgrowth) to the endoprosthesis ends. When tumour extends toward the duodenum, biliary obstruction may be associated with gastric outlet syndrome.

Independent of the biopsy result, and if the patient's condition permits, new cholangiography for endoprosthesis revision is performed. Revision consisted of stent cleaning with a semi-inflated balloon, which was moved upward and downward in the endoprosthesis lumen. If cleaning therapy was not successful, or if stent kinking was present, balloon dilatation was performed. In the case of stent occlusion, if the patient was not in end stage of the disease, new stent placement was performed; otherwise, reintervention was limited to drainage catheter insertion.

Study End Points and Definitions

Major study end points were the assessment of technical success, safety of stent implantation, patient survival, stent patency, and comparison between the two groups. Minor study end points were the characterization of the type of stent dysfunction in each group and comparison between the two groups.

Technical success was achieved when the stent or stent-graft was correctly deployed in the expected location with residual stenosis at the end of the procedure <30%. Safety of stent implantation was correlated to the incidence of periprocedural and interprocedural complications. Complications were considered early if they occurred in the first 30 days after stent placement; otherwise, they were considered late complications and were classified according to North American Society of Interventional Radiology (SIR) criteria [29].

Stent patency corresponds to the absence of recurrent symptomatic biliary obstruction. Primary patency was defined as the interval time between initial placement and recurrence of obstruction. If there was no evidence of obstruction during the patient's life, the patency period was considered equal to the survival period but was censored.

Cost-Effectiveness Analysis

The total cost of both procedures was analyzed and compared. Cost was subject to variations regarding type and number of stents used, total number of necessary sessions for stent placement, duration of hospital stay, and cost associated with number and type of complications and reinterventions. An arbitrary mean cost was defined for each of the procedures to avoid differences between the two centres. When duodenal stents were used, their cost was not added to the procedure's total cost.

Statistical Analysis

Cumulative stent patency and patient survival were estimated using the Kaplan–Meier technique and supplemented by log-rank test for comparisons between groups [30]. Unpaired Student *t* test was used for comparison of quantitative variables, and Fisher's exact test was used for comparison of qualitative variables. Statistical analysis was performed with NCSS 97 statistical software (NCSS, Salt Lake City, UT).

Results

One hundred thirty-four patients with malignant jaundice and diagnosis of pancreatic cancer were treated in our units between January 2005 and December 2008. Fifty-one of the patients did not meet the inclusion criteria (laboratory values, age, and presence of metastases) and thus were excluded from the study, and three patients were eligible but refused to participate.

Eighty patients were included in the study, and on a randomized basis one of the two different endoprostheses was used for palliation of malignant jaundice. Patients were followed-up until September 2009. No patient was lost to follow-up. In total, there were 53 men and 27 women, and there was no statistical difference in sex distribution between the two groups.

Left-sided access was used in 6 patients in the bare-stent group and in 3 patients in the covered-stent group. Stent insertion was performed in the same session with PTC (primary stenting) in 12 patients in the bare-stent group and in 6 patients in the covered-stent group, whereas secondary stenting was performed in the remaining 28 and 34 patients in the two groups, respectively. Balloon dilatation was performed in 5 (12.5%) patients in the bare-stent group and in 6 (15%) patients in the covered-stent group. Mean wait time between PTC and stent placement was 2.7 days for the Luminexx group and 3.2 days for the Viabil group. Control cholangiography and catheter removal was performed 3.6 days after stenting in both groups.

Technical Success and Complications

All stents were successfully inserted and deployed, and no case of stent migration was observed; the technical success rate reached 100% in both groups. Early complications were observed in four (10%) patients in the bare-stent group and in five (12.5%) patients in the covered-stent group. In the uncovered-stent group, two cases of peritoneal irritation occurred immediately after stent placement and resolved within 24 h with intravenous antibiotic therapy. Catheter removal time was not influenced by this complication, which is considered minor (class B according to SIR) [29]. In the same group, two cases of self-limited biliary haemorrhage occurred after primary stent placement. The patients remained haemodynamically stable, were no transfused or embolized, and ceased bleeding spontaneously without influenced hospitalization time (class A complication). In the covered-stent group, three cases of peritoneal irritation occurred after primary stenting that resolved within the next 24 h without delay in patient management (class B complication). The same complication, i.e., self-limited biliary haemorrhage, occurred also in two other patients after primary stent placement. Haemorrhage, which manifested as hemobilia, was detected at intervention and continued for the next 24 h in the external drainage sac. The patients remained stable, were not transfused or embolized, and ceased bleeding spontaneously without influenced recovery time (class A complication).

Patency and Survival

Median follow-up after stent placement was 192 days (range 104–603). No patient was alive by the end of the study. The 30-day mortality rate was zero for both groups. According to Kaplan–Meier analysis, survival rates at 3, 6, and 12 months were 100, 57.5, and 7.5%, for the bare-stent group and 97.5, 55, and 20% for the covered-stent group, respectively. Median survival time was 203.2 days (SE 11.8, SD 74.8) for the bare-stent group and 247 days (SE 20, SD 126.7) for the covered-stent group. There was no statistically significant difference regarding survival between the two groups ($p = 0.063$) (Fig. 2).

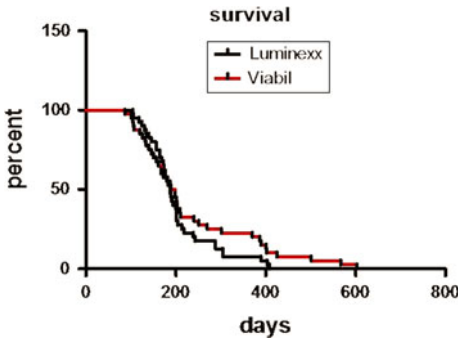

Fig. 2 Kaplan–Meier statistical analysis of survival cases in the two groups

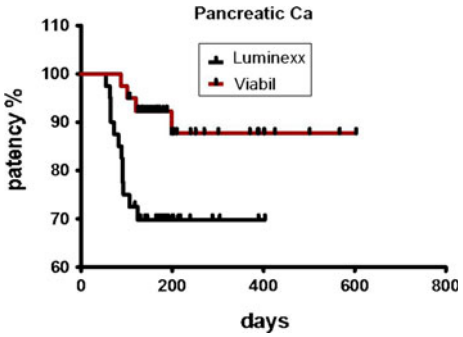

Fig. 3 Kaplan–Meier statistical analysis of primary stent patency cases in the two groups

Stent premature occlusion occurred in both groups. Primary patency rates for the bare-stent group at 3, 6, and 12 months were 77.5, 69.8 and 69.8% and for the covered-stent group were 97.5, 92.2, and 87.6%. Mean primary patency was 166 days (SE 13.1, SD 82.8) and 234 days (SE 20.8, SD 132) for the two groups, respectively. According to Kaplan–Meier survival analysis, there was a significant difference in the patency rates between the two groups, indicating superiority of the covered stent ($p = 0.007$) (Fig. 3).

Endoprosthesis dysfunction occurred in 12 patients in the bare-stent group (30%) after a mean period of 82.9 days (SE 5.8, SD 20.1). Forceps biopsy showed that the cause of dysfunction was tumour ingrowth in 11 of 12 patients (91.6%). In 3 of those patients, tumour overgrowth was also present. Occlusion caused by sludge formation occurred in just 1 patient 54 days after stent placement. Dysfunction occurred in 4 patients in the Viabil biliary stent group (10%) after a mean period of 126.5 days

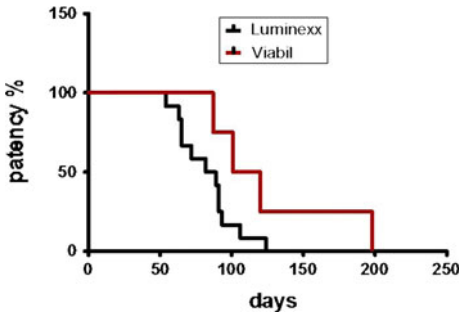

Fig. 4 Kaplan–Meier statistical analysis of dysfunction cases in the two groups

Table 4 Overall comparison of the two groups

Parameter	Uncovered group	Covered group	*p*
Length of survival (d)	203.2	247	NS
Incidence of complications (%)	10	12.5	NS
Dysfunction (%)	30	10	$p = 0.04$
Patency (d)	166	234	$p = 0.007$
Ingrowth rate (%)	91.6	None	$p = 0.002$

NS = not significant

(SE 24.7, SD 59.5) (Fig. 4). Forceps biopsy was successfully performed, and obstruction was attributed to tumour overgrowth in 2 (50%) patients and sludge formation in another 2 (50%) patients. In the latter 2 patients, stent kinking was noted, and balloon dilatation was performed. There was a significant difference ($p = 0.002$) regarding the occurrence of tumour ingrowth in the 2 groups. No case of gastric outlet syndrome occurred in either group. Table 4 lists an overall comparison between the 2 groups.

Reintervention for stent obstruction was performed transhepatically in all patients. In eight patients in the bare-stent group and two patients in the covered-stent, new metallic stents were coaxially inserted. New Luminexx nitinol biliary stents were used in the bare-stent group, and Wallstent (Boston Scientific) stents were used in the covered-stent group. In four patients in the bare-stent group and two patients in the covered-stent group, an 8F drainage catheter was left in situ due to the patients' impaired condition after balloon dilatation and cleaning. Mean secondary patency was 123.7 days (SE 22.4, SD 77.9) for the bare-stent group and 130.3 days (SE 21.4, SD 42.8) for the covered-stent group.

Cost-Effectiveness Analysis

The cost difference between the two groups was calculated by taking into account the type of device used initially, total hospital stay, and number and type of reinterventions needed. The number of reinterventions was defined by the frequency of endoprosthesis dysfunction, considering that the patient was readmitted to the hospital and stent revision performed. The materials used for deployment of a Luminexx nitinol biliary stent (puncture set, guidewires, catheters, stent, contrast medium) amounted at a mean cost of 2112 € (range 1840–4192, SE 82.3, SD 520.9), and the mean cost for the Viabil biliary stent deployment was 2438 € (range 2310–4620, SE 57, SD 360.7). The mean hospital stay for patients treated with a Luminexx nitinol biliary stent was 5 (SE 0.1, SD 1.1) and for the group treated with a Viabil biliary stent was 4.8 days (SE 0.1, SD 1). Considering a mean price for each hospital day of 600 €, the total cost of the first intervention was 5092 € (range 3640–7192, SE 122.3, SD 773,4) for the bare-stent group and 5318 € (range 4250–7020, SE 105.8, SD 668.9) for the covered-stent group. There was no significantly statistical difference between the two groups ($p = 0.16$).

Considering the number and type of reinterventions and total hospital stay, mean cost for the Luminexx group was 5863 € (range 3640–9592, SE 239, SD 1,513) and for the Viabil biliary stent group was 5620 € (range 5310–990, SE 189, SD 1,195). There was no significant difference between the two groups ($p = 0.42$).

Discussion

Pancreatic adenocarcinoma is a disease with a devastating prognosis. The incidence in Europe and the United States is approximately 10–12 cases/100,000 population/y [1, 2]. Approximately 80% of the cases occur when the patient is between 60 and 80 years of age, and it is more common in men than women, with a male-to-female ratio of 1.5 to 2 [31]. This relation was also observed in our study population (53 men and 27 women). It is usually diagnosed late and has a biologic phenotype characterized by resistance to all cancer treatment modalities and early metastasis. At the time of diagnosis, approximately 65% to 75% of patients with pancreatic head adenocarcinoma suffer from symptomatic biliary obstruction caused by blockage of the intrapancreatic portion of the common bile duct [32]. Biliary stasis is associated with pruritus, anorexia, diarrhea, and cholangitis [33].

Palliation may be offered surgically or with metallic self-expandable stents. Plastic stents have been replaced from metallic ones as the latter have shown to offer a more valid and cost-effective option for the palliation of malignant jaundice [11]. Both methods seem to offer similar overall survival rates, but metallic stents are likely to be associated with lower rates of early complications, procedure-related mortality, cost, and better quality of patient life [6–10]. In more recent studies, palliative surgery has

shown more promising results than in the past due to the use of modern and less-invasive surgical techniques; however, these results are described in single-center retrospective studies and depend mainly on local expertise [34, 35]. Surgical treatment is associated with longer hospital stay and higher initial morbidity and mortality, but the reintervention rate appears to be low. Stent treatment offers lower initial mortality and morbidity rates, but it leads more frequently to late biliary complications and reinterventions caused by clotting of the stent, tumour ingrowth or/and overgrowth, and gastric outlet obstruction [6–9].

To improve stent performance and offer a palliative method leading to fewer reinterventions for the oncologic patient, covered metallic stents have been developed [12–17]. Initial data on covered stents was controversial, but recent studies have shown more promising results [18–23, 36]. Currently, there is not enough evidence to support the routine use of covered stents in malignant obstruction from pancreatic head tumour, and their use is limited to selected patients.

This article reports a prospective, randomized study from two different centres that aimed to compare the clinical results of Viabil covered metallic biliary stents with those of Luminexx bare nitinol biliary stents in an effort to elucidate the role of covered stents in the palliation of malignant jaundice caused by pancreatic head adenocarcinoma. Patients included in the study were expected to have a median survival time >3 months to avoid any influence of the results from early patient mortality. The study exclusion criteria were based on previous publications that delineated the biochemical markers influencing survival in patients with pancreatic cancer [24–27] and were associated with ECOG performance status and presence of metastasis.

No case of migration or technical failure occurred in either group. Potential migration is a main concern when using covered stents. Currently, apart from Viabil endoprosthesis there are two other types of commercially available covered biliary stents that have been used in other studies: the covered Wallstent (Boston Scientific) and the ComVi stent (Taewoong Medical, Seoul, Korea). Other commercially available covered stents, such as the Fluency (Bard), have not been extensively used in series of patients to treat malignant strictures. Both the covered Wallstent and the ComVi have been shown to be prone to migration, particularly the former [37, 38]. This problem was not encountered with Viabil biliary stents as shown from this and previous studies [19–23]. This important characteristic may be explained by the fact that the ePTFE/FEP layer is located internally to the nitinol skeleton, thus allowing better attachment to the tumour. It also provides proximally and distally lateral anchoring fins for better fixing of the stent inside the mass.

Our study has shown that ePTFE/FEP–covered endoprostheses are clearly superior to bare nitinol stents regarding patency, with Kaplan–Meier survival analysis yielding $p = 0.007$. The 6-month patency rate was 69.8% for bare stents and 92.2% for covered stents. Other investigators have reported similar or even better results with bare stents in the past. In a large multicenter study with 240 patients, which was published in 1994, Rossi et al. reported a 25-week patency rate of 67% for bare Wallstents but a 25-week patency rate of 78% for nitinol Strecker stents [39]. In the study by Lee et al., the 25-week patency rate was 81% in 100 patients in whom six different types of bare stents were used [40]. In a more recent study, Brountzos et al., who used four types of bare metallic stents, reported a cumulative primary patency rate of 81% at 6 months [41]. The high 6-month patency rate (92.2%) of the Viabil biliary stents in our study is slightly lower than the 6-month patency rate reported by Fanelli et al. [21] (92.6%) and superior to the rates reported by Schoeder [19], (76%), Bezzi [20], (77%) and Hatzidakis [21] (i.e., 75% for fully covered stents).

The relatively lower 6-month patency rate in the bare-stent group was mainly attributed to dysfunction caused by tumour ingrowth. Tumour ingrowth occurred exclusively in the bare-stent group ($p = 0.002$). Similar results were reported in a study by Katsinelos et al., in which Luminexx nitinol biliary stents were used and dysfunction caused by tumour ingrowth occurred in 24% of patients [42]. In contrast, Viabil biliary stents are likely to prevent occlusion from tumor ingrowth, as shown by Hatzidakis et al., due to their low-porosity, ultrathin (0.010 mm) ePTFE/FEP membrane [21].

Tumor ingrowth was noticed because patient survival was >3 months. According to Boguth et al., epithelization of a bare metallic endoprosthesis does not occur until the first 3–6 months after placement, then granulation tissue is formed, giant cells are recruited, and tumor ingrowth occurs through the stent's open cells [43]. This process is more likely to occur in patients with invasive malignancies, such as cholangiocarcinoma or pancreatic adenocarcinoma, whereas it is quite unlikely that the stricture is caused by enlarged lymph nodes. This difference of behavior between the different tumours leads to the necessity of a tumour type–oriented approach to determining malignant jaundice before stent placement and, in particular, the decision of whether to use a bare or covered stent. In all previous studies of bare metallic stents, lymph node enlargement was part of the stricture types treated. The relatively low 6-month patency rate for bare stents in our study may be explained by the fact that the study was tumor-type oriented. Tumor ingrowth may occur in Luminexx nitinol biliary stents when they are deployed in patients with pancreatic adenocarcinoma and in those who survive >3 months, whereas it does not occur at all in Viabil

covered biliary stents. In addition, it is unlikely that patients with lymph node enlargement will benefit from the use a covered stent; therefore, bare stents should be the best solution in all such cases.

Covered-stent dysfunction was present due to sludge formation and tumour overgrowth. Neither sludge nor food accumulated in the duodenal edge of the endoprostheses, although they were deployed quite distally, approximately 1–2 cm below the papilla. Use of covered stents near the papilla of Vater does not necessarily lead to acute pancreatitis, probably because the distal part of the duct is already infiltrated and obstructed by the tumour. If during PTC the pancreatic duct shows retrograde filling of contrast, one should avoid use of a covered stent in that area.

Sludge was found in the mid-portion of two of the covered stents due to kinking. This acute angulation was not noted at the moment of deployment; otherwise, post stenting balloon dilatation would have been performed and their deployment considered as technical failures. In both patients, cleaning and balloon dilatation were performed. Dysfunction caused by tumor overgrowth may rarely occur in the patients with pancreatic tumors. We encountered two cases in patients with fully covered stents. An explanation might be that in both patients, a relatively short (4-cm) Viabil biliary stent was used, long enough to cover the low CBD stricture but apparently not long enough to prevent tumour overgrowth. In this case, we could have used a lower covered stent with proximal side holes or a coaxial uncovered metal stent extension.

Covered stents have also shown longer but not statistically significant survival (203.2 vs. 247 days). The overall survival rate is limited as would be expected in this disease. We also believe that the superiority of covered stents regarding this aspect is purely casual. The benefit that covered stents may offer is focused on the quality of life of the oncologic patient by requiring fewer reinterventions. If overall survival had been higher, the gap between the two groups may have been wider. Nevertheless, overall survival in these patients depends mainly on the tumour's metastatic rate and presence of eventual comorbidities, unless serious complications occur during palliation.

The complications noted were minor (classes A and B according to SIR classification) and quite similar in the two groups (10% in bare vs. 12.5% in covered stents). Peritoneal irritation may occur when infected bile leaks toward the peritoneal cavity; however, in all cases this reaction was limited by administration of intravenous antibiotics, with all patients feeling much better the nest day. We expected a higher percentage of peritoneal-irritation cases in the covered stent group considering the use of larger-bore carrying catheter (9–10F vs. 6F or the bare stent), but it is likely that this risk can be limited by using appropriately sized sheaths. Another option would have been to plug the biliary tract with glue or gelfoam, but in such a case, control cholangiography would not be possible. We believe that this is the safest approach in order to evaluate satisfactory stent's expansion and contrast runoff, offering also the possibility of reintervention, even though in none of our cases stent's revision was not necessary. This might lead to the assumption that tract embolization may have also limited the (few) cases in which peritoneal irritation occurred. Biliary haemorrhage may occur because of the high vascularisation of the liver; nevertheless, in most cases it seems to be rather minor and self-limiting. We did not encounter any case of cholecystitis or pancreatitis, both of which have been reported in other covered-stent series [37, 38].

No significant difference was noted regarding overall cost between the two groups, although the cost of a single session is higher for the covered endoprostheses. This is probably due to the fact that the reintervention rate was higher for the bare-stent group and also because the bare stents used were quite expensive. Katsinellos et al., in a multicenter study, has shown that Luminexx nitinol biliary stents were not been superior to Hanaro bare stents (M. I. Tech, Ceo Kim, Chul Soo, Korea), whereas the cost of the latter was 34% less [43]. If we had used this more economic solution, then maybe there would have been a difference regarding the cost between the two groups in favour of the bare-stent group. Nevertheless, we used Luminexx nitinol biliary stents because they are dedicated biliary stents and because their cost, apart from the economic Hanarostent (M. I. Tech), is similar to that of most bare endoprostheses on the market.

From this prospective, randomized, two-centre, tumour type-oriented study on the palliation of malignant jaundice, we conclude that ePTFE/FEP–covered stents are significantly superior to bare nitinol stents in cases of inoperable pancreatic head cancer regarding primary patency and ingrowth rate and have comparable cost and complication rates. Covered stents do not seem to influence overall survival rate; nevertheless, after appropriate patient selection, percutaneously placed ePTFE/FEP–covered endoprostheses seem to offer a better quality of life to the patient with inoperable pancreatic head cancer.

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