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A 17 years retrospective study on multiple metal stents for complex malignant hilar biliary strictures: Survival, stents patency and outcomes of re-interventions for occluded metal stents

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ABSTRACT

Background: Endoscopic placement of SEMSs for malignant hilar biliary strictures (MHBS) is well-established palliative treatment for inoperable patients. Objectives of this study were evaluation of survival and stents patency after placement of multiple SEMS for palliation of complex MHBS.
Methods: Retrospective review of patients with MHBS that underwent ERCP with insertion of multiple SEMSs for palliation. Survival-associated factors and stents patency were analyzed by Cox multivariate analysis.
Results: Between January 1998 and January 2015, 740 patients with nonoperable MHBS that underwent ERCP were identified and only 18.2% of these received multiple SEMSs. Complications were observed in 7.5% of the patients with no procedure-related mortality. Palliative therapies (chemotherapy, external beam radiotherapy and high dose rate brachytherapy) were done in some patients, and outcomes were evaluated. Overall mean survival of the 134 patients was 323 days. Of these, 59% did not had stents malfunction while 41% patients had episodes of SEMSs malfunction and mean survival after re-interventions was 502.9 days. Survival was not influenced by type of tumor, sex or age.
Conclusions: Endoscopic multiple SEMSs placement is safe and effective in patients with complex MHBS. Survival is independent from the type and complexity of MHBS while is prolonged in patients undergoing HDR brachytherapy. Prompt recognition of SEMSs malfunction is fundamental for survival.

1. Introduction

Heterogeneous types of tumors can cause malignant hilar biliary strictures (MHBS). The most common causes for MHBS are cholangiocarcinoma (CCA) and gallbladder carcinoma (GBC), but the hepatic hilum can be also compressed by lymph node metastases (LNM) and hepatocellular carcinoma (HCC). Two thirds of patients with MHBS are diagnosed at an advanced stage when the management is mainly palliative. The degree of obstruction of the intrahepatic bile ducts, compression of the hepatic parenchyma and compression and/or infiltration of adjacent vascular structures and presence or absence of metastases are directly connected to the overall survival [1].

A complete surgical resection (R0) is the only potentially curative treatment for hilar CCA and GBC [2–10]. Unfortunately, at the time of the onset presentation, less than one third of the patients with hilar CCA and GBC are candidates for resection or liver transplantation, thus palliation is the only lasting source.

The main purpose of MHBS palliation of is to relieve jaundice and pruritus. This not only prolongs patients survival but can also give way to other systemic treatments [11].

Palliation can be done endoscopically and/or percutaneously, is often centre dependent, and is determined on a case-by-case basis [12].

Two or more plastic stents should be sufficient to drain the biliary tree, albeit it has been widely shown that self-expandable

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metal stents (SEMS) are superior to plastic in terms of patency, lower re-interventions and longer survival rates [13].

The terms "bilateral" and/or "complete" drainage with "two or more stents" is widely misused in literature. The placement of "two or more stents" does not mean that a "bilateral" and/or "complete" drainage was carried out. For instance, in many cases two stents are placed in the same liver lobe or sectors of that lobe, with 50% or less of the liver parenchyma drained.

The ideal endoscopic palliation is defined by the quality of life improvement via minimal invasiveness, low-procedural related adverse events, short hospitalization and low costs. Considering that SEMS are superior to plastic stents, ideally, SEMS should be chosen for palliation in selected patients. Endoscopic biliary drainage of complex MHBS with multiple SEMS is technically demanding and expensive. Even though SEMS have been widely used in the past two decades, still little is known to date of the clinical impact on survival, efficacy and patency of placement of multiple SEMS in complex MHBS. Correctly selecting the patient for this type of palliation is also an issue. Considering that "patients with complex MHBS are also complex patients" they should be evaluated by a multidisciplinary team of surgeons, oncologists, radiologists, and gastroenterologists. Therefore the concept of personalized medicine should be applied to every single patient with a complex MHBS in order to achieve excellent technical success and durable palliation.

Primary objective of the present study was the evaluation of overall survival after SEMS placement while secondary objectives were the evaluation of stent patency and associated risk factors. The study was approved by the hospital Ethical Committee (approval number P/778/CE/2012).

2. Patients and methods

Consecutive patients who underwent palliation of complex MHBS with 2 or more SEMS, between January 1998 and January 2015, were retrospectively identified from our prospective database. In line with the position of the Italian authority for data protection and the local Ethical Committee, informed consent was not required considering the large number of patients and the patients' type of disease. of the patients.

MHBS were classified according to the Bismuth and Corlette classification [14] and only patients with complex strictures (type II, III and IV) receiving multiple SEMS were included in the analysis. Also patients with previously placed multiple plastic stents or percutaneous biliary drainage were also included.

All the cholangiograms during Endoscopic Retrograde Cholangio-Pancreatography (ERCP) and available radiological imaging were reviewed for each patient at inclusion. Only patients in which SEMS were inserted with the aim to drain all the intrahepatic ducts (complete drainage), or at least to drain all opacified ducts to reduce the risk of cholangitis, and in which there was effective reduction of liver function tests and symptoms were included in the study. Patients who had undergone a combined treatment with SEMS plus PTC and/or SEMS plus plastic stents were excluded.

Tissue sampling was done by brushing and/or endobiliary biopsies during ERCP, Echoendoscopy with fine needle aspiration and/or fine needle biopsy or was previously obtained by surgery.

SEMS malfunction was defined as elevation of liver function tests associated with elevation of markers infection (PCR, Procalcitonine, white blood cells count etc.), clinical signs (onset of cholangitis), and evidence of dilation of the bile ducts above the stents (abdominal ultrasound, CT-scan etc.).

Overall patients survival was defined by the number of days between the initial endoscopic procedure with SEMS placement to the death of the patient.

SEMS patency was defined as days between the first multiple SEMS placement and the first stent malfunction (as documented from the onset of cholangitis with the need for repeated ERCP) or until the death of the patients death. Days between re-interventions for SEMS occlusion were also calculated.

Signs and symptoms of possible stents malfunctions were explained to all the patients and their relatives and both patients and relatives were instructed on what to do in case of onset.

Procedure-related adverse events (cholangitis, pancreatitis, perforations and bleeding) were analyzed and defined as onset in the first 24–48 h. Procedure-related mortality was defined as death directly related to early adverse events occurring after endoscopic SEMS placement.

2.1. Follow-up

Patients and/or relatives were contacted by phone and every informations about the clinical status or date and, where possible, causes of death were noted. All the data collected from the prospective database (date of tumour diagnosis, date of SEMS or plastic stent placement, and all dates of re-interventions for occluded stents) were inserted in the database. All the cholangiograms of each revision during ERCP were reviewed for each patient.

Follow-up was done until death occurred. For patients and/or relatives that were not reachable by phone, death certificates were provided by the Italian National Population Registry with previous authorisation.

2.2. Technique of endoscopic stenting

Multiple SEMS insertion for complex HMBS is difficult, can be long lasting and requires optimal sedation and analgesia to relief discomfort and anxiety. All available radiological imaging, specially CT scans and magnetic resonance cholangio-pancreatography (MRCP), were carefully evaluated before ERCP. All procedures were performed using a therapeutic duodenoscope with a 4.2 mm working channel (TJF 140, 160, 180 Olympus, Tokyo, Japan).

Endoscopic biliary sphincterotomy was routinely performed to facilitate the insertion of multiple stents. Previously placed plastic stents or percutaneous drains were removed in the same procedure. Selective cannulation was carried out with hydrophilic wires followed by opacification as recommended to prevent post-operative cholangitis. Hydrostatic balloon dilation was performed with 4 mm–6 mm balloon (Boston Scientific, Natick, MA, USA or Cook Endoscopy, Winston-Salem, NC, USA) only in tight strictures to facilitate stent placement.

Wallstent and Wallflex (Boston Scientific, Natick, MA, USA), Niti-S (Taewoong Medical Inc., Seoul, South Korea) and Evolution (Cook Endoscopy, Winston-Salem, NC, USA) SEMS were used in this study.

After selective opacification and cannulation of the intra-hepatic ducts above the MHBS, 2–4 hydrophilic guidewires (according to the Bismuth type of stricture: II to IV) were left in place into the ducts to be drained; SEMS were advanced "side-by-side" over the previously placed guidewires and their release carefully controlled by fluoroscopy and endoscopy. SEMS were released trans-papillary, to facilitate future re-interventions. The number of stents were chosen according to the complexity of the stricture. Ideally, to obtain complete biliary drainage 2 stents were placed (one per lobe) for Bismuth type II strictures, 3 stents for type III and, 4 stents for type IV (Fig. 1a and b). When thin bile duct was detected below the stricture, hydrostatic dilation was carried out and/or 8.5 French stents were used.

The "rendezvous" technique was performed only in complex cases and only in patients with a previous percutaneous drainage.

SEMS types were chosen according to availability. In selected cases partially covered stents were also inserted.

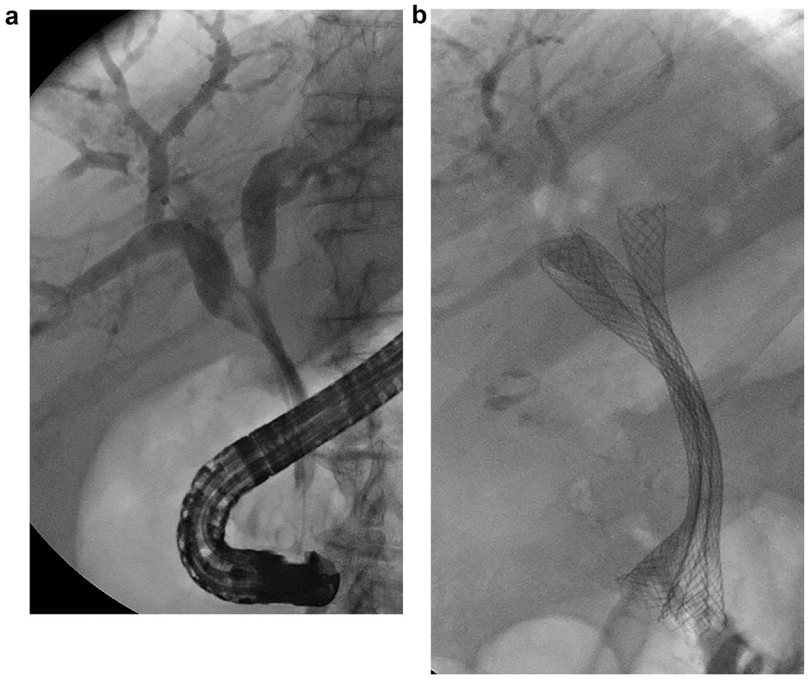

Fig. 1. (a) Bismuth type III malignant hilar stricture. After placing three guide wires, three self-expandable metal stents are inserted (Uncovered Wallflex, Boston Scientific). (b) Final appearance of the stents, note the rapid contrast outflow and onset of aerobilia.

2.3. Techniques for re-intervention in occluded stents

SEMS malfunction is usually due to overgrowth, ingrowth, sludge formation, haemobilia, and food scraps. To avoid passage through the meshes of the stents, an angled guidewire was used to perform deep cannulation of the biliary three trough the occluded stent. Sludge, clots and food scraps were mechanically removed with Fogarty balloon. Subsequently, flushing was carried out with saline until complete clearance of the ducts. Ingrowth and overgrowth were treated by placing an uncovered "bridging" SEMS inside the previous one (Fig. 2).

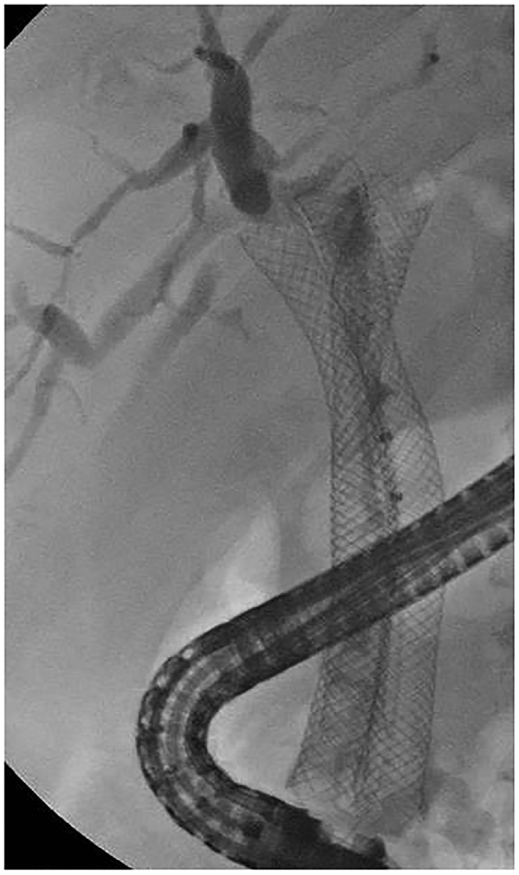

Fig. 2. Ingrowth and overgrowth treated by placing an uncovered "bridging" SEMS inside a previous one.

2.4. Statistical analysis

Follow-up and survival data were obtained from medical records, the Italian National Population Registry (in case of impossible contact with patient or relatives) and by telephone contact with the patient or relatives. All data were inserted into a database *(Microsoft Office Excel)*. Cumulative rates of survival were calculated based on the type of stricture by the Kaplan–Meier curves. To identify independent factors associated with stent patency and survival, a multivariate analysis was performed according to the Cox proportional hazard model. P values <0.05 were considered statistically significant (CI of 95%). Statistical analysis was performed with SPSS version 18.0 for Windows (SPSS Chicago, Illinois). Days between date of diagnosis, SEMS insertion and death, and also between SEMS insertion and re-interventions were calculated.

3. Results

Between January 1998 and June 2015, 740 patients with complex (Bismuth and Corlette II, III and IV) MHBS that underwent ERCP for palliation were identified. Among these, 134 (18.2%) patients were treated with two or more multiple SEMS (72 female; mean age 67.2 years, range 40–90). Demographic data are presented in Table 1.

Table 1
Results of the multivariate analysis results resulting from the Cox model: patients characteristics, tumor types and prognostic factors for survival (n = 134 patients).

Characteristics	No. patinents (%)	*P* value	HR	CI (95.0%) Lower–upper
Age, mean (range), years	67.2 (40–90)	0.511	0.994	(0.976–1.012)
Sex	72 F (55.2)	0.609	0.897	(0.590–1.362)
Malignant cause of stricture				
Cholangiocarcinoma	79 (59)	0.327	1.258	(0.795–1.990)
Gallbladder cancer	38 (28.3)	0.943	0.975	(0.795–1.990
Lymph node metastaes	13 (9.7)	0.246	0.534	(0.185–1.541)
Hepatocellular carcinoma	4 (3)	0.142	0.438	(0.146–1.319)
Bismuth type				
II	38 (28.3)	0.437	–	–
III	68 (50.7)	0.994	0.998	(0.614–1.622)
IV	28 (21)	0.290	1.387	(0.756–2.545)
Palliative radiochemotherapy				
Chemotherapy	51 (38)	0.397	0.797	(0.614–1.622)
External beam radiotherapy	16 (12)	0.305	0.667	(0.307–1.447)
High Dose Rate brachytherapy	11 (8.2)	0.001	0.487	(0.237–0.681)
Re-interventions for occluded SEMS	55 (41)	0.001	0.449	(0.283–0.712)

HR: hazard ratio; SEMS: self-expandable metal stents; F: female.

3.1. Histological proof

Tissue sampling before multiple SEMS placement was carried out in 116 patients (86.6%), by brushing cytology, and/or biopsy and/or Echoendoscopy with fine needle biopsy or aspiration, but also during surgical exploration, and was positive in 83.5% of cases. Malignancy was confirmed on CT scan or other imaging modalities (i.e. evidence of metastases) in those patients who had negative tissue sampling (3%).

Tissue sampling was not carried out in 13.4% of patients, but there were clear radiological findings of malignancy (for example gallbladder cancer diagnosed on CT-scan with metastases), and interestingly, these patients were treated in the period between 2002 and 2008.

The most common cause of the complex MHBS was CCA (n = 79; 59%), followed by GBC (n = 38; 28.3%). Hilar lymph node metastases in 13 patients (9.7%) while in 4 (3%) the hepatic hilum was involved by HCC.

3.2. Endoscopic management

On cholangiography, the most common type of stricture was Bismuth III (50.7%), followed by type II and IV (28.3% and 21% respectively).

Of the 134 patients, 76 (56.7%) were previously treated with multiple plastic stents (up to four 8.5 and/or 10 French) and 34 (25.4%) had one or more percutaneous biliary drainages, whilst 24 patients (17.9%) were drained with SEMS at the first ERCP. Technical success of multiple SEMS placement was 100%. The mean patency of the previously placed plastic stents was 75.3 days. All patients had jaundice and/or cholangitis at the time of endoscopic SEMS placement.

A total of 354 SEMS were placed over a 17 years period (2.6 stents/patient including re-interventions). The length of the metal stents was chosen mostly on the basis of the type of stricture on the cholangiogram. All the SEMS used were 10 mm in diameter.

In this retrospective series partially covered SEMS were used, and only in the period between 1999 and 2003. After reviewing the cholangiograms and the ERCP reports we found out that partially covered SEMS were placed in 67 patients only in association with uncovered SEMS. From the analysis of the cholangiograms it emerged that these stents were placed only in “anatomically suitable” ducts, and particularly in the left hepatic duct, taking care not to occlude side branches or inside previous uncovered stents as a bridge of ingrowth.

Complications related to multiple SEMS placement were observed in 7.5% of patients. Five patients had self-limiting haemobilia after multiple SEMS placement and no transfusion was required. Two patients had biliary duct perforation following hydrostatic dilation while 3 patients developed pancreatitis. These events were however mild and resolved with medical therapy. No procedure related deaths were observed.

3.3. Adjuvant therapies

Fifty-one patients (38%) underwent palliative chemotherapy, while external beam radiotherapy was done in 16 (12%). High dose rate (HDR) brachytherapy was performed through endoscopically inserted nasobiliary drains in another 11 (8.2%) patients with CCA and GBC.

3.4. Overall survival

The overall mean survival of the 134 patients after SEMS placement was 323 days (range (27–1700). In a sub-analysis of the 24 patients (17.9%) that were drained with multiple SEMS at first ERCP the survival was 410 days (range 28–1700). Survival was neither influenced by the type of tumor (Fig. 3), nor by the sex or the age of patients (Table 1). In a sub analysis of the data it also emerged that survival was neither influenced by the use of partially covered stents (P = 0.5) nor by the complexity of the malignant stricture (Fig. 4). A longer survival rate was observed in patients that who underwent HDR brachytherapy with Iridium 192 (P = 0.001), but not in those that underwent external beam radiotherapy (P = 0.3). Concomitant palliative chemotherapy did not influenced the survival rate (P = 0.5). All patients were dead at the time of the final review of the database.

There were essentially two groups of patients: those who did not develop SEMS occlusions and those who had recurrent episodes of SEMS occlusions.

Seventy-nine (59%) patients did not resort to the emergency department for eventual ERCP with stent revision. Furthermore, after talking with the relatives and consulting the certificates of death of the Italian National Population Registry the reported cause of disease was “primary disease progression”, while the terms “cholangitis” and/or related symptoms were not mentioned or

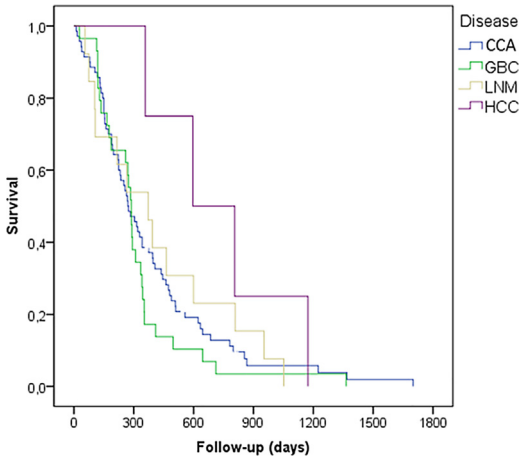

Fig. 3. Cumulative survival curve by Kaplan–Meier analysis shows no difference in survival between types of tumor (P = 0.4). Cholangiocarcinoma (CCA), Gallbladder cancer (GBC), Lymph node metastases (LNM), hepatocellular carcinoma (HCC).

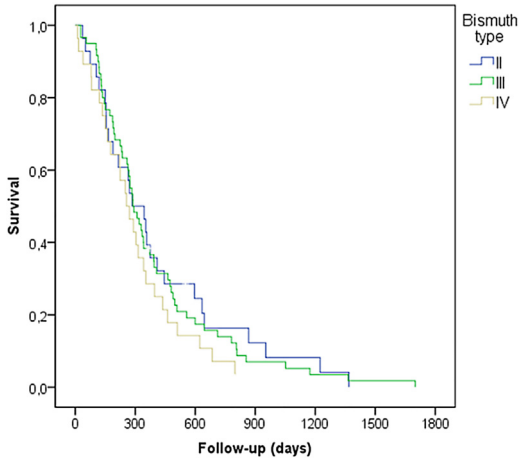

Fig. 4. Cumulative stent patency curve by Kaplan–Meier analysis shows no difference in survival between types of Bismuth type malignant hilar stricture (P = 0.4).

reported. The mean survival of these patients after SEMS placement was 218 days (range 14–956).

Fifty-five patients returned to our attention with clinical signs of SEMS obstruction and were re-treated.

3.5. Re-interventions

Fifty-five (41%) patients experienced one or more episodes of SEMS obstruction. These patients underwent 93 endoscopic re-interventions (1–6/patient). The mean cumulative SEMS patency in these patients was 201 days (32–867) from the initial multiple SEMS insertion and mean 140 days (30–330) between further re-interventions. Mostly SEMS were clogged by sludge, which was found in 65.9% of the re-interventions, associated with overgrowth and ingrowth 34.1% of the cases.

The survival was longer in these (P = 0.001) patients compared to the 79 patients who did not resort to the emergency department (mean survival 502.9 days range 50–1700) (Fig. 5).

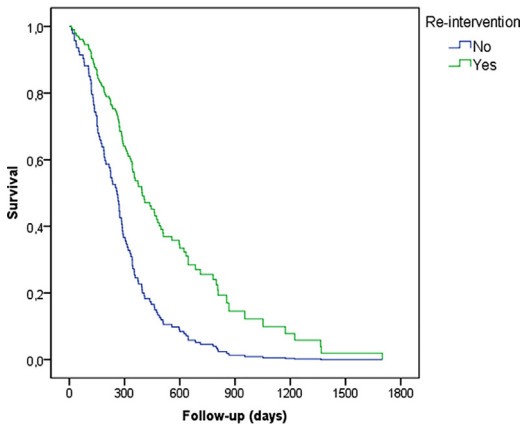

Fig. 5. Cumulative stent patency curve by Kaplan–Meier analysis in all patients. Cumulative survival rates were significantly higher in patients who underwent re-interventions for occluded SEMS (green line) (P = 0.001).

4. Discussion

Complex MHBS usually presents at an unresectable stage with low survival rates. Common clinical practice for the palliation of complex MHBS is the placement of plastic stents as treatment of choice. This is dependent on the cost of SEMS, difficult predictability of live expectancy and uncertain malignancy. Furthermore, when patients with both plastic stents or SEMS develop cholangitis, if untreated they will certainly die from cholangitis.

The aim of the present study was to evaluate patients survival and SEMS patency after endoscopic insertion of multiple metal stents for palliation of unresectable complex MHBS.

Out of the 740 patients with inoperable MHBS treated over a 17 years period in our Endoscopy Unit, in 18.2% palliation was carried out with multiple SEMS, while all the other patients had biliary palliative drainage with plastic stents. Due to the retrospective nature of the study and the long period of observation we do not know if this was done according to the estimated survival metal stents availability, tumor resecability status or other reasons.

Superiority in patency of metal stents over plastic stents has already been previously demonstrated [13,15–24] and is not the aim of the present study.

Placement of multiple SEMS during the first endoscopic treatment is, technically demanding, mostly due to a thin common bile duct, therefore previous plastic stenting usually facilitates the placement of multiple SEMS [17]. Furthermore, when jaundice due to MHBS occurs, as the surgical status of the patient and nature of the stricture is unclear, in many cases initial plastic stenting is still recommended [23].

The overall mean survival of the 134 patients after SEMS placement was almost one year (323 days). Interestingly, the survival of the 24 patients (17.9%) that were drained with multiple SEMS at first ERCP was 410 days. Even if this number is very limited, this is a point that should be furtherly investigated.

Tissue sampling in our series was done in 86.6% of patients and was positive in 83.5%, while in the remaining patients there were clear signs of malignancy on the CT-scan or other imaging modalities. In our daily practice the histological definition of hilar tumors has been is mandatory before SEMS placement for several years. In these series tissue sampling was not carried out in 13.4% of patients, even though there were clear radiological findings of malignancy and these patients were treated before 2008. For instance in other series tissue sampling before biliary drainage was performed in much fewer patients compared to ours [17,25,26].

The guidelines of the European Society of Medical Oncology focus on the diagnosis and pathology/molecular biology, staging, risk assessment and management, including follow-up and long-term implications on the treatment of cancer of the biliary tract [27]. These guidelines emphasize the importance and the role of chemo and radiotherapy in complex MHBS.

Radiotherapy alone is mostly recommended after resection of GBC and CCA [28–33], nevertheless external beam radiotherapy

combined or not with chemotherapy had no influence on the survival rate in our series. Survival was neither influenced by chemotherapy alone.

All patients who underwent HDR brachytherapy with Iridium 192 (P = 0.02) had longer survival rates, this was also demonstrated by other groups [34]. Considering the scarce data in literature on this approach, further investigation is deemed necessary.

Surprisingly, neither the type of tumor nor the complexity of the stricture influenced the survival and we presumed that complete biliary drainage with multiple SEMS might be the main reason for this. In a fact, as previously mentioned, one of the most discussed and controversial issues in palliative endoscopic biliary drainage is the quantity of liver parenchyma that should be drained [35–41]. According to some authors bilateral or complete biliary drainage offers longer survival and prolongs stents patency [26,35,36]. In a retrospective study of Vienne et al. on 107 patients with complex MHBS, the drainage of more than 50% of the liver volume seemed to be an important predictor of clinical effectiveness [42]. A randomized clinical trial on 133 patients with inoperable complex MHBS Lee TH et al. showed that bilateral drainage with SEMS resulted in fewer re-interventions and more durable stent patency in patients compared to unilateral bilateral drainage [43].

Recently, in a retrospective cross-sectional study on 77 patients Kerdsirichairat et al. performed targeted placement of multifenestrated plastic stents (41 patients) and SEMS (36 patients) draining more than 50% of the parenchyma [44]. Interestingly the authors found similar technical, clinical success and survival rates while stent patency was significantly shorter in the plastic stents group. Furthermore, in this study the survival rates were independent from the Bismuth type.

We consider an important bias the use of partially covered stents in our study although their use did not influence the survival rate (P = 0.5). As previously described, these stents were placed only in anatomically suitable ducts, as a stent in stent to bridge ingrowth and prior to 2003 when no guidelines were available. However, the use of partially covered stents in complex MHBS should be strongly discouraged due to the possibility of side branches closure [23].

One of the major limitations of the present study is the impossibility to know whether seventy-nine patients who did not resort to the emergency department for eventual ERCP with stent revision died of cholangitis or not. As reported above, we made all possible efforts to better understand the cause for death in these patients even if the terms “cholangitis” and/or related symptoms were not mentioned neither reported in the death certificates. It is difficult to believe that these patients or at least a part of them died without episodes of cholangitis. Probably the best solution to this problem is to create a time scheduled re-call system for the follow-up of these patients just like for those with benign biliary strictures and establish a direct contact with the endoscopists and/or oncologists. This point should be better evaluated in a prospective trial.

Less than half the patients in the present series experienced one or more episodes of SEMS occlusion and the mean cumulative stent patency in these patients was 201 days from the initial multiple SEMS insertion and mean 140 days between further re-interventions. Similar rates were also reported by other authors [18,43].

The current study is limited by its retrospective nature, single-arm, non-randomized and single center, the heterogeneous group of malignancies, and by the selection bias of patients and type of stents. Besides this, we found that about 20% of all patients with new diagnosis of complex MHBS are candidates for endoscopic placement of SEMS as safe and effective treatment in terms of prolonged survival, independently form the tumor or stricture type. Furthermore, in our experience HDR brachytherapy prolonged the survival. Personalized medicine on multidisciplinary fashion should be the best approach for these patients especially by choosing the best type of metal stents and the best combined adjuvant therapy. Another important point here is that early recognition of SEMS malfunction and prompt endoscopic re-intervention prolongs the survival. In this view both patients and relatives should be instructed on how to recognize signs and symptoms of early SEMS malfunction.

In conclusion, this study shows that endoscopic palliation with multiple SEMS of complex MHBS is safe and effective, and most of all, a technically feasible treatment modality that prolongs the patients’ survival when the intent is to drain “as much parenchyma as possible” or at least all opacified bile ducts.

Conflicts of interest

Prof. Guido Costamagna is a consultant for Cook Medical and Boston Scientific. Dr. Ivo Boškoski is a consultant for Cook Medical and Apollo Endosurgery. Dr. Andrea Tringali, Pietro Familiari, Vincenzo Bove, Rosario Landi, Fabia Attili, Processor Vincenzo Perri, Graziano Onder and Massimiliano Mutignani have no conflicts of interest.

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