A prospective randomised trial comparing plastic and uncovered self-expanding metal stents for palliation of symptomatic jaundice in patients with malignant distal biliary obstruction

by

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DECLARATION

I, Marc Michael Bernon hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

Objectives

The aim of this study was to determine the safety and clinical effectiveness of 10Fr plastic biliary stents compared to uncovered self-expanding metal stents (SEMS) for palliative treatment of patients with inoperable malignant distal biliary obstruction in a public hospital in South Africa.

Methods

From January 2009 to December 2013, 40 patients who were admitted to a tertiary academic centre because of distal malignant biliary obstruction were enrolled in a prospective randomised study. Patients were randomly assigned to receive either an uncovered SEMS or a plastic stent deployed through the biliary stricture during endoscopic retrograde cholangiopancreatography.

Results

Patient survival time in the two groups did not differ significantly (median: SEMS - 114 days; plastic - 107 days) ($p=0.181$). Stent failure was more common in the plastic stent group (7/19 vs. 1/20) ($p=0.043$). The results became significant after 6 months of follow up. There was no significant difference between the two groups in the incidence of serious adverse events.

Conclusions

SEMS had a longer duration of patency than plastic stents, which favours their use in the palliative treatment of patients with biliary obstruction due to distal malignant biliary obstruction.

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Abbreviations

ERCP	Endoscopic retrograde cholangio-pancreatography
SEMS	Self-expanding metal stent
Fr	French
PTFE	Polytetrafluroethylene (Polyethylene)
HREC	University of Cape Town Human Research Ethics Committee
ECOG	Eastern Cooperative Oncology Group
US	Ultra-sound
CT	Computed tomography
MRI	Magnetic resonance imaging
MDT	Multi-disciplinary team

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Chapter 1: Introduction

1.1 Context and Literature

1) Introduction

Tumours causing malignant distal biliary obstruction may originate in the head of the pancreas, ampulla or distal common bile duct. Head of pancreas ductal adenocarcinoma accounts for about two-thirds of periampullary cancers followed by ampullary cancer (about 20%) and distal cholangiocarcinoma (about 15%)[1].

Despite improvements in surgical technique, critical care, radiotherapy and chemotherapy the survival of patients with periampullary cancer remains poor and has not improved significantly over the last 30 years. The overall 5-year survival of pancreatic ductal adenocarcinoma is still only about 5%[1]. Although there have been recent advances in the molecular subtyping of pancreatic cancer, which have helped in the understanding of the complex biology of the tumour, these developments have not yet translated into new treatments[2-5].

Tumours causing distal malignant biliary obstruction are often asymptomatic in the early stages and 80% of patients are not candidates for surgical resection and require palliative treatment. The most common symptoms that require palliation are obstructive jaundice, gastric outlet obstruction and pain. Seventy to ninety percent of patients with periampullary cancers have obstructive jaundice at presentation. Before the 1980s the only means for effective palliation of obstructive jaundice was a surgical

bypass. In some series as many as 57% of patients with unresectable pancreatic cancer underwent a surgical bypass. Operative palliation has since been replaced with biliary stenting, either via percutaneous access or via endoscopic retrograde cholangio-pancreatography (ERCP). There are advantages and disadvantages to each of these three techniques and these need to be taken into account when deciding on the best option for each patient[6-8].

2) Historical perspective

The first endoscopic biliary stent insertion, using a modified 7Fr angiographic pigtail catheter, was performed in 1979[9]. Initial duodenoscopes had relatively small instrumentation channels which limited the passage of larger stents. There was a high incidence of cholangitis due to stent occlusion that was attributed to the small calibre of the prostheses that were being used[9,10].

Huibregtse and colleagues were the first to insert a larger stent in Amsterdam in 1981[11]. It was placed with a forward viewing gastroscope and was a straight 10FR polyethylene stent with flaps on either end. This type of stent is often referred to as the Cotton-Huibregtse or Amsterdam type stent. The first duodenoscopes with larger (3.7mm) instrumentation channels, capable of passing 10Fr stents were developed in 1981. This simplified the process of placing 10Fr stents and in 1982 the Amsterdam group published a series of 45 patients with obstructive jaundice that were treated with 10Fr polyethylene stents. Jaundice improved in 43 patients. Eleven patients developed cholangitis. These results were significantly better than with the 7Fr stents.

Endoscopic stenting became a well established palliative treatment modality in the mid 1980s, as the technical success rates of endoscopic stenting for distal biliary strictures improved[11-13].

The first report of a expandable metal mesh tube, the prelude to modern self expanding metal stents (SEMS), dates back to the early 1970s with the so called Didcott dilator which was used to treat oesphageal strictures. Colin Didcott was a South African trained surgeon and developed the stents while working in South Africa, Rhodesia and the United Kingdom[14-16]. The first reports of SEMS being used for treatment of biliary strictures were published in 1989[16,17]. The initial SEMS were uncovered and constructed from stainless steel with a diameter of 8-10mm (when deployed) [17,18].

Nitinol is a nickel-titanium alloy that has properties of shape memory, superelasticity and force hysteresis. The properties of Nitinol were discovered in 1959 at the Naval Ordnance Laboratory in Maryland, USA. These properties are useful when designing and constructing SEMS and the majority of commercially available SEMS are constructed from nitinol[19-21]. Covered and partially covered SEMS were developed in the 1990s in an attempt to prolong stent patency by reducing tumour ingrowth. Covered stents do not embed in the bile duct to the same extent as uncovered stents making them easier to remove but also more likely to migrate than uncovered SEMS[22].

Apart from feasibility and safety studies, trials of biliary stents can be divided into four main groups, which are grouped as follows:

a) Trials comparing the efficacy of different types of plastic stents

b) Trials comparing biliary stents to surgical bypass

c) Trials comparing plastic stents to SEMS

d) Trials comparing different types of SEMS

3) Plastic stents

Trials comparing different stent materials and calibres are summarized in Table 1. Different materials, size and shapes have been used in an attempt to develop the optimal plastic stent. The ideal stent should be technically easy to insert, should not occlude and should not injure the bile duct or duodenum[23]. Stent calibres from 7Fr to 12Fr have been tested. As the stent calibre increases above 10Fr the technical difficulty of stent insertion increases. Increasing stent calibre above 10Fr does not improve stent patency. Hence, a diameter of 10Fr is thought to be the best combination of patency and ease of stent insertion[13,24-26].

Polyethylene, polyurethane and polytetrafluoroethylene (Teflon) have been used for plastic stents. The characteristics of the different materials are tabulated in Table 2[27]. Teflon has a lower coefficient of friction than polyethylene and polyurethane. In vitro studies showed a direct correlation between the coefficient of friction and stent clogging. Teflon has the lowest coefficient of all polymers but this benefit has not been demonstrated in clinical practice. A meta-analysis suggested better patency of polyethylene stents in distal malignant biliary obstruction compared to Teflon stents although the differences were not statistically significant[27-30]. Polyurethane stents have

not been shown to have better patency than Teflon or polyethylene stents and tend to become brittle over time and frequently fragment during attempted removal[31,32].

Various stent designs have been attempted to decrease stent blockage. Flanged stents which have a single flap and a side hole proximally and distally (Cotton-Huibregste or Amsterdam type stent) are most commonly used. These stents may be straight, angled or curved. The addition of side holes along the entire length of the stent has been shown to increase the incidence of stent occlusion which is thought to be due to slower bile transit though the stent[23]. The Tannenbaum stent with two proximal and two distal flaps (with or without side holes) was developed in 1994[33]. Initial superior results, comparing the stent to conventional plastic stents, in prospective non-randomised trials were encouraging but could not be confirmed in subsequent randomised control trials. Three studies showed a higher risk of therapeutic failure with 10Fr Tannenbaum Teflon stents compared to conventional polyethylene stents[34-36].

The addition of an anti-reflux valve at the end of the stent preventing reflux of material from the duodenum into the stent has not been shown to improve patency rates. The use of a star shaped stent with a limited central lumen has also been attempted but was not shown to be beneficial[37,38]. Various other modifications have been tried in attempts to decrease biofilm creation to prolong stent patency. These include specialized coatings and double layer design. To date no studies on these modified stents have shown increases in stent patency[23].

Table 1. Trials comparing various types of plastic stents[13,24,26,28,31,32,36,39]

Study	Study type	Comparison	Patients	Result
Speer (1988)	Retrospective analysis	8Fr polyethylene pigtail stents vs. straight 10Fr polyethylene stents	65	Significantly lower incidence of cholangitis with 10Fr vs. 8Fr stents (5% vs. 34%)
Kadakia (1992)	Retrospective analysis	10Fr vs. 11Fr polyethylene stents (Amsterdam type)	63	No significant difference in stent patency
Pereira-Lima (1996)	Retrospective analysis	10Fr vs. 11.5Fr polyethylene stents (Amsterdam type)	87	No significant difference in stent patency
Van Berkel (1998)	Prospective randomised	10Fr polyethylene vs. 10Fr Teflon stents (Amsterdam type)	84	No significant difference in stent patency
Benz (1998)	Prospective randomised trial	10Fr Teflon (Tannenbaum) vs. hydrophilic-coated polyurethane stents	48	No significant difference in stent patency
Terruzzi 2000)	Prospective randomised	10Fr Teflon Tannenbaum vs. 10Fr polyethylene stents (Amsterdam type)	57	No significant difference in stent patency
Costamagna (2000)	Prospective randomised	10Fr hydromer coated polyurethane stents vs. 10Fr polyethylene stents (Amsterdam type)	83	No significant difference in stent patency
Landoni (2000)	Prospective randomised	10Fr polyurethane vs. 10Fr polyethylene stents (Amsterdam type)	38	No significant difference in stent patency

Table 2. Characteristics of commonly used materials for plastic stents[27]

	Polyethylene	**Polyurethane**	**Polytetrafluroethylene**
Coefficient of friction	0.75	0.60	0.15
Inner surface (electron microscopy)	Surface projections, not entirely smooth	Smooth	Irregular with pits and ridges
Other	Soft	Becomes brittle with time	Stiff, higher incidence of perforation in some studies

4) Surgery compared to stenting

Various surgical procedures can be used for biliary drainage. Historically external drainage with a T-tube was used. This was associated with fluid and electrolyte losses and the associated complications thereof. Internal drainage is thus preferred with cholecystojejunostomy, hepaticojejunostomy, choledochojejunostomy or choledochoduodenostomy[40]. Cholecystojejunostomy is a relatively simple procedure but has been shown to have a higher rate of recurrent jaundice and cholangitis compared to a hepaticojejunostomy. Choledochoduodenotomy results in a higher rate of recurrent jaundice compared to a hepaticojejunostomy, due to tumour infiltration into the duodenum and distal common bile duct[40-42].

Five randomised controlled trials have compared percutaneous or endoscopic stenting to surgical drainage (see Table 3) [43-47].

Table 3. Prospective randomised controlled studies comparing bypass surgery to stenting[43-47]

	Bornman (1986)		Shepherd (1988)		Anderson (1989)		Smith (1994)		Nieveen (2003)	
	Stent n=25	**Bypass n=25**	**Stent n=23**	**Bypass n=25**	**Stent n=25**	**Bypass n=25**	**Stent n=100**	**Bypass n=101**	**Stent n=14**	**Bypass n=13**
Type of stent/ bypass	Percutaneous Plastic		10Fr Plastic*		7 or 10Fr Plastic*		10 Fr Teflon		SEMS**	
Success (%)	84	76	80	92	96	88	95	93	100	100
Peri-procedural Mortality (%)	8	20	9	20	20	24	15	8	0	0
Peri-procedural Morbidity (%)	28	32	30	56	36	20	29	58	7	8
Recurrent jaundice (%)	38	16	30	0	0	0	36	2	Not published	
Survival (weeks)	19	15	22	18	12	14	21	26	17	17
Gastric outlet obstruction (%)	14	0	9	4	0	0	19	11		

* Polyethylene ** Uncovered 10mm nitinol SEMS

The Bornman study compared percutaneous transhepatic biliary stenting to surgical drainage whereas the other four studies compared endoscopic stent insertion to surgical bypass. Deficiencies in the studies included small numbers of patients, poorly defined outcomes and inadequate blinding[43]. Furthermore, there was no consistency in the definition of serious complications. The only study to evaluate quality of life was by Smith et. al. which also included the largest number of patients[48]. It has been suggested that the stent arm results in these studies would have been better if SEMS had been used[49]. However the Nieveen study, the only study to use SEMS, included only a small number of patients and the incidence of recurrent jaundice was not mentioned. Forty three percent of the stented patients in this study developed a complication during follow up compared to 32% of the patients who underwent a surgical bypass procedure.

Despite the limitations mentioned above some conclusions can be drawn from these studies. Surgical treatment is associated with a higher early morbidity, a higher 30-day mortality, and a longer initial hospital stay compared to endoscopic stent insertion. Although there is an initially lower morbidity and mortality in endoscopically treated patients they have a higher incidence of recurrent jaundice, are more likely to require re-interventions and have more readmissions. There was no significant difference in the overall survival between the two groups.

5. Plastic vs. Self-Expanding Metal Stent

Seven prospective trials have been published comparing plastic stents and SEMS (Table 4)[50-56]. Technical success and complication rates related to stent insertion were similar.

Plastic stents had a higher occlusion rate and shorter patency duration compared to SEMS. There was no significant difference in survival in any of the trials. As patients with plastic stents are more likely to develop recurrent jaundice they were more likely to require additional interventions, accounting for the longer hospital stay and the higher number of ERCPs in the plastic stent groups. Plastic stents have some advantages over SEMS. Should the need arise they can be easily removed, which is useful in situations where the diagnosis of malignancy has not been established. In addition plastic stents are cheaper than SEMS. A cost analysis was performed in most of the above trials. The methodology of calculating the costs is not described in detail in any of the trials and in some of the trials there is only an estimation of cost.

The additional cost of SEMS is offset by the expense of additional hospital admissions and procedures related to stent dysfunction, which is more likely with a plastic stent[57]. The cost benefit of plastic stents decreases with increased survival, as patients who survive longer are more likely to develop stent dysfunction. Yeoh et. al. performed a comparative cost analysis of metal and plastic biliary stents for malignant obstructive jaundice[57]. The cost of a particular stent strategy depends on the cost of the respective stents relative to the procedural costs of an ERCP and patient survival. In the United States healthcare environment a plastic stent strategy was less costly for patients who survived less than 4 months. The presence of metastatic disease and poor performance status are the most accurate predictors of poor survival. It is suggested that these two indicators should be used to identify patients with limited life expectancy in whom a plastic stent would be sufficient[57,58].

Table 4. Prospective randomised studies comparing plastic stents and SEMS[50-56]

	Stents	Technical success	Procedure related complications	Recurrent jaundice	First stent patency (Median duration days)	Median number of ERCPs	Median days in hospital	Median survival (days)
Carr-Locke 1993	PTFE 10Fr or 11.5Fr N=78	Data not available - only published in abstract form	NA	13%	**62**	NA	NA	NA
	Uncovered SEMS N=86			13%	**111**			
Davids 1992	PTFE 10Fr N= 56	Successful in 99%. One failed deployment in the SEMS group	11%	**54%**	**126**	**1.8**	7.4	147
	Uncovered SEMS N=49		12%	**33%**	**273**	**1.3**	10.6	175
Prat 1998	PTFE 11.5Fr N=33	Successful in 97.1%	All patient: Mortality 3.9%; Morbidity 11.9%	**72.7%**	96	1.7	7.4	144
	PTFE11.5Fr changed 3 monthly N=34			58.8%	NA	**2.5**	10.6	168
	Uncovered SEMS N=34			**17.5%**	144	1.2	5.5	135

NA not applicable; statistically significant results in bold type

Table 4. Prospective randomised studies comparing plastic stents and SEMS (cont.) [50-56]

	Stents	Technical success	Procedure related complications	Recurrent jaundice	First stent patency (Median duration - days)	Median number of ERCPs (days)	Median days in hospital	Median survival (days)
Rosch 1997	PTFE 10Fr (with and without side holes)	Data not available- only published in abstract form	NA	**25% no side holes; 40% with side holes**	NA	NA	NA	
	Uncovered SEMS			**8%**				
Kassis 2003	Tannenbaum 10Fr N= 59	Successful in 97.5%	1.7%	**37.3%**	NA	NA	246	99
	Uncovered SEMS N=59		6.8%	**18.7%**	NA	NA	80	153
Kastinelos 2006	Tannenbaum 10Fr N= 24	Successful in all patients	**16.7%**	**66.7%**	**123.5**	2.5	NA	207
	Uncovered SEMS N=23		**0%**	**30%**	**255**	1.7	NA	272
Soderlund 2006	PTFE 10Fr N=51	100%. 2 (2%) patients required initial PTC and rendezvous procedure	0%	**43.1%**	**108**	NA	NA	117
	Partially covered SEMS N=49		4.1%	**18.4%**	**54**	NA	NA	159

NA not applicable; statistically significant results in bold type

6. Different Types of Metal Stents

There are three main types of SEMS, namely uncovered, partially covered and fully covered. Covered stents were developed to prevent tumour ingrowth, which is a common cause for obstruction of uncovered stents. The first covered stents were developed in Japan in 1994. Various materials have been evaluated for the covering membrane including polyurethane, Gore-Tex and silicone[59].

The advantages and disadvantages of the various stents are tabulated in Table 5. Covered and partially covered SEMS may occlude the pancreatic and cystic ducts causing pancreatitis or cholecystitis. In addition covered stents are more prone to migration.

Table 5. Characteristics with potential advantages/disadvantages of uncovered and covered SEMS[60]

Type of SEMS	Advantages	Disadvantages
Uncovered	Low probability of migration Less shortening than covered stents making deployment easier	Obstruction by tumour ingrowth Removal difficult
Partially Covered	No tumour ingrowth Removal - possible	Migration Pancreatitis/Cholecystitis Tumour overgrowth more likely than with a fully covered stent
Fully Covered	No tumour ingrowth Removal - high possibility	Migration Pancreatitis/cholecystitis

There have been a number of prospective randomised trials and three meta-analyses

comparing uncovered and covered SEMS (Table 6) [61-66]. Only trials in which stents were inserted endoscopically and full-text articles were included. Analysis of these trials shows a number of pitfalls. There was no uniformity in the inclusion and exclusion criteria. There was inconsistency in the inclusion of patients with metastatic disease and poor performance status. Furthermore, definitions used and details of the causes of stent dysfunction varied between the trials. A variety of different stents were used and the stents used in the Isayama trial are not commercially available[61].

The results of the randomised controlled trials are conflicting and inconclusive. The Isayama and Kitano studies showed a significantly lower incidence of stent-related complications in the covered SEMS group compared to the uncovered group[61,65]. This was in contrast to two studies (Telford et. al. and Lee et. al.), which showed a higher incidence of stent-related complications in the covered SEMS group[63,66]. The migration rate of covered SEMS in the Telford study was particularly high (11.8%). In all studies except the Isayama study stent blockage due to particle occlusion was higher in the covered SEMS group. In two studies (Kullman et. al. and Ung et. al.) there were no significant differences in the overall incidence of stent-related complications. However, there was a significantly higher incidence of tumour ingrowth in the uncovered SEMS group in the Kullman study[62,64].

The findings of the meta-analyses are also conflicting. The Almadi meta-analysis showed no difference in stent patency at 6 and 12 months[67]. There were no differences in the rates of pancreatitis, cholecystitis, perforation, bleeding, cholangitis or recurrent biliary obstruction. The Saleem meta-analysis demonstrated that covered SEMS provided a significantly longer mean stent patency of 61 days[68]. The mechanism

of recurrent jaundice in the two groups differed with uncovered SEMS more likely to block from tumour ingrowth and covered SEMS more likely to migrate or block with debris. The latest meta-analysis by Moole et. al. included 13 studies[69]. There was no significant difference in overall adverse event rate or survival. Covered SEMS had significantly lower occlusion rates, an increased incidence of migration and increased odds for pancreatitis.1

The three meta-analyses[67-69]included studies that were excluded from the above analysis. The Saleem meta-analysis included two studies using percutaneous stent insertion. Apart from these studies, the Almadi meta-analysis included four studies that were only published in abstract form. Neither of these meta-analyses included the Ung or Lee studies, as these had not been published at the time of the meta-analysis[64,66]. The Moole meta-analysis included the Ung and Lee studies as well as a randomised control trial (Krokidis et. al.) using percutaneously placed SEMS and a number of non-randomised and retrospective studies[64,66,70]. All three meta-analyses are limited by a small number of analysed studies and lack of uniform end-points. Almadi et. al. point out the need for standardised selection criteria, technical approaches and outcomes/endpoints.

In conclusion, an analysis of the results above suggests that uncovered SEMS are less likely to migrate than covered SEMS. Covered SEMS are less likely to occlude due to tumour ingrowth but are more likely to block due to proximal tumour overgrowth and debris. There is insufficient evidence to conclude that covered SEMS are superior to uncovered SEMS.

Table 6. Prospective randomised trials comparing uncovered and covered SEMS [61-66]

Trial	Type of Stent	Median Survival/ Median stent patency (days)	Stent related complication	Blocked stent	Other complication	Mean number of reinterventions **
Isayama (2004)	Uncovered wallstent N= 55	237/193	23 (42%)*	21 (38%)* Ingrowth 16* Overgrowth 2 Debris 2 Other 1	Migration 1(1.8%) Cholecystitis 0 Pancreatitis 1(1,8%)	0.72*
	Partially covered (with polyurethane) wallstent N=57	255/225	16 (28%)*	8 (14%)* Ingrowth 0* Overgrowth 4 Debris 2 Other2	Migration 1(1.8%) Cholecystitiis 2(3.5%) Pancreatitis 5(8.8%)	0.32*
Kullman (2010)	Uncovered nitinol wallstent N=191	174/not clear	47(24.6%)	45 (23.5%) Ingrowth 21* Overgrowth 10 Debris 4 Unknown 10	Migration 0* Cholecystitis 2(1.1%) Pancreatitis 4(2.0%)	0.19
	Fully covered (with polycarbonate-polyuretahne) wallstent N=188	116/not clear	52(27.7%)	41(21.8%) Ingrowth 9* Overgrowth 18 Debris 12 Other 2	Migration 6(3%)* Cholecystitis 2(1.1%) Pancreatitis 3(1.5%)	0.24

* stastically significant

** Mean number of reinterventions per patient

Table 6. Prospective randomised trials comparing uncovered and covered self-expanding metal stents (continued) [61-66]

Trial	Type of Stent	Median Survival/ Median stent patency (days)	Stent related complication	Blocked stent	Other complication	Mean number of reinterventions
Telford (2010)	Uncovered wallstent N= 61	239/711	15 (24.6%)*	11 (18%) Ingrowth 8 Overgrowth 0 Debris 1 Other 2	Migration 0* Cholecystitis 3(4.9%) Pancreatitis 1(1,6%)	Not clear
	Partially covered (with permalume) wallstent N=68	227/357	26 (38.2%)*	15 (22.1%) Ingrowth 6 Overgrowth 3 Debris 4 Other2	Migration 8(11.8%)* Cholecystitiis 3(4.4%) Pancreatitis 0	Not clear
Ung (2013)	Uncovered nitinol Hanorostent N=34	157/127		17%	Migration – Not clear Cholecystitis 0 Pancreatitis 0	Not clear
	Fully covered (with silicone) nitinol Hanorostent N=34	154/153		13%	Migration –Not clear Cholecystitis 0 Pancreatitis 1(2.9%)	Not clear

* stastically significant

Table 6. Prospective randomised trials comparing uncovered and covered self-expanding metal stents (continued) [61-66]

Trial	Type of Stent	Median Survival/ Median stent patency (days)	Stent related complication	Blocked stent	Other complication	Mean number of reinterventions
Kitano (2013)	Uncovered nitinol SEMS N=60	222/167*	22(36.7%)	23 (38.3%) Ingrowth 15* Overgrowth 2 Debris 6	Migration 0 Cholecystitis 2 Pancreatitis 0	Not Clear
	Silicone covered nitinol SEMS (with an antimigration system) N=60	285/219*	14(23.3%)	14(23.3%) Ingrowth 0* Overgrowth 3 Debris 11	Migration 0 Cholecystitis 1 Pancreatitis 1	Not Clear
Lee (2014)	Uncovered nitinol SEMS N= 20	359/413	4(20%)*	4(20%)* Ingrowth 2 Overgrowth 1 Debris 1	Migration 0 Cholecystitis 0 Pancreatitis 0	Not clear
	Partially covered (with PTFE) SEMS N=20	350/207	10(50.0%)	8 (40%)* Ingrowth 0 Overgrowth 4 Debris 4	Migration 2 (10%) Cholecystitiis 1 (5%) Pancreatitis 0	Not clear

* stastically significant

7. New Developments and Strategies

Drug-eluting Stents

Drug-eluting stents in which the chemotherapeutic agent is incorporated into the covering membrane may improve stent patency by local delivery of chemotherapeutic agents, theoretically preventing or delaying tumour ingrowth or overgrowth. Paclitaxel is the most frequently used stent-eluting chemotherapeutic agent. Gemcitabine and 5-fluorouracil, the most commonly used systemic chemotherapeutic agents in patients with malignant biliary obstruction, are hydrophilic, resulting in initial rapid drug release but little sustained elution when incorporated into a membrane[71]. Current evidence suggests that drug-eluting SEMS are safe but there is no strong evidence that they are more effective than standard SEMS. The majority of the studies have been conducted in animals. There is only one study in humans comparing drug-eluting stents to conventional stents (Table 7) [72-77].

Bioabsorbable stents

Self-expanding bioabsorbable stents have been studied in both malignant and benign disease. The main potential advantage of these stents is avoiding an additional endoscopic procedure to remove the stent, an unlikely event in malignant biliary obstruction. These stents are therefore more likely to be of benefit in the treatment of patients with benign strictures and bile leaks. Materials used to construct these stents include polylactide and polydioxanone that exert weaker radial force than nitinol SEMS and stent expansion with balloon dilatation is required for optimal deployment. These stents require further development and clinical investigation before routine clinical use[59,78-80].

Table 7. Studies on drug-eluting biliary stents[72-77]

Study	Subjects	Drug	Result
Lee (2005)	2 pigs	Paclitaxel	Drug release and histological changes best with 10% wt/v paclitaxel stent
Suk (2007)	21 humans	Paclitaxel	Mean patency 429 days; mean survival 350 days
Lee (2009)	11 dogs	Paclitaxel	Mucosal hyperplasia in 3/6 dogs with a drug eluting stent but in none of the dogs with standard stents
Chung (2012)	2 pigs	Gemcitabine	Increasing inflammation as the concentration of gemcitabine is increased
Jang (2012)	8 pigs	Paclitaxel	Correlated serum paclitaxel levels in pluronic-containing membranes
Jang (2013)	106 humans	Paclitaxel	Prospective comparative study comparing 60 patients who received drug-eluting stents vs. 46 who received standard covered stents. No difference in complications. No significant difference in stent patency or survival. (Trend towards improved patency in the drug eluting group)

Multiple Plastic Stents

Multiple plastic stents have been used in the management of benign strictures. A number of randomised trials have compared multiple plastic stents to covered SEMS in patients with strictures due to chronic pancreatitis and anastomotic strictures following orthotopic liver transplantation[81-87]. Stricture resolution rates are similar in

patients treated with covered SEMS and multiple plastic stents. In a study on patients with chronic pancreatitis, Siiki et. al. showed a trend towards more durable stricture resolution with covered SEMS[86]. Patients treated with covered SEMS required fewer endoscopic interventions.

There have been no randomised control trials comparing multiple plastic stents to SEMS in patients with malignant biliary obstruction. It has been shown that multiple plastic stents have a longer patency in patients with benign strictures. Lawrence et. al. performed a retrospective review of 20 patients with distal malignant biliary strictures who received double plastic stents[88]. The median stent patency was 221 days approaching the stent patency achieved with SEMS. Multiple plastic stents may be more cost effective than SEMS.

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1.2 Ethics

Ethical approval for the trial was obtained from the University of Cape Town Human Research Ethics Committee (HREC). The HREC reference number is 144/2007. The amended protocol that was submitted to the HREC can be found in Appendix 1 and the approval letter can be found in Appendix 2.

Patients were only included in the study after giving their informed consent. The patient information form and consent form can be found in Appendix 3. There was no additional risk, cost or investigations for patients included in the study and their treatment did not differ substantially from the treatment that they would have received if not included in the study.

Once patients were entered in the trial their demographic data was captured. Patients were followed up monthly until death. The forms used to capture the data can be found in Appendix 4. The completed forms will be destroyed once the study has been published.

1.3 Journal for submission

The manuscript will be submitted to the South African Journal of Surgery. There have been a number of trials comparing metal and plastic stents in distal malignant biliary obstruction. As far as we are aware this is the first prospective randomised trial comparing different types of biliary stents in Africa and we thus felt it would be appropriate to submit the manuscript to a local journal.

The instructions for the authours can be found in Appendix 5.

Chapter 2: Publication Ready Manuscript

1. Introduction

Tumours causing distal malignant biliary obstruction may arise in the head of the pancreas, duodenum, ampulla or distal common bile duct. Pancreatic ductal adenocarcinoma account for about two thirds of these cases, followed by ampullary cancers (about 20%) and distal cholangiocarcinomas (15%). Eighty percent of patients who present with distal malignant biliary obstruction are not candidates for surgical resection and require palliative treatment[1]. Endoscopic biliary stenting has become the preferred method for relieving obstructive jaundice in these patients[2]. There have been significant advances in stent technology since the first plastic endoscopic biliary stent was placed in 1979[3]. A major improvement was the development of self-expanding metal stents (SEMS). Initially SEMS were uncovered but there are now also commercially available fully covered and partially covered SEMS. There have been a number of studies comparing plastic stents to SEMS, but no such studies have been performed in an African institution[4-9]. The studies that have been conducted have consistently shown that plastic stents have a higher occlusion rate and shorter patency compared to SEMS. Plastic stents do have some advantages over SEMS. They are cheaper and are easily removable, as opposed to in particular non-covered SEMS.

2. Aim

The aim of this study was to determine the safety and clinical effectiveness of single 10Fr plastic biliary stents compared to uncovered self-expanding metal stents for the

palliative treatment of patients with inoperable distal malignant biliary obstruction in Groote Schhur Hospital.

3. Patients and Methods

Between January 2009 and December 2013 eligble patients with symptomatic jaundice due to irresectable periampullary cancer were randomised to either a 10Fr plastic stent or an uncovered SEMS. The inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1) Clinical data suggestive of a distal malignant bile duct obstruction. 2) 18 years of age or older 3) Information given and informed consent obtained 4) Bilirubin >50 mol/L (normal 26 mol/L) 5) Typical radiological appearance of malignant common bile duct stenosis at ERCP 6) Proximal margin of malignant bile duct stenosis >2 cm from the hepatic confluence 7) ECOG* performance status 0-2	1) Metastatic disease 2) Resectable patients 3) Previous gastric surgery or duodenal obstruction preventing ERCP 4) Previous inclusion in the study 5) Participation in another clinical trial in the preceding 90 days

*ECOG Eastern Cooperative Oncology Group

Randomisation was on a 1:1 basis, using sequentially numbered opaque envelopes. Patients were randomised once a guidewire had successfully been positioned across the stricture during ERCP. A standard polyethylene plastic stent (BostonScientific, Massachusetts, USA) with proximal and distal flanges or an uncovered SEMS (Wallflex, BostonScientific, Massachusetts, USA) with a 10mm diameter was used. The lengths of the stents were chosen according to the extent of the stricture. Adhering to the CONSORT criteria all patients presenting with periampullary carcinoma were entered in a database. Patients were evaluated with US, CT and/or MRI and reviewed at a MDT meeting to assess resectability.

Demographic and clinical data, post-procedural duration of hospital stay, complications and the need for any additional interventions were documented. Patients were followed up monthly for 12 months or until time of death. At follow-up liver function tests were performed in patients with a clinical suspicion of stent dysfunction. Re-interventions were documented. For patients with stent dysfunction the salvage strategy was left to the treating endoscopist. Any hospital readmissions were recorded, specifying the indication for admission. The primary endpoint in the study was effective palliation of biliary obstruction, defined as a functioning stent at time of death or at 12 months. Secondary endpoints included the ability to safely deploy the stent in a satisfactory position, procedure-related adverse events and the need for re-intervention. Ethical approval for the trial and the registries from which data was extracted was obtained from the University of Cape Town Human Research Ethics Committee (HREC no: 144/2007).

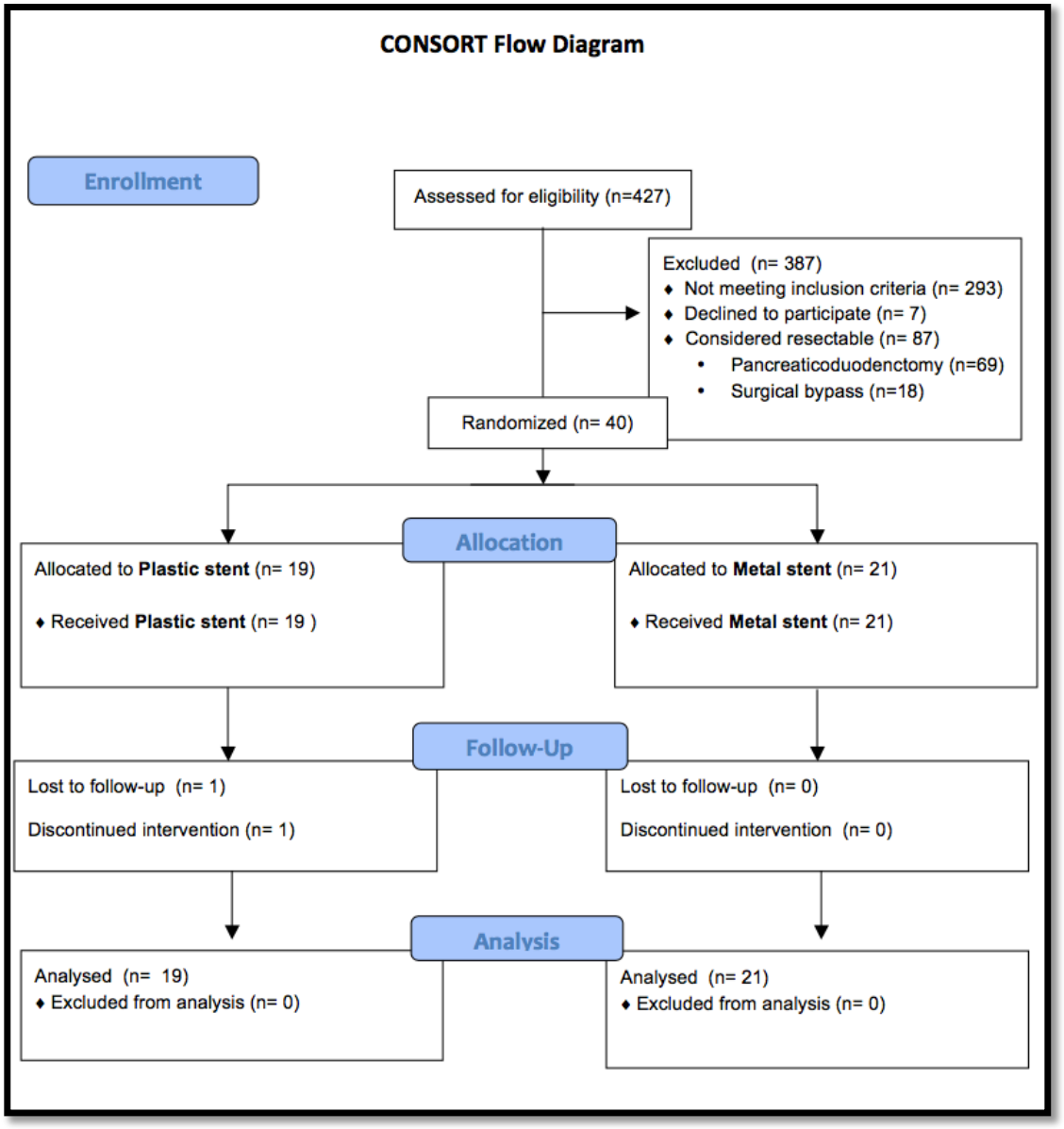
Statistical analysis

Descriptive statistics as appropriate were used to present clinical and treatment characteristics and outcome of the study subjects. The Fisher exact test and student (unpaired) t-test were used to assess differences between the two groups. The Kaplan-Meier method was used to estimate survival time and probabilities for survival and stent patency times. The censored events for stent patency were loss to follow up, death, or patency after 1 year of follow up. Censored events for survival were loss to follow up. Differences in survival and stent patency probabilities were calculated with the log-rank test using Stata (version 13.1; Stata Corp, College Station, Texas, USA). A $p<0.05$ was considered statistically significant where appropriate.

4. Results

A CONSORT flowchart illustrating the inclusion of patients is shown in Figure 1. Forty patients with obstructive jaundice due to periampullary cancer were randomised. The demographic and clinical characteristics of the patients are summarized in Table 2. There were no significant differences between the two groups. The intention to treat cohort included 17 men and 23 women, with a median age of 68 years (range 50-85). Thirty-six patients had pancreatic cancer and 4 had distal cholangiocarcinoma. No patients had ampullary or duodenal carcinoma.

Figure 1. Consort Flow Diagram



Follow-up

Patients were followed up until death or for 12 months. In the plastic stent group one patient was lost to follow up after three months and another withdrew consent. These patients were included in the final intention to treat analysis.

Table 2. Patient demographic and clinical characteristics at inclusion

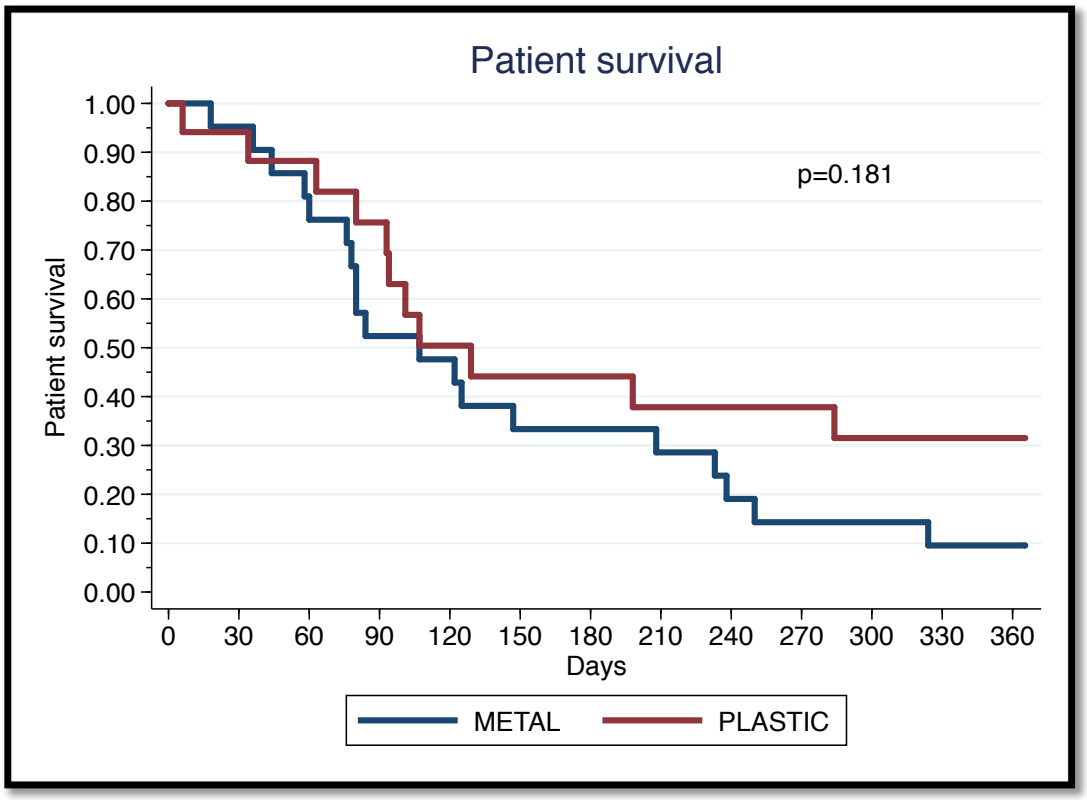
	Plastic Stent	**SEMS**	**p-value**
No of Patients n (%)	19 (47.5%)	21 (52.5%)	
Males/Females	8/11	9/12	p=0.61
Median Age (IQR)*	65 (60-80)	69.5 (59.5-74)	p=0.68
Performance status(ECOG) **0** 1 2 3 4 5	0 4 (21.1%) 15 (78.9%) 0 0 0	1 (4.8%) 5 (23.8%) 15 (71.4%) 0 0 0	p=0.520 p=0.569 p=0.4291
Pancreatic cancer **Cholangiocarcinoma** **Ampullary carcinoma**	17 2 0	18 3 0	p=0.5494
Median tumour size cm (range)	3.0 (1.0-4.9)	3.0 (2.0-6.8)	p=0.55
Median Bilirubin umol/l (range)	338 (71-651)	357 (40-681)	p=0.66
Median Ca-19.9 U/ml (range)	392 (1->1000)	256 (16- >1 000)	p=0.43

Survival

Median survival in the two groups was similar as assessed by the Kaplan-Meier method and the log-rank test (p=0.18) (figure 2). Thirty patients (75%) died during the study

period, 13 in the plastic stent group and 19 in the SEMS group. The median survival in the SEMS group was 114 days compared to 107 days in the plastic stent group.

Figure 2. Kaplan Meier Graph comparing survival in the two groups



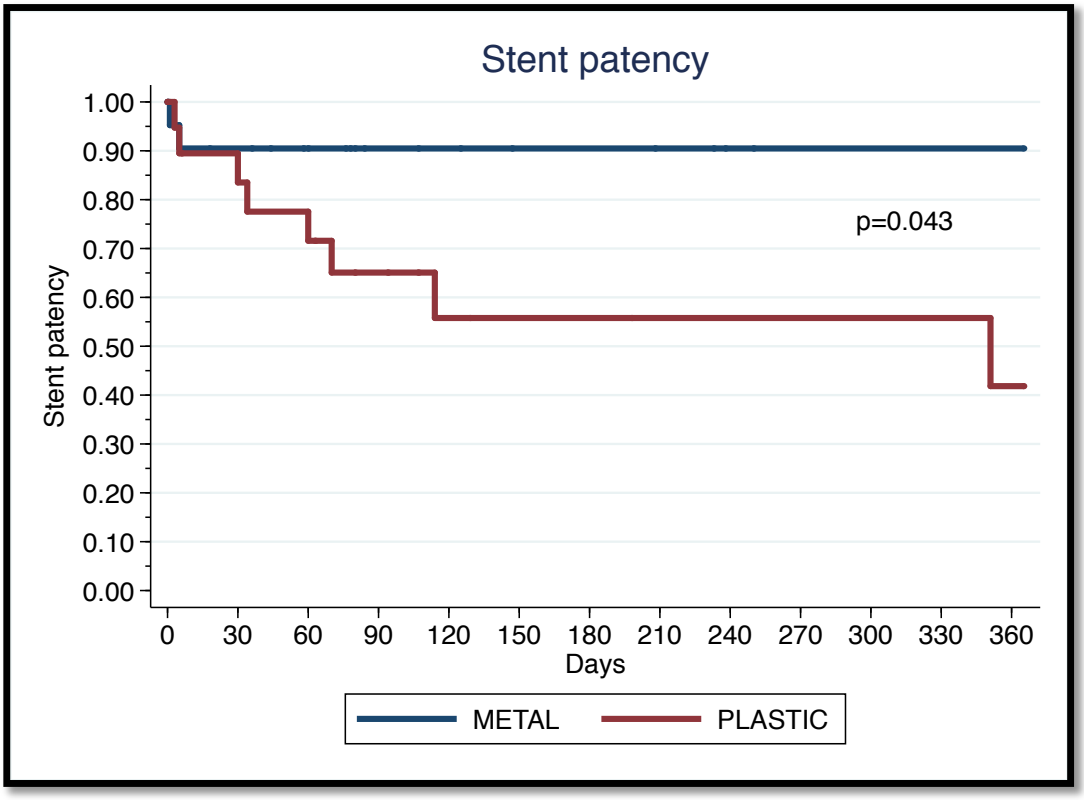
Stent patency

There was a significant difference in stent patency (p=0.043) with one of the SEMS (4.7%) and seven of the plastic stents (38.8%) occluding during the study period. The patient with the blocked SEMS had a stone above the malignant stricture that impacted in the stent 3 days after insertion. The difference in stent patency became significant after six months (Table 3, Figure 3). The plastic stents had 25% failure at 60 days and a 50% failure at 351 days.

Table 3. Survival and stent blockage in both groups

	Plastic	**Metal**	**p value**
Discharge from hospital (blocked/alive)	0/18	1/21	1.0
At 1 month (blocked/alive)	1/15	1/20	0.65
At 3 months (blocked/alive)	2/11	1/11	0.3306
At 6 months (blocked/alive)	5/7	1/7	0.0395
At 9 months (blocked/alive)	5/5	1/3	0.0395
At 12 months (blocked/alive)	6/4	1/2	0.0174

Figure 3. Kaplan Meier Graph comparing stent patency in the two groups



Stent deployment and complications

All patients had successful stent deployment and there were no ERCP related complications. There were no unanticipated adverse device effects, and no deaths were attributed to the investigational device. In two patients (one in each group) jaundice did not subside despite patent stents. The cause of the prolonged cholestasis could not be ascertained. Four of the seven patients with blocked plastic stents presented with cholangitis. One patient in each group developed gastric outlet obstruction. They were both treated with an uncovered duodenal SEMS. One patient in the SEMS group was admitted with a bleeding gastric ulcer. Seven patients in the plastic stent group spent a total of 44 days in hospital with stent related complications compared to one patient in the SEMS group who was hospitalized for 21 days. None of the patients developed cholecystitis or pancreatitis.

5. Discussion

This is the first randomised control trial from an African institution that compares uncovered SEMS with traditional plastic stents for the endoscopic palliation of jaundice in patients with periampullary tumours. The findings in the study were in keeping with previously reported results, comparing uncovered SEMS and plastic stents, showing a lower incidence of stent dysfunction and longer stent patency in the SEMS groups[4-9]. However, the improvement in stent patency comes at a considerable expense, with SEMS being up to 10 times more expensive than plastic stents. These costs are offset by the increased need for re-intervention in patients with plastic stents[10,11]. In this study the difference became significant after six months of follow up. Although the study did not address the cost effectiveness of SEMS it has been shown that SEMS are more cost effective in patients with a longer projected survival.

Follow up of patients in our patient population can be challenging. In spite of this only one patient was lost to follow up. In our healthcare environment, some patients who reside in rural areas have poor access to health facilities. These patients often experience considerable delays in getting appropriate treatment when they develop stent dysfunction. Increased use of SEMS in these patients is particularly useful.

There have been a number of randomised control trials comparing different types of SEMS (covered, partially covered, uncovered) to each other and there has been one randomised control trial comparing covered SEMS and plastic stents. Although the

reason for stent failure differs with the different types of SEMS (ingrowth in uncovered SEMS vs. migration in covered SEMS), patency rates are similar[12-18].

As the intention of the trial was to test the stents in patients with a life expectancy over six months only patients without metastatic disease and a good performance status (ECOG 0-2) were included. The strict inclusion criteria resulted in a long enrollment period and was the main reason for the small number of patients included in the study.

None of the patients in this study had a tissue diagnosis or received palliative chemotherapy. The diagnosis of malignancy was based on the clinical presentation and cross sectional imaging. With improved access to endoscopic ultrasound we now more frequently attempt to get a tissue diagnosis and a greater proportion of patients are receiving palliative chemotherapy.

Multiple plastic stents are frequently used to treat patients with benign strictures and have been shown to have better patency rates than single plastic stents. It has been suggested that that multiple plastic stents may have a stent patency similar to SEMS in malignant strictures[19]. There has never been a randomised trial comparing multiple plastic stents to SEMS. Two or three plastic stents are still considerably cheaper than a SEMS.

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Chapter 3: Appendices

3.1 Appendix 1: Protocol

Title of Project: Distal malignant biliary obstruction: A prospective randomised trial comparing metal and plastic stents in the palliation of symptomatic jaundice at Groote Schuur Hospital.

Principle Investigator: M Bernon

Co-investigators: J Shaw, PC Bornman, JEJ Krige

1. Background and literature

Symptomatic obstructive jaundice remains a distressing symptom in patients who have inoperable malignant distal common bile duct strictures. Endoscopic biliary stenting is a well-established palliative treatment in this context, and surgical bypass is no longer the only therapeutic option available to patients.

Surgical bypass was considered the gold standard and is the most durable method of palliating obstructive jaundice in patients with irresectable distal malignant biliary obstruction. Stent dysfunction results in morbidity, mortality and reduction in the quality of life. Surgery is however associated with increased early morbidity and a longer initial hospital stay. In addition many of these patients are old and frail and not good surgical candidates[1-3].

The majority of patients presenting to our institution with malignant distal common bile duct strictures are not good surgical candidates and endoscopic stent insertion is the treatment modality of choice. Percutaneous stent insertion is considered when endoscopic stent insertion fails or is not possible. The consensus is that this offers good palliation of symptomatic obstructive jaundice with lower morbidity and mortality than surgical bypass, which is particularly relevant in patients with limited life expectancy.

There are several trials demonstrating superior results of stenting compared to surgery with regard to morbidity, mortality and cost effectiveness in the short term[4-9]. Recurrent blockages particularly with plastic stents, however, have been shown to erode this benefit especially in patients who survive for longer than six months[10]. The current area of interest is plastic versus metal stents with regard to patency, cost and quality of life. The best method of selecting patients to receive metal or plastic stents in a resource limited environment remains topical due to the great discrepancy in cost (plastic stents cost approximately R250.00 and metal stents approximately R4500 in State hospitals). The international literature shows that metal stents have lower occlusion rates and are more cost effective than plastic stents if survival is estimated to be longer than 3 months. This saving is as a result of fewer hospital admissions and repeat endoscopic procedures to exchange blocked stents. In the context of the South African State sector one has to factor in the vast distances patients have to travel to access medical care. This results in long periods away from family and social support structures, impacting on quality of life.

There have been no local randomised trials comparing metal and plastic stents. Our current practice has been to place a plastic stent. If life expectancy is estimated to be longer than 3-months, the endoscopist may elect to use a metal stent.

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2. Aims

Hypothesis to be tested

Metal stents are superior to plastic stents in terms of patency, resulting in more cost effective palliation of inoperable distal malignant biliary obstruction and better quality of life due to fewer hospital admissions and less re-interventions.

Primary end point

To assess effective palliation of biliary obstruction, defined as a functioning stent at the time of death or at 12 months.

Secondary endpoints

Ability to safely deploy the stent in a satisfactory position, procedure-related adverse events and the need for re-intervention.

Methods

Study design

Prospective randomised trial to compare uncovered self-expanding metal stent (SEMS) or plastic stent in the palliation of distal malignat biliary obstruction.

Study population

All patients with symptomatic jaundice due to an irresectable distal malignant stricture will be entered in a database and assessed for inclusion into the study. In order to exclude patients with a short life expectancy, patients with metastatic disease or a poor performance status will be excluded (Table 1 - inclusion and exclusion criteria). Patients will be evaluated with US, CT and/or MRI and reviewed at a multi-disciplinary meeting, to assess resectability.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Clinical data suggestive of a distal malignant bile duct obstruction. 2. 18 years of age or older 3. Information given and informed consent obtained 4. Bilirubin >50 mol/L (normal 26 mol/L) 5. Typical radiological appearance of malignant common bile duct stenosis at ERCP 6. Proximal margin of malignant bile duct stenosis >2 cm from the hepatic confluence 7. ECOG* performance status 0-2	1. Metastatic disease 2. Resectable patients 3. Previous gastric surgery or duodenal obstruction preventing ERCP 4. Previous inclusion in the study 5. Participation in another clinical trial in the preceding 90 days

Informed consent

Potential candidates for the study will be given an information sheet and will only considered for inclusion after giving informed consent. The consent must be obtained by the principle investigator or one of the co investigators.

Randomisation

Randomisation will be on a 1:1 basis, using sequentially numbered opaque envelopes, once a guidewire had successfully been positioned across the stricture during ERCP.

Stents

A standard polyethylene (Cotton-Huibrigste) plastic stent (Boston) with proximal and distal flanges or an uncovered SEMS (Boston) with 10mm diameter were used. The lengths of the stents were chosen according to the extent of the stricture.

Follow up

Demographic and clinical data, post-procedural duration of hospital stay, complications and need for any additional interventions will be documented. Patients will be followed up monthly for 12 months or until time of death. At follow up liver function tests will be performed in patients with a clinical suspicion of stent dysfunction. Re-interventions and re-admissions will be documented. For patients with stent dysfunction the salvage strategy will be at the discretion of the treating endoscopist.

Ethical Considerations

Ethical approval will be obtained from the Human Research Ethics Committee of the University of Cape Town. The trial will be performed according to the guidelines described in the Helsinki Declaration for biomedical research involving human subjects. There will be no additional risk, cost or investigations to the patients.

If we are able to demonstrate the expected benefit of foreign experience with metal stents (longer patency and fewer readmissions) our current practice of routine plastic

stent use at Groote Schuur Hospital may change. This may benefit future patients and allow more cost-effective care.

Statistical planning

We plan to commence the study with a sample of 15 patients in each arm. The interim results will allow us to be accurate in determining an appropriate sample size to give a statistically significant result.

Use of Data

We will use a qualified statistician to analyse the data. A manuscript will be submitted to a peer-reviewed journal for publication.

3.2. Appendix 2: Ethics Approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

22 May 2007

REC REF: 144/2007

Dr JM Shaw
Upper GI Surgery
Surgery

Dear Dr Shaw

PROJECT TITLE: DISTAL MALIGNANT BILIARY OBSTRUCTION: A PROSPECTIVE RANDOMISED TRIAL COMPARING METAL AND PLASTIC STENTS IN THE PALLIATION OF SYMPTOMATIC JAUNDICE AT GROOTE SCHUUR HOSPITAL.

Thank you for your letter to the Research Ethics Committee dated 16 May 2007.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Your comments to the queries raised are noted with thanks.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

A/PROF. M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

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HUMAN RESEARCH ETHICS COMMITTEE
-3 NOV 2014
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.10.2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	5/11/14

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22nd October 2014		
HREC REF Number	144/2007	Current Ethics Approval was granted until	
Protocol title	Distal malignant biliary obstruction: A prospective randomized trial comparing metal and plastic stents in the palliation of symptomatic jaundice at Groote Schuur Hospital		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Marc Bernon		
Department / Office Internal Mail Address	General surgery marcbernon@mail.com		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☑ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☑ No
1.3 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☑ No

3.3. Appendix 3: Consent Form

Information Sheet
Distal malignant biliary obstruction: metal versus plastic stent

Main Investigator: Dr J Shaw, HPB/Upper GI Surgery, Groote Schuur Hospital

Your doctor has discussed the fact that you have been diagnosed with a malignant (cancerous) blockage to the main bile tube that has caused the yellow-jaundice and other symptoms you may be experiencing (itching, dark urine and/or pale stool).

It is not possible to remove the cancer you have with an operation. The best and fastest way to relieve the blockage to the bile tube and the symptoms you are experiencing is to place a small tube (stent) through the blocked section via a small camera which is passed through your mouth and into your stomach and duodenum while you are heavily sedated and unaware of the procedure (called an ERCP). This procedure will be done by a surgeon specially trained and experienced in this procedure. However, the two main risks associated with this procedure are developing inflammation in the pancreas (4 in 100 chance) and occasionally some bleeding from the opening we make in the entrance to the bile tube (less than 1 in 100 chance). These potential problems are with any ERCP and are not special problems related to this study.

These tubes do block and may get infected from time to time and do need to be replaced if this occurs. At the moment, normal medical care in this hospital is to use stents made of plastic. There are tubes (stents) made of a type of metal which are also widely used throughout the world as a way to treat these blockages. At the moment, our hospital only uses this type of stent if the plastic stents keep blocking after they have been put in place.

We are busy doing a study to see whether using metal stents are as good or better than plastic ones. We are asking you to take part in this study where you will be randomly given either a plastic or a metal stent. You will not know which type you have been given and you will have a 1 in 2 chance of getting each kind of stent (this is like flipping a coin). We will follow you closely to check for any complications like early blocking of the stent after it has been placed. This study will help us work out which is the best stent to use and it might help us treat patients with bile tube blockages better in the future, and find a way to reduce some of the problems that can be caused by blocked stents.

The care that you will get and all the tests and follow-up are exactly the same as normal medical care for patients with your condition who come to Groote Schuur Hospital. If you get a plastic stent that later blocks you will get another stent to open the blockage again, just as you will if you get a metal stent. This means that everyone who takes part in this study, whether you get a plastic or a metal stent will get the same medical care in the beginning and later if you develop problems with your stent. This is our standard treatment for anyone with a blocked stent.

If you take part in the study you will be asked to complete a questionnaire at your normal monthly follow-up visits. This will take about 5 minutes of your time. You will not have to pay for any additional tests or procedures (the cost to you is the same whether you do or don't take part in this study)

This study has been approved by the Human Research Ethics Committee of the University of Cape Town Health Sciences Faculty. The committee is in place to ensure the safety of any patients who take part in studies in this hospital. You can contact them xxxxx.

Should you not wish to participate in the study, you will automatically receive a plastic tube. If you decide not to take part, the care that you receive will not be compromised in any way and you will receive any medical care that you need.

All information about you that will be used for this study will be treated in a confidential way. Your privacy will be protected and your name will not be used in any publication of the results.

Consent Form

I have read or have had read to me the information about this study. I agree to participate and understand it is by my own free choice. All my questions were answered and I was given enough time to decide about taking part.

Name and Surname _____ Date _____

Signature _____

Witness _____ Date _____

Signature _____

Investigator taking consent _____ Date _____

Signature _____

3.4. Appendix 4: Data Capturing Forms

Plastic vs. SEMS
enrollment sheet

Patient number	
Name	
Hospital Number	
Date Randomised	
Stent type	Plastic / SEMS

Diagnosis (histology)	
Reason no resection	Locally advanced Advanced age Co-morbidity
ECOG on enrollment	1 2 3 4 5
QLQ completed on enrollment	Yes / No
Radiology US CT EUS Date:	Tumour size: Location: Mets: LN:
ERCP Date	Sphincterotomy: Yes / No Stricture: Comment:

Bloods prior to ERCP	FBC LFT Ca 19-9 INR
Symptoms (including analgesia requirements)	Pain Puritis vomiting
Length of stay post stent (days)	
Complications post ERCP	Non-functioning stent Cholangitis Bleed Pancreatitis Other
Therapy post ERCP before discharge	
Comment	

Readmission Data

Readmission date	
Date and type of first stent	
Reason for admission	
Action (stent replaced)	
Number of days in hospital	
Management (detailed for costing)	

3.5. Appendix 5: Instructions for Authors: South African Journal of Surgery

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP

Named authors must consent to publication. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL

Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to surgery. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...' Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...' All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software. Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more

than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**.

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

PROOFS A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

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