Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial (CME)

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Background: Most patients with malignant common bile duct strictures are suited only for palliation of jaundice by placement of a polyethylene (PE) stent using an endoscopic retrograde cholangiographic technique. Occlusion of these stents occurs after 3 to 4 months, whereas uncovered self-expanding metal stents (SEMS) remain open twice as long. The initial higher cost of the latter might be balanced by a decreased need for repeat intervention.

Objective: To compare the patency of 10F PE stents and covered 30F steel SEMS (Wallstent; Boston Scientific Nordic AB, Helsingborg, Sweden).

Design: Single–center, prospective, randomized, controlled trial.

Setting: General hospital in Stockholm, Sweden, which has a catchment area of 0.6 million people.

Patients: Non-referred, unresectable malignant common bile duct strictures.

Interventions: Endoscopic retrograde cholangiography with plastic stents or covered SEMS.

Main Outcome Measurements: Time to stent failure, requiring a new stent.

Limitations: Similar setting and patients, and costs in Scandinavia.

Results: Fifty-one and 49 patients were allocated to the PE stent and SEMS groups, respectively. Fifty-six patients died without stent failure within 10 months (median, 2.6 months). Twenty-two PE stent and 9 SEMS patients ($P = .009$) developed failure after a median of 1.1 and 3.5 months, respectively ($P = .007$). Median patency times were 1.8 and 3.6 months in the PE and SEMS groups, respectively ($P = .002$). Median survival was 4.5 months; in 35 patients with distant metastases, the median survival was 2.5 months ($P = .002$)(PE group, 1.9 months).

Conclusions: The more-effective SEMS are recommended in unresectable patients with malignant common bile duct strictures, who survive a median of 4.5 months. Less costly plastic stents are preferable in the one third of patients who have distant metastases. In our study, the cost was equal. (Gastrointest Endosc 2006;63:986-95.)

Fewer than 20% of patients with a malignant stricture of the common bile duct can be offered a cure by resection.[1,2] In the others, the best method for palliation of jaundice is the placement of a polyethylene (PE) endoprosthesis (EP) by using an endoscopic retrograde cholangiographic (ERC) technique.[3,4] However, partial or total occlusion of the EP, frequently accompanied by cholangitis, usually occurs 3 to 4 months after the insertion of a standard 10F PE stent,[4,5] and it must then be replaced.

Stent dysfunction mainly is associated with the diameter of the EP lumen. In 4 randomized controlled studies (RCTs), wide-bore self-expanding metal stents (SEMS) have remained patent up to a median of 9 months.[6-9] SEMS are much more expensive, but if they stay open about twice as long as conventional plastic stents, the high initial cost will be offset by a reduction in the need for endoscopic repeat intervention and/or rehospitalization. Therefore, the choice of a plastic or metal EP may be dependent on an estimate of the patient survival rate, ie, prognostic factors that are not fully understood.[10,11] SEMS, such as the Wallstent (Boston Scientific Nordic AB, Helsingborg, Sweden), are inserted using an 8F catheter system and are composed of a wire mesh that expands to a maximum of 30F when released across the stricture.

Metal EPs are also available in a silicone polymer-covered version (C-SEMS). The plastic covering of the mesh may counteract tumor ingrowth, one of the known mechanisms for dysfunction of the metal stent.[12]

Our aim was to compare the patency of conventional endoscopically inserted 10F plastic stents with that of C-SEMS in our Scandinavian setting of a large urban district general hospital. Therefore, we conducted a prospective RCT in patients with malignant distal bile duct strictures unsuitable for radical surgery.

PATIENTS AND METHODS

The study eligibility and exclusion criteria are shown in Table 1. Between August 2001 and April 2003, 100 patients fulfilled our criteria for randomization. A Consolidated Standards for Reporting Trials (CONSORT) flowchart is shown in Figure 1.

Randomization

When the patients met all the inclusion criteria and none of the exclusion criteria, and after informed consent was obtained, the patients were randomized (without blocking or stratification) to one of two groups: the PE stent or the C-SEMS group. The randomization process, which used the opaque, sealed envelope and random table technique, was done by one of the authors when the patient was in the ERCP suite, after the guidewire was in place. The stent then was immediately inserted. Blinding at or after randomization was not applied.

Stent insertion

A traditional straight, PE plastic, 10F EP (5, 7, or 10 cm in length) with distal and proximal side flaps and adjacent side holes, or a silicone polymer-covered (5 mm bare ends), self-expandable, steel metal (4, 6, or 8 cm in length) Wallstent (both from Boston Scientific Nordic AB, Helsingborg, Sweden) was inserted by the ERC transduodenal route. If the patient had not been investigated adequately (eg, with CT or evaluated for possible radical surgery), a 8.5F thin PE stent was inserted first. At a second session (as soon as possible, but always within 1 month), after the patient was enrolled in the study, randomization was done, and the stent was switched to a 10F PE EP or C-SEMS. Endoscopic sphincterotomy was performed routinely before stent insertion.

Follow-up and end points

The patients attended the outpatient clinic at 1 month, 4 months, and 10 months (end point), where we performed a physical examination, obtained blood samples for tests including liver function tests, and assessed them with the World Health Organization performance classification and the Visick grading system. Our main aim was to look for signs or a history of stent occlusion and to decide

Capsule Summary

What is already known on this topic

- When used for malignant common bile duct strictures, wide-bore, self-expanding metal stents (SEMS) remain patent longer than plastic stents, but are more expensive.
- Plastic-covered SEMS counteract tumor ingrowth, the main cause of occlusion.

What this study adds to our knowledge

- In a single-center, randomized, prospective study comparing plastic stents to plastic-covered SEMS, the plastic stent group had significantly more stent failures and shorter patency times than the SEMS group.
- Because the survival period in patients with distant metastases and the patency time in the plastic stent group are similar, the more-expensive SEMS may be reserved for patients who do not have distant metastases.

whether ERCP or other investigations should be done to confirm or intervene because of stent dysfunction.

The study end points were an uneventful follow-up for 10 months, death, and confirmed (ERC with intervention) stent failure. Survival data and stent patency data also were available after 10 months. Stent failure was defined as clinical (cholangitis) and laboratory (S-bilirubin > 50 μmol/L, previously normal) signs of stent occlusion confirmed by ERC (dilation of bile ducts proximal to the stricture, occluded or dislocated stent with little, if any, passage of contrast dye) and requiring insertion of a new stent.

The patients and caregivers were told about the symptoms of cholangitis and were asked to contact our hospital immediately in case of signs of obstruction. If stent obstruction was suspected, ERC was performed. The stent was switched to a SEMS in cases of an occluded PE stent; in those with occlusion of a metal EP, a PE stent was inserted inside the SEMS. Records from hospices and other primary care facilities were also evaluated for signs of stent dysfunction.

Evaluation

Our main outcome measure was the time to proven stent failure, as defined earlier. The primary aim was to compare the two groups for stent patency (ie, episodes of cholangitis) detected clinically, subsiding spontaneously, or confirmed and requiring repeat intervention (stent failure was the end point).

The secondary aims were to determine the technical success rate for insertion of the 2 types of stents, the complications at insertion, and the need for one or more sessions, as well as a simple cost calculation. The criteria for a successful stent insertion included the views of the endoscopist and radiologist (not involved in the trial)

TABLE 1. Criteria for eligibility and exclusion

Eligibility criteria

    1. Patients: Clinical data and a history suggestive of malignant bile duct occlusion; after investigation, found not to be amenable to curative resection.

    2. Jaundice: Typical radiological appearance of a common bile duct malignant stricture at diagnostic ERC; bilirubin level exceeding 50 μmol/L (normal, <26 μmol/L).

    3. Investigations: US and CT and/or magnetic resonance imaging performed before inclusion. If doubt whether radical surgery can be performed, inclusion should be postponed until after diagnostic laparoscopy and/or laparotomy. A temporary (<4 weeks) thin plastic stent (8.5F) may be inserted at diagnostic ERC to gain time for further investigations.

    4. Informed consent: Patient agrees to participate in study and randomization. Oral and written information about the nature of the trial given to all those considered for inclusion. This study was approved by the regional Ethics Committee of Karolinska Institutet, Stockholm, Sweden.

Exclusion criteria

    1. Informed consent not obtained or withdrawn.

    2. Extremely poor general condition. ERC with stent insertion impossible for ethical reasons.

    3. Candidate for surgical resection.

    4. Proper investigations (US, CT, MRI) not performed.

    5. Stenosis situated in hilus or close to hilus of the liver.

    6. Suspected nonmalignant obstruction; more investigations needed.

    7. Previous Bilroth type II gastric resection, pyloric or duodenal obstruction making ERCP difficult.

    8. Previous treatment with bile duct stent (exception: 8.5F stent placement <4 weeks).

    9. Previous inclusion.

    10. Severe coagulation disturbance (prothrombin index, <30% of normal), sphincterotomy dangerous.

ERC, Endoscopic retrograde cholangiography.

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that the stent was in a satisfactory position in the stenosed duct, and a 30% decline in the serum bilirubin level during the first 3 days (or on the day of discharge, if earlier).

Sample size and statistical analysis

We expected a failure rate of up to 50% in the PE stent group (at 3 months), with failure defined as clinical cholangitis and/or confirmed stent occlusion with or without ERC intervention. To show a reduction to 15% (70% reduction) with a metal stent, with an α error of 0.05 and a power of 0.8, at least 75 patients would have to be included.[13] Therefore, we included 100 patients.

The χ^2 test or Fisher exact test was used to evaluate differences in the distribution of the absolute numbers of patients. The Student unpaired *t* test was used to compare the laboratory tests, age, and stent length in the 2 groups, and Cox univariate regression analysis was used to compare survival and stent patency, after confirmation that the groups were equal as regards possible confounders. The Kaplan-Meier method and the log-rank test also were used to assess differences in survival and stent patency.

An intention-to-treat analysis was performed, but 2 patients (PE group) were censored at their operations because of a protocol violation. The analyses also were performed on a per-protocol basis.

The trial was approved by the Ethics Committee of Karolinska Institutet, Stockholm. Study design was reviewed and improved by the Cochrane Hepatic Group, Copenhagen, Denmark.

Approximate costs

We calculated the costs on the basis of those in our institution, South Hospital in Stockholm, Sweden. Wallstents cost €1070 and PE stents €130. The overall costs of therapy were determined by adding the cost of hospitalization (€480 per day) to the costs of the stent and ERC. The patients were hospitalized for a median of 2.5 days for the treatment of stent failure.

RESULTS

One hundred patients were randomized into the study between August 2002 and March 2004, 49 patients to the C-SEMS group and 51 to the PE stent group. A CONSORT flowchart shows the course of the patients (Fig. 1). Patient characteristics at inclusion are listed in Table 2, and no differences were detected between the two groups.

Histological confirmation of malignant disease was obtained in half of the patients (26 patients in the SEMS group,
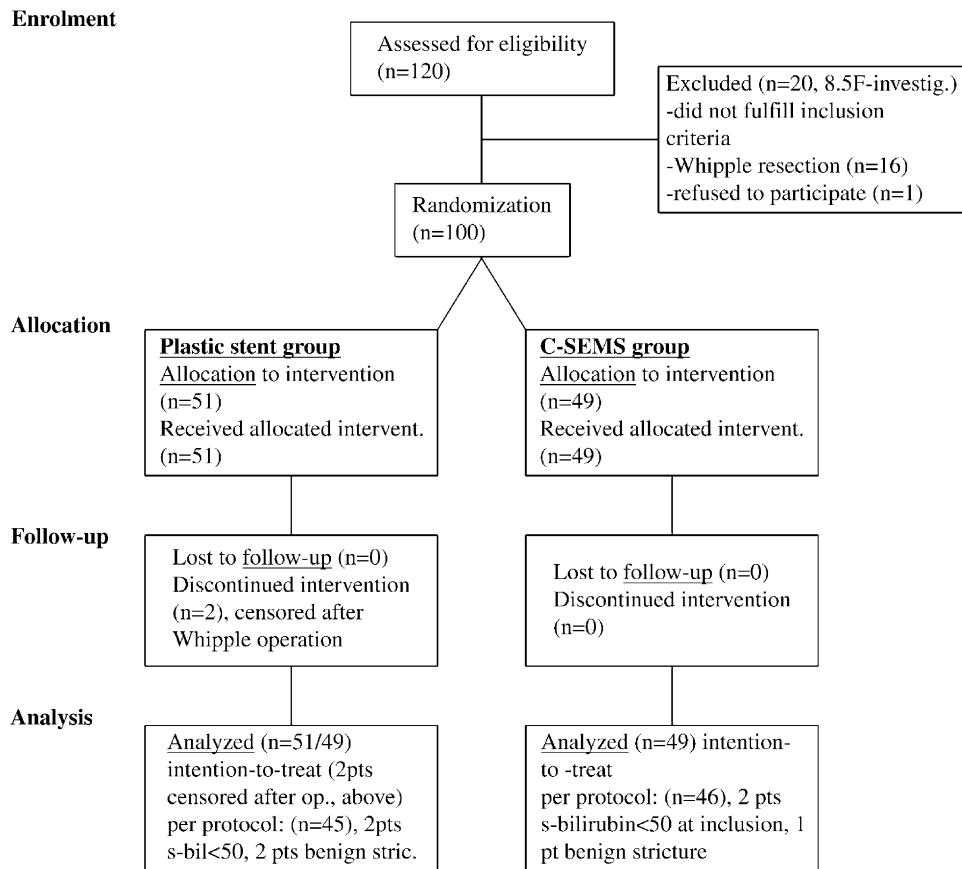
Enrolment

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                              ┌──────────────────────────┐
                              │ Assessed for eligibility │
                              │ (n=120)                  │
                              └──────────────────────────┘
                                          │        ┌─────────────────────────────────┐
                                          │        │ Excluded (n=20, 8.5F-investig.) │
                                          │        │ -did not fulfill inclusion      │
                                          │        │ criteria                        │
                                          │        │ -Whipple resection (n=16)       │
                                          │        │ -refused to participate (n=1)   │
                                          │        └─────────────────────────────────┘
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                              │ Randomization      │
                              │ (n=100)            │
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Allocation

Plastic stent group	C-SEMS group
<u>Allocation</u> to intervention (n=51)	<u>Allocation</u> to intervention (n=49)
Received allocated intervent. (n=51)	Received allocated intervent. (n=49)

Follow-up

Lost to <u>follow-up</u> (n=0) Discontinued intervention (n=2), censored after Whipple operation	Lost to <u>follow-up</u> (n=0) Discontinued intervention (n=0)

Analysis

<u>Analyzed</u> (n=51/49) intention-to-treat (2pts censored after op., above) per protocol: (n=45), 2pts s-bil<50, 2 pts benign stric.	<u>Analyzed</u> (n=49) intention-to -treat per protocol: (n=46), 2 pts s-bilirubin<50 at inclusion, 1 pt benign stricture

Figure 1. CONSORT flowchart showing the patients' course during the study.

24 in the PE group). In the others (with 3 exceptions; see protocol violations), US, CT, and clinical course were typical of malignant disease. No patient was lost to follow-up.

Stent insertion and complications

ERC was initially unsuccessful in 2 patients due to technical problems (a large diverticulum and tumor infiltration of the duodenum, respectively). After percutaneous transhepatic cholangiography with small-caliber stent placement (8.5F), ERC was successful; the patients were randomized, one to each stent group, and the stents were inserted using the rendezvous technique.

In 2 patients in the SEMS group, a second ERC session within 24 hours was necessary because of proximal dislocation of the too-short and unsatisfactorily positioned (not in the middle of the stricture) metal stents. No problems were encountered with the plastic stents.

The bilirubin level did not decline as expected in 3 patients (2 in the SEMS group). In 2 SEMS patients, the initial radiological evaluation was incomplete; both had a malignant distal stricture but also an initially undetected hilar metastasis, which caused a second stenosis that was not bridged by the too-short metal stent. We do not know why the bilirubin did not decline in the third (PE) stent patient (patent stent).

Four patients (4.0%) developed early complications. Two had cholangitis (PE group), one of whom died of multiorgan failure on the second day; the other was treated successfully. One patient in the SEMS group had moderately severe postprocedure pancreatitis, which subsided with conservative treatment after 1 week. Another in the SEMS group developed bleeding in the area of the stent, which stopped after endoscopic epinephrine injections.

Protocol violations

Two PE patients and two SEMS patients had protocol violations because their serum bilirubin levels were below 50 μmol/L (normal, <26 μmol/L) at randomization (all were included in the follow-up). Two patients (PE group) subsequently underwent a Whipple procedure and were censored from follow-up after that (2 and 21 weeks, respectively); both were resected radically and survived 18 and 4 months later, respectively. One of these patients had chronic obstructive respiratory disease and initially was turned down by the anesthesiologists as unfit for major surgery; the other was downstaged after intense oncologic therapy. These events were not foreseen in the design of the protocol.

Two patients in the PE group (Mirizzi syndrome and unknown etiology, respectively) and 1 in the SEMS group

TABLE 2. Patients' characteristics at inclusion

	SEMS	PE
No. patients	49	51
Age, y, median (range)	77 (48-92)	78 (49-93)
Gender (male/female), no.	22/27	28/23
WHO classification (0/1/2/3/4), No.	8/20/14/5/2	8/19/16/6/2
Concomitant serious disease, No.	29	35
Hepatic or pulmonary metastases, No.	19	16
General condition (poor/intermediate/good), No.	4/30/15	5/28/18
Etiology, No.		
Pancreatic cancer	40	38
Ampullary tumor	1	1
Cholangiocarcinoma	5	4
Metastatic disease	2	5
Carcinoid	0	1
Benign stricture	1	2
Bilirubin, median, μmol/L (range) [normal, <26 μmol/L]	199 (18-685)	237 (8-629)
Alkaline phosphatase, median, μkat/L (range) [normal, 0.8-4.6 μkat/L]	22.4 (5.0-82.9)	21.3 (2.3-76.5)
Aspartate aminotransferase, median, μkat/L (range) [normal, <0.60 μkat/L]	3.1 (0.7-13.2)	2.6 (0.6-9.6)
Length of stents, No.	4 cm: 12 6 cm: 29 8 cm: 8	5 cm: 9 7 cm: 34 10 cm: 8
8.5F stent before inclusion, No.	14	19
No. days with 8.5F before inclusion, median (range)	8 (2-29)	8 (3-23)

SEMS, Self-expanding metal stents; *PE*, polyethylene stent; *WHO*, World Health Organization.

TABLE 3. Median survival and stent patency times in the SEMS and PE stent groups

	SEMS	PE	RH	CI	P
Survival time,* SEMS vs PE	5.3	3.9	1.25	0.84, 1.87	.2776
Survival time,† SEMS vs PE	5.4	3.8	1.51	0.99, 2.32	.0571
Patency time (overall),* SEMS vs PE	3.6	1.8	1.94	1.24, 2.95	.0020
Patency time (overall),† SEMS vs PE	3.6	1.8	2.14	1.38, 3.30	.0006
Patency time (failures),* SEMS vs PE	3.5	1.1	3.53	1.41, 8.87	.0072

Cox regression analysis; time given in months; *SEMS*, self-expanding metal stent; *PE*, polyethylene stent; *RH*, relative hazards, *CI*, 95% confidence intervals.
*Intention-to-treat analysis.
†Per-protocol analysis.

staged and received radical surgery (PE stent group) are still alive, as are the 3 misdiagnosed patients (1 in the SEMS group, 2 in the PE group) who were found to have a benign stricture (Table 2). Two more patients are alive, 1 with a carcinoid tumor (PE group) and one 92-year-old woman with an ampullary tumor (SEMS group). With the possible exception of this older patient (patho-anatomical diagnosis not obtained), none with adenocarcinoma is alive.

Survival is shown in Table 3 and Fig. 2A. Median survival was 4.5 months (5.3 and 3.9 months in the SEMS and PE groups, respectively; $P = .28$). The survival was similar using the Kaplan-Meier method and the log-rank test ($P = .27$). At present 47 of 49 patients in the SEMS group and 46 of 49 in the PE stent group have died. In a per-protocol-based analysis, there was borderline significance for a longer survival in the SEMS group ($P = .057$) (Table 3).

Thirty-five patients had hepatic (29 patients) or pulmonary (5 patients; 1 patient with both) metastases at inclusion (Table 2). Their median survival was 2.5 months (2.8 and 1.9 months in the SEMS and PE groups, respectively), which was shorter ($P = .002$, log rank test) than that of the whole group. The mortality rate in relation to the duration of follow-up is also shown in Table 4.

Stent patency

Nine SEMS and 22 PE patients developed stent failures in the 10-month follow-up ($P = .009$) (Tables 3-5, Fig. 2B). The median patency time was 3.6 months in the SEMS group and 1.8 months in the PE stent group ($P = .002$)(Table 3). Nine other patients (3 in the SEMS group, 6 in the PE group; $P = .268$) had clinical stent failure; that is, they were not referred for ERC because of the advanced stage of the cancer, but they showed definite
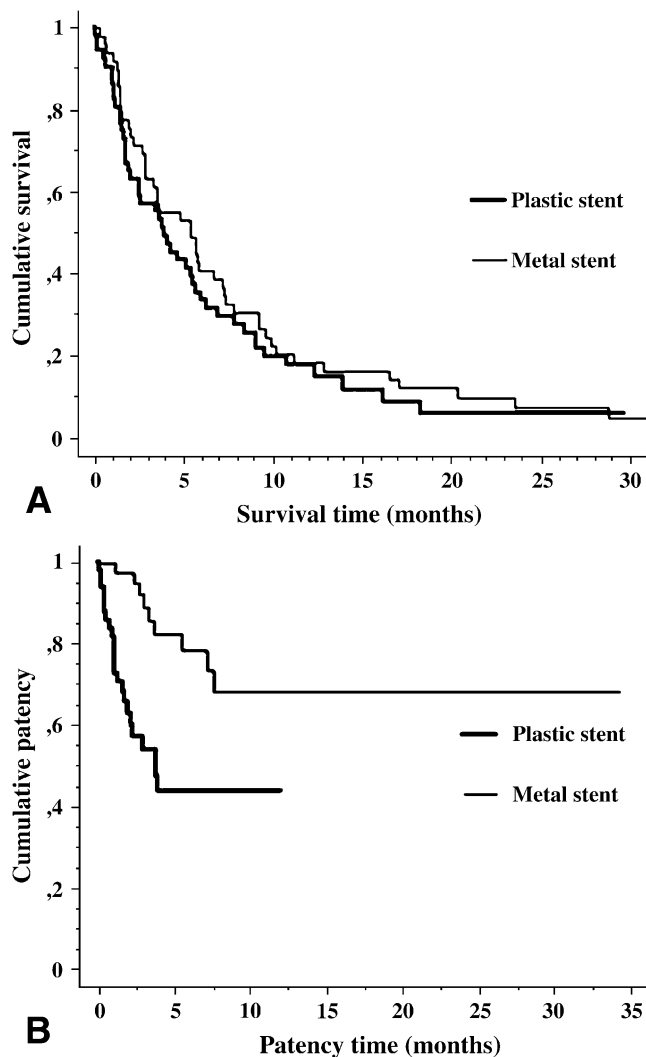
(chronic pancreatitis) eventually were found to have benign strictures. All patients were included in the analysis on an intention-to-treat basis. A per-protocol analysis that included only patients who had no protocol violations was also performed.

Survival

Seven patients are alive after a median of 18 months (range, 10-31 months). The 2 patients who were down-

Figure 2. A, Patient survival using the Kaplan-Meier method (intention-to-treat analysis). No differences were found between the PE stent and the SEMS groups (P = .2738). **B,** Kaplan-Meier life-table analysis of stent patency (intention-to-treat analysis). The patency time was significantly longer in the SEMS group (P = .0015).

signs of cholangitis, including recurrent jaundice. When stent occlusion was diagnosed at ERC, a PE stent was usually inserted in an occluded SEMS, and a PE stent was usually changed to a metal stent (Table 5, Fig. 3). The reasons for occlusion are listed in Table 5. In a per-protocol analysis, the difference in median stent patency was similar between the PE and SEMS groups (Table 3).

The levels of aspartate aminotransferase declined faster (P = .036) and serum bilirubin levels tended to decline faster (P = .267) in the SEMS group than in the PE group at 2 days.

Eight SEMS patients and 3 plastic EP patients survived 10 months with patent stents (Table 5). Five of these SEMS patients died with patent EPs after a median of 20 months (range, 10-23 months). Occlusion occurred in 2 SEMS patients after 11.5 and 33 months (past our end point of 10 months), and a third SEMS patient is still alive

TABLE 4. Stent failures and mortality (without failure) at follow-up

	SEMS (n = 49)		PE (n = 49†)		P value*	
	Failure	Died	Failure	Died	Failure	Died
On day of discharge from hospital, No.	0	0	1	3		
At 1 month	0	4	7	5	.013	.999
At 4 months	6	22	14	16	.045	.300
At 10 months‡	9	32	22	24	.009	.163

SEMS, Self-expanding metal stent; *PE,* polyethylene stent.
*Fisher exact test.
†2 patients censored after Whipple operation.
‡Alive without stent failure at 10 months: SEMS, 8 patients; PE, 3 patients.

with no signs of occlusion after 18 months. Two of the 3 PE EP patients who were alive without occlusion after 10 months had a benign stricture, which had been treated with dilatation and stent exchange before occlusion but after 10 months; they are alive and well today. The third PE patient died after 18 months; his PE stent had been exchanged after the 10-month end point.

Approximate costs

Thirteen more patients in the PE stent group than in the SEMS group required hospitalization for stent exchange because of failure (Table 5). Their median hospital stay of 2.5 days (range, 1-22 days) cost €480 each day (€1200 in total).

The cost of the ERCP procedure (with participation of two endoscopic nurses, but no radiology or anesthesiology personnel) was the same (€1200), except for the stents, each of which cost €1070 (SEMS) or €130 (PE stent). At failure, 17 more stents in the plastic group than in the SEMS group were changed to SEMS (Table 5). (For this calculation, the patient with surgical bypass was assessed as a percutaneous transhepatic cholangiography with plastic stent insertion; in our hospital, this costs the same as ERC with SEMS insertion. Therefore, the patient count is 17, not 16). In the PE group, the extra cost for failure was €17,410 ([17 × 1070] − [6 × 130]) for the stents, €31,200 (2400 × 13) for hospitalization and ERC procedures, for a total of €48,610. The cost of the initial SEMS for the SEMS group was €46,060, more than for the plastic EPs.

DISCUSSION

This is the first RCT published in full that compares covered steel self-expanding stents with traditional plastic stents for endoscopic palliation of jaundice due to malignant common bile duct stenosis. Previous similar RCTs

TABLE 5. Stent failure

	SEMS	PE	P value
Alive >10 months without stent failure, No.	8	3	.199
Stent failure, proven, No.	9	22	.009
Clinical failure, No.	2	6	.268
Time-to-proven stent failure, months	3.5	1.1	.007
Etiology of stent failure			
Tumor overgrowth, No.	5	0	.056
Dislocation, No.	3	2	.999
Sludge, No.	1	20	
Measures taken at stent failure			
PE stent, No.	7	1	.012
SEMS, No.	1	17	.008
PTC stent	1	1	
None (except ERC)		2*	
Operative shunt		1	
Died without (proven) stent failure <10 months	32	24	.163
Total No. patients	49	49†	

SEMS, Self-expanding metal stent; *PE,* polyethylene stent; *PTC,* percutaneous transhepatic cholangiography; *ERC,* endoscopic retrograde cholangiography.
*EP not possible at ERC due to local tumor growth, PTC not performed due to poor general condition.
†2 patients censored after Whipple operation.
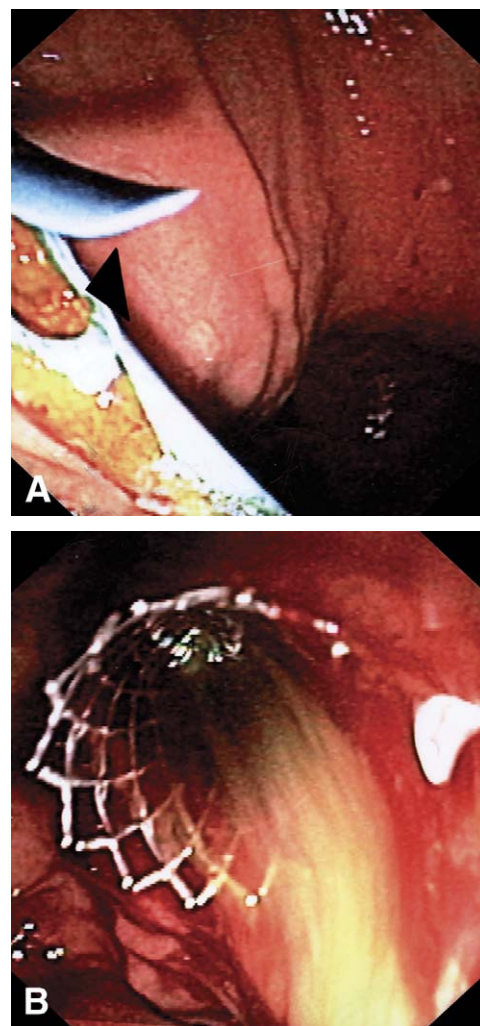
Figure 3. A, Occluded plastic stent. Solid material is seen through the side hole at the flap (arrowhead). **B**, Infected bile poured out when plastic stent was changed to a metal one.

from Amsterdam,[6] Kassel/Marburg and Rochester,[7] Lyon,[8] and other French centers[9] have evaluated uncovered steel stents (Wallstents). In brief, they found 2 to 3 times more stent failures in the plastic stent groups, a shorter time from insertion to stent failure in PE EPs, greater cost-effectiveness of metal stents (above a certain limit of patient survival), and different causes of stent occlusion in metal and plastic stents (Figs. 3 and 4).

In the present study, the median patency time of C-SEMS was 3.6 months, which is shorter than the ≥9 months in 3 RCTs.[6,8,13] This may be explained partly by the short median survival time in our series, 4.5 months, which is also reflected by the short PE stent patency time. All of our patients came from the adjacent primary catchment area, unlike those in the series from tertiary referral centers, which could be one reason for the relatively short survival. A recent, large prospective series of covered steel SEMS[14] (not an RCT) found a mean patency time of 5.7 months, 2 months longer than the median patency time of the present trial (but similar to our 6 months in the SEMS group when we recalculated the mean patency

time). However, the median survival and stent patency times are presented in the RCTs.[6-9,13] Similarly short median patency times also have been noted in other (uncovered) Wallstent RCTs[8,15] (3.7 to 4.5 months) and in studies of covered SEMS.[16] Therefore, the covering seems to account only for differences in the mode of occlusion in SEMS (from ingrowth to overgrowth) in combination with dislocation, facilitated by the covering and the strong expansile force of steel SEMS, as opposed to nitinol SEMS, but not to prolong the patency times; however, a direct comparison is needed to draw definite conclusions. The only RCT concerning this question was done in Japan; those authors compared covered and uncovered nitinol SEMS[17] and found significantly longer patency times by using the former, but no dislocation. However, a recent editorial[18] points out that studies of plastic stents and SEMS that have not been randomized tend to overestimate the advantages (including the patency times) of various stent modifications.
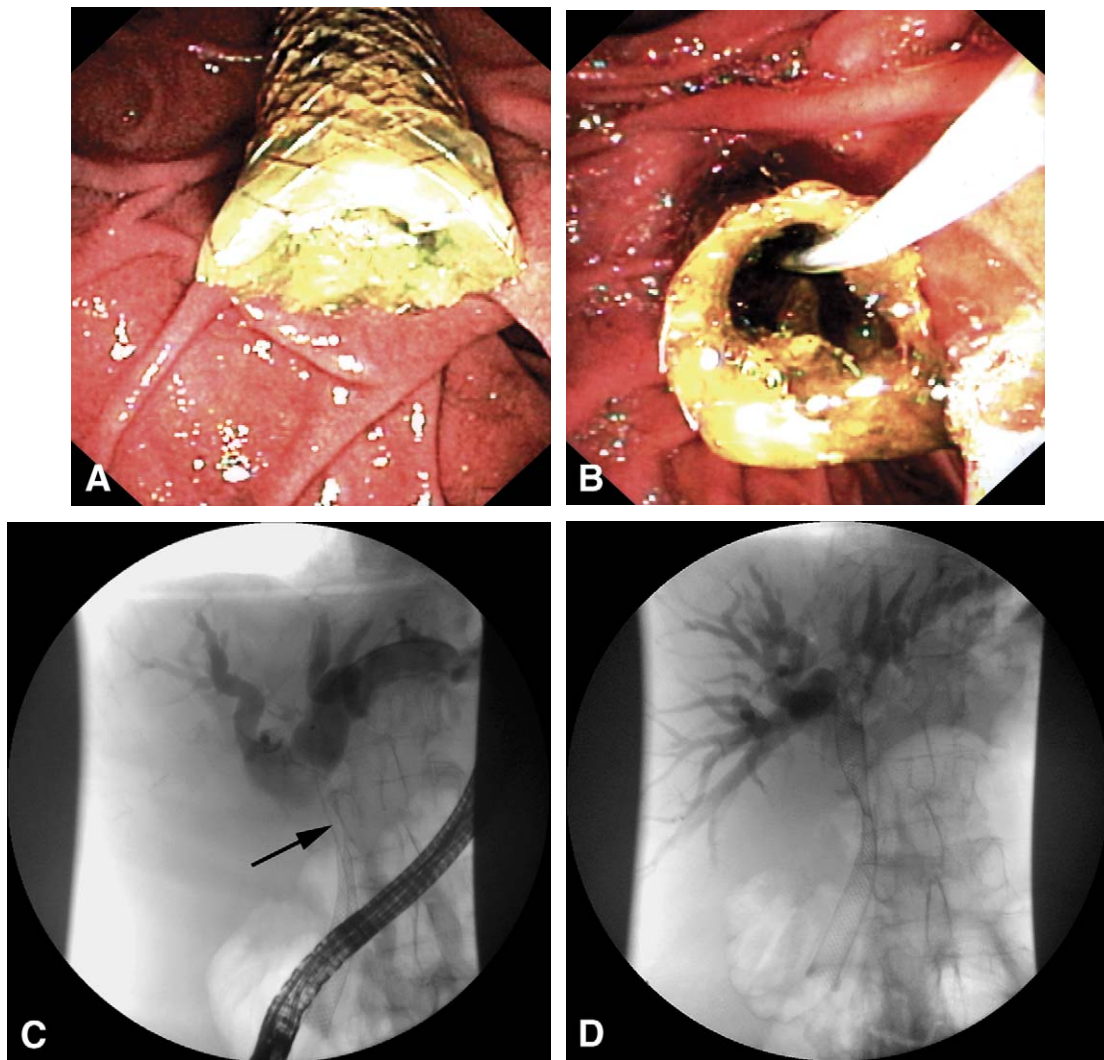
Figure 4. A, Completely occluded metal stent. **B**, The stent is cannulated. **C**, Tumor overgrowth (arrow) and distal dislocation caused the occlusion. **D**, The problem was solved by inserting a second metal stent that overlapped the first one and placing it in a more proximal position.

The causes of occlusion in plastic and metal stents differ. Tumor ingrowth through the metal mesh in uncovered SEMS and bacterial colonization, biofilm, and sludge deposition in PE stents (Fig. 3) are the main causes.[4,6-9,13,14,19,20] In patients with covered SEMS, we and others[19] have found that occlusion is due to overgrowth by the tumor, sometimes associated with partial stent dislocation (Fig. 4). The latter seems to be facilitated by the strong expansile force of the steel SEMS and a slippery action of the covering, both at deployment and follow-up. This force can be an advantage in accelerating drainage with a large bore, but the whole stent migrated upwards, proximal to the stricture, in 2 of our patients when deployed over the stenosis, so a second stent had to be inserted. Therefore, it is important to choose a correct stent length and to place the stent carefully in the middle of the stricture, to avoid a migrating force in either direction when the stent expands or is subjected to

greater pressure by the tumor as it becomes larger. Placement of a second Wallstent (Fig. 4) or a plastic stent in an occluded metal stent has been shown to be effective.[21] We usually preferred a plastic stent because of short life expectancy after metal stent failure (Table 5). Occlusion in the PE stent group occurred earlier, and we replaced these stents with a metal stent at failure (Fig. 3). An unexpected advantage of the covered SEMS is the ease with which it can be removed, using a plastic stent extraction forceps when needed, eg, if a stricture later proves to be benign (3 patients), as in 1 of our patients in the SEMS group.

The social and health care system in Sweden facilitates close follow-up (including the detection of stent failure) because the patients have to rely on general practitioners (GPs), home care, and hospices near their homes (ie, in the catchment area of our hospital). Those with stent-related problems, which were explained in detail to the patients and their caretakers, contacted our

hospital (not another, which might not be able to provide ERC), or their GPs called us for advice (private care or similar types of care are very unusual in our setting). In Sweden, GPs, physicians in hospices, and nurses in home care must keep detailed patient records, which are easily accessible to us. We doubt that a similarly close follow-up of every stent patient can be done in a tertiary university center because many of the patients reside far away. Although formal blinding was not a practical option, the GPs and physicians in home care and the hospices did not know which type of stent the patients had received. Our type of center and setting could also be a study disadvantage, because it could be difficult or impossible to extrapolate the findings (particularly the costs) to other institutions.

In both groups, a thin (8.5F) plastic stent was inserted in one third of the patients for a median of 8 days before the randomization (Table 2). This approach can be disputed, but ERC usually was done at the beginning of our investigation/treatment of jaundiced patients. Our aim was to drain patients with biliary obstruction as soon as possible. Although we could not alter this routine in all patients, we wished to include every patient who fulfilled the criteria in Table 1. Therefore, we temporarily inserted thin plastic stents so as to perform various investigations (eg, CT) and to decide whether radical resection would be possible. Because most endoscopists would agree that contrast should not be injected into obstructed bile ducts without decompression, plastic stent placement for a short period enabled us to avoid this problem.

Tissue diagnosis usually is not made before the radical pancreatic resection for suspected cancer of the pancreas. Of the resected patients, 5% to 10% eventually prove to have benign disease (usually pancreatitis), despite every presurgical effort to ensure that the condition was malignant. We were in a similar situation. For practical and ethical reasons, we could not obtain a biopsy specimen from every patient, and a 3% frequency of benign conditions is acceptable in such cases. Two patients were reevaluated and underwent radical resection after randomization; they were censored when the stent was removed (ie, on the day of surgery). Four more patients (2 in each group) did not fulfill the criteria because they had a serum bilirubin levels lower than the required 50 μmol/L on inclusion. All of these patients were included in the follow-up, and calculations were made on an intention-to-treat basis, but a formal per-protocol analysis that considered only patients without protocol violations yielded similar results (Table 3).

Covered SEMS are thought to cause cholecystitis and even pancreatitis[17,18] by obstructing the cystic and/or pancreatic ducts, although the pathological findings produced by occlusion of the bile ducts by C-SEMS were not seen in an animal study.[22] As in one series of 80 patients with covered SEMS,[14] none of our patients developed pancreatitis during the follow-up; those authors ascribed this to the protective effect of sphincterotomy, which was performed in the present study as well. More data are needed to determine whether cholecystitis after C-SEMS insertion is due to tumor overgrowth, as reported by Isayama et al,[17] or to stasis induced by the plastic covering. None of our patients had cholecystitis, and the frequency also has been low (ie, about 3.5%) in other series with C-SEMS.[14,16]

The median survival was a mere 4.5 months, no different than the 3.6 to 5.0 months found in similar studies[6,8,9,13] and the same as in 2 studies of advanced pancreatic carcinoma.[10] However, the survival was even lower, 2.5 months (SEMS group, 2.8 months; PE group, 1.9 months) in the patients with hepatic and/or pulmonary metastases.[9] Interestingly, there was a borderline significance for a longer survival time in the SEMS group in the per-protocol analysis (Table 3). A similar tendency has not been described by others. With the median survival in the PE group only 3.9 months in our study, most of these patients probably would have died with a patent SEMS (if all patients had received SEMS). In the view of Prat et al,[8,11] the cut-off point should be a survival time of at least 3 months for the more-expensive metal stent to be cost-effective in comparison with a plastic stent. They also regarded a tumor diameter >3 cm as a negative factor in the prediction of survival. Our calculations and those of others show that the total cost of stent insertion varies and is mainly affected by local (national) logistics rather than the cost of the stent itself (eg, the number of days in hospital and different reimbursement systems).[4,23,24] In our setting, the total cost of metal or plastic stents was about the same, irrespective of a long- or short-survival time.

The plastic stent group had significantly more stent failures and shorter stent patency. However, the length of survival in PE patients with distant metastases and the patency time in the plastic stent group were very similar (1.9 and 1.8 months, respectively). Therefore, we recommend plastic stents for such patients. The more expensive SEMS should be reserved for patients who do not have distant metastases.

DISCLOSURE

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