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REVIEW

Percutaneous Minimally Invasive Treatment of Malignant Biliary Strictures: Current Status

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Abstract The concept of percutaneous management of malignant biliary obstruction has not significantly changed in the last two decades and is based on the successful drainage of bile toward the duodenum, which normalizes liver function and prevents the development of cholangitis and sepsis. However, patient survival has changed slightly in the last two decades due to the advance of the diagnostic methods, chemo-radiotherapy protocols, and minimally invasive local control of the disease. Bare metal stents have not improved; however, newly developed covered biliary stents have been designed, and there is now evidence supporting their use in the clinical practice. However, other novel devices that may potentially offer benefit to patients with malignant biliary obstruction have been developed, such as drug-eluting biliary stents and intraductal ablation devices, and first feasibility trials have been published that offer encouraging results. These new technological developments, in combination with increased patient survival, bring new exciting data in this constantly developing area. The purpose of this review article is to investigate the latest published evidence on percutaneous minimal invasive palliation of malignant biliary disease and to delineate current trends.

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Introduction

The growth of neoplastic tissue within or around the biliary tree causes stenosis and blockage of the bile ducts, and the bile that is produced from the hepatocytes cannot follow their natural pathway and reach the duodenum to assist in the process of digestion. In the majority of cases, the neoplastic tissue is either pancreatic adenocarcinoma or cholangiocarcinoma [1]. Less frequently, the cause of stricture is gallbladder cancer or enlarged lymph nodes of the hepatic hilum (usually metastatic from primary gastric or lung cancer). Initial symptoms are painless jaundice with/without cholangitis. The diagnosis is usually made when the disease is already in an advanced stage such that the disease is already considered inoperable. In such cases, palliation with drainage of the biliary tree is of paramount importance for quality of life of these oncologic patients [2].

Palliative biliary drainage aims to improve liver function, resolve jaundice, and decrease sepsis risk. In cases of biliary obstruction combined with liver dysfunction, chemotherapy cannot be administered, jaundice is associated with pruritus, and increased bilirubin levels and, eventually, with encephalopathy and multiorgan failure. The lack of bile flow toward the bowel predisposes to increased bowel wall permeability, portal system bacteraemia, and systemic sepsis [3].

Initially, palliation used to be performed surgically; however, during the last two decades the preferred option is

the use of percutaneously or endoscopically inserted stents [4, 5]. Stents have evolved from plastic to bare metallic, and from bare metallic to covered metallic, and recently from covered metallic to drug eluting in an effort to increase patency and decrease tumour ingrowth [6]. A stent's patency period is crucial for such patients; both the patient's quality of life and the procedure's cost-effectiveness depend on stent occlusion [7, 8]. Stents therefore evolved from uncovered to covered and then to drug-eluting aiming to obtain longer patency and better palliation [9]. In conjunction with the evolution of metallic stents, other minimally invasive techniques have also evolved for percutaneous minimal invasive treatment of malignant biliary strictures. In particular, high dose rate intraluminal brachytherapy (HDR-ILBT) has already been in use for the last two decades; however, endoluminal biliary radiofrequency ablation (EBRFA) [9] has recently been introduced.

Despite the variety of the new devices in this field, patients with malignant biliary stricture remain a high-risk group, and the procedures performed may frequently lead to serious complications. A recent registry organized by the British Society of Interventional Radiologists (BSIR) has shown that mortality after percutaneous transhepatic biliary interventions may be as high as nearly 20 % (19.8 %) [10]. The registry concluded that percutaneous biliary drainage procedures must be performed in centres with appropriate experience and after the optimization of all of the risk factors. In addition, appropriate patient selection and decrease of risk factors is required to limit high periprocedural morbidity and mortality.

Plastic Versus Metallic Stents

Although the use of plastic stents for malignant biliary strictures is not the preference of choice for the majority of operators, there are some groups that still use plastic stents in neoplastic patients. Three studies showed that metallic stents provide longer patency without increasing survival compared with plastic stents [11–13]. In addition, two systematic reviews showed that metal stents are linked to lower risk of recurrent obstruction without significant difference regarding technical or therapeutic failure, complication rate, and 30-day mortality rate [14, 15]. Two recently published randomized control trials [16, 17] showed that self-expandable metallic stents are better than plastic stents in terms of patency and reintervention rate. Furthermore, a recently published meta-analysis, which included 10 randomized trials with 785 patients (392 of which received a metallic and 393 a plastic stent), confirmed that metal stents were associated with a significantly longer patency, fewer reinterventions, and longer survival, thus indicating once again that metal stents are superior to plastic ones in patients with malignant biliary disease [18]. Despite this, some groups still use plastic stents for palliative treatment of malignant strictures.

Covered Versus Uncovered Stents

Covered biliary stents were developed to prohibit tumour stent ingrowth, which seems to be a major limitation of bare metallic stents, and therefore to increase patency of the biliary endoprostheses. Since their initial design, investigators have tested several types of covered stents with a great variety of covering membranes; however, this was without clear evidence of any benefit versus the uncovered ones [19–24]. The use of a new covering material, expanded-polytetrafluoroethylene/fluorinated ethylene propylene (ePTFE/FEP) (Viabil; W. L. Gore and Associates, Flagstaff, AZ), initially showed promising results in four feasibility studies [25–28]. In two recently published randomized control trials, these stents were directly compared with bare stents in patients with pancreatic adenocarcinoma and with cholangiocarcinoma, respectively [29, 30]. The investigators considered that there are two main types tumours causing ingrowth and that there is no benefit in using covered stents in strictures from lymph nodes where ingrowth is very unlikely to occur. The results of the two randomized trials showed that ePTFE/FEP-covered biliary stents provide greater patency than bare stents with fewer reinterventions.

The two above-mentioned studies were included in a recently published meta-analysis including 781 patients [31], where in total five multicentre prospective randomized trials were included [29, 30, 32–34]. In two of the studies, stents partially covered with permalume (Wallstent; Boston Scientific, Natick, MA) and with polyurethane coverage (Diamond; Boston-Scientific, Microvasive Inc., Natick, MA), respectively, were used. In the three other studies, fully covered stents coated with either polycarbonate-polyurethane (Nitinella; ELLA-CS, Hradec Kralove, Czech Republic) or ePTFE/FEP (Viabil) were deployed (Table 1). Covered stents, compared with uncovered ones, proved to be associated with significantly longer patency and longer time to stent dysfunction. Occlusion due to tumour ingrowth was significantly lower by using covered stents. However, the use of covered stents was associated with prolonged patient survival in only two of five studies. No difference was noted between the rates of cholecystitis and pancreatitis. Interestingly, the rates of tumour overgrowth and stent migration were greater for the covered stents. However, migration was noted only in the studies where stents without barbs or fins were used. Thus, use of anchoring fins is crucial for biliary covered stent design because migration has always been a major limiting factor (Fig. 1). The fact that significant

Table 1 Multicenter randomized trials on the use of covered stents included in the meta-analysis of Saleem et al. [31]

Study	Procedure	No. of patients	Stent type	Covering membrane	Length (range) of FU
Isayama et al. [34]	Endoscopic	57	Covered Diamond	Polyurethane (partially)	246 (11–115)
		55	Uncovered Diamond	Bare	246 (11–115)
Krokidis et al. [30]	Percutaneous	30	Viabil	ePTFE/FEP	212 (45–675)
		30	Wallstent	Bare	212 (45–675)
Krokidis et al. [29]	Percutaneous	40	Viabil	ePTFE/FEP	192 (104–603)
		40	Luminexx (Karlsruhe, Germany)	Bare	192 (104–603)
Kullman et al. [33]	Endoscopic	200	Covered Nitinella	Polycarbonate-polyurethane (partial)	360
		200	Uncovered Nitinella	Bare	360
Telford et al. [32]	Endoscopic	68	Covered Wallstent	Permalume (partially)	201 (0–1,302)
		61	Uncovered Wallstent	Bare	201 (0–1,302)

FU follow-up

overgrowth occurred may also be explain that none of the covered stents used is designed specifically to decrease overgrowth. A bare intrahepatic extension is perhaps required to limit proximal overgrowth, thus introducing a new promising concept in biliary stents design (Fig. 2). Gwon et al. [35] also followed the concept of "overstenting" and used a double stent (bare and covered) for treatment of 45 patients. However, overgrowth occurred in 6 % of patients despite the fact that the uncovered part proximately protruded 2 to 3 cm, thus indicating that an even longer proximal bare stent might be required to prevent tumour overgrowth.

Drug-Eluting Stents

The use of drug delivery through stents has offered a revolutionary field in vascular disease treatment. To date, there are few published studies on the use of drug-eluting stents for malignant biliary disease in humans. Mezawa et al. [36] developed a percutaneous biliary drainage tube coated with carboplatin. The tube was initially tested in vitro and in an animal mode and then in five patients with cholangiocarcinoma. Results were somehow encouraging considering that overall efficacy was 60 % without any side effects. In 2007, Suk et al. [37] published the first biliary study for the use of drug-eluting stents in humans. The investigators reviewed 21 patients with unresectable malignant biliary obstruction and evaluated the safety and efficacy of endoscopic placement of stents covered with a paclitaxel-incorporated membrane. Mean follow-up period was 329 days (range 68–811); occlusion of the drug-eluting stents was observed in 9 of 21 patients (43 %) after a mean time of 196 days [median 175 days (range 95–327)]. The causes of stent occlusion were bile sludge or clog in four, tumour overgrowth in three, and tumour ingrowth in two cases.

In 2011, Song et al. [38] published a prospective randomized pilot study comparing paclitaxel-eluting covered biliary stents to control covered stents in patients with malignant biliary obstruction. The investigators included 49 patients in whom a double-layered covered stent was used: 24 received a drug-eluting stent, and 25 received a conventional stent. The outer layer of the drug-eluting stent was made of a solution of polyurethane and paclitaxel (20 % wt/vol), and the outer layer of the conventional covered stent was made of polyurethane. The inner layer in both versions was made of silicone to protect the polyurethane membrane from bile flow and to prevent paclitaxel leakage into the bile ducts. The stents were 10-mm wide and 6- and 8-cm long, and the majority of malignancies were pancreatic carcinoma and cholangiocarcinoma. Mean follow-up was 194.0 ± 144.2 days for the drug-eluting and 238.8 ± 147.4 days for the covered stent group without significant difference between the two groups. Neither stent patency nor survival time was significantly different after the comparison of the results of the two groups. Stent dysfunction from tumour ingrowth occurred in the drug-eluting group in five patients and in the conventional group in four patients and also without significant difference between the two groups. In three patients in the drug-eluting group, early cholangitis occurred the day after stent insertion; however, this improved within 2 to 3 days with conservative management. One case of pancreatitis occurred in each group. The investigators correlated the fact that in two of the patients in whom cholangitis occurred, stent patency was greater (339 and 486 days) due to the initial severe inflammatory response, which probably has an antitumour effect. However, the desirable effect from drug-eluting stents is a

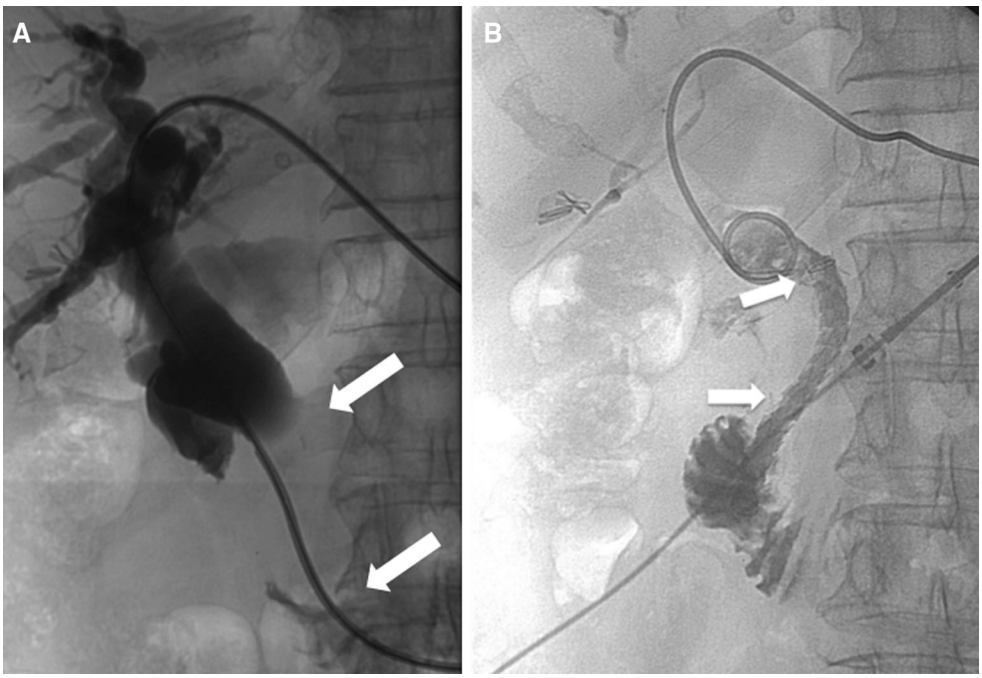

Fig. 1 (**A**) Cholangiography in a 54-year-old male patient with pancreatic head carcinoma showing obstruction at the distal common bile duct. *Arrows* indicate the level and length of the obstruction. An 8F internal–external locking pigtail biliary drainage catheter is inserted through the left liver lobe and advanced in the duodenum. (**B**) A 10 × 80-mm ePTFE/FEP-covered biliary stent (Viabil) with presence of anchoring fins (*arrows*) is deployed through the stenotic area. Cholangiogram from an external drain is performed before catheter removal

longer duration of high local drug concentration, for which unfortunately no data are available; however, it is probably still low. Tumour may initially respond to the inflammatory event; however, it is not completely treated, so it continues to grow. In addition, polyurethane membrane is prone to microcracks, and thus tumour ingrowth occurs [39]. Therefore, the type of membrane still appears to be the most crucial factor for prevention of tumour ingrowth at the moment considering that the drug effect is not long acting. In this study, a greater concentration of paclitaxel was used compared with the study of Suk et al. [37] (20 vs. 10 % wt/vol), which was also proven to be safe. Paclitaxel is expected to have a synergistic effect to systemic chemotherapy; however, it was not administered in this trial because the selected patients refused to undergo chemotherapy or radiotherapy. Therefore, drug-eluting stents, until now, do not appear to offer an advantage in the palliation of malignant biliary disease, at least not in terms of stent patency. The main targets for stent design remain the same as described for covered stents with antimigrational barbs, intrahepatic extension, and an effective microporous membrane. Addition of another drug, such gemcitabine, which seems to have better efficacy in both pancreatic cancer and cholangiocarcinoma [40] and provides a longer release time, might provide more encouraging results in the future. However, the main limitation of gemcitabine is its high water-solubility [41].

Moon et al. [42] captured the concept of creating a gemcitabine-eluting biliary stent with a membrane made of polytetrafluoroethylene (PTFE) and pullulan acetate, which was applied as the drug-loading release membrane (double-layered polymeric membrane). The device was tested on an animal model, and the results were positive regarding long-term biological activity of the released gemcitabine and apoptosis of tumour tissues. Finally, Chung et al. [43] performed a similar study showing that gemcitabine-eluting biliary stents could be safely used in bile ducts of pigs. However, both studies are experimental conducted on animal models, and clinical studies with gemcitabine eluting biliary stents have not yet been published.

Intraluminal Brachytherapy

Using brachytherapy, a greater radiation dose may be locally delivered to a defined volume of tissue, therefore minimizing radiation risks to adjacent organs [44–46]. There are also some reports in the literature about the use of brachytherapy with a combination of stents [47, 48]. Singh et al. [49] reported a small series of eight patients with Bismuth type II obstruction due to gallbladder cancer who were initially stented and 4 weeks later underwent brachytherapy endoscopically applied using a high-dose rate pellet source of iridium-192. No complications

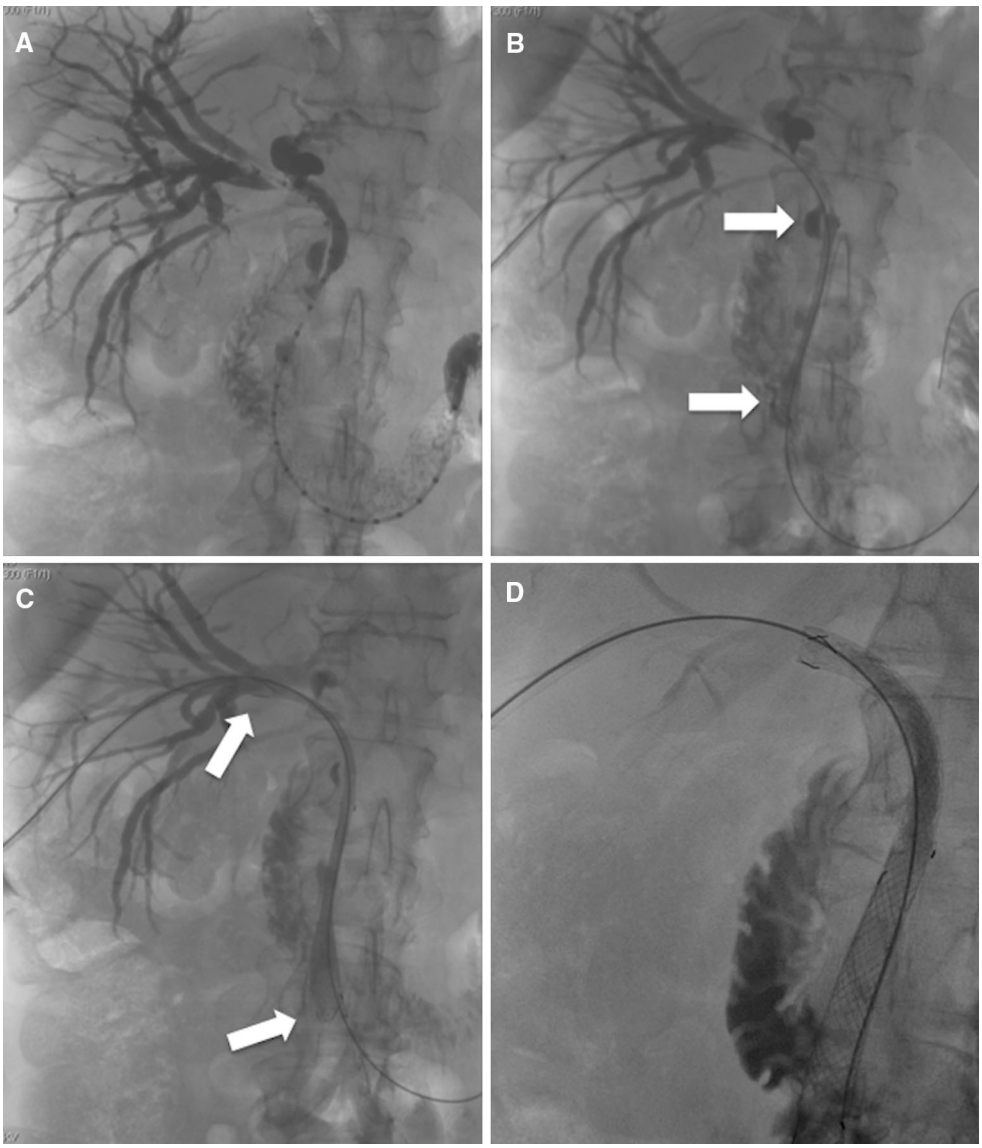

Fig. 2 (**A**) Cholangiography in a 65-year-old female patient with cholangiocarcinoma showing obstruction of the distal common bile duct and the presence of a hilar stricture. A metric pigtail is inserted to measure the exact length of the stenotic area. (**B**) A 10 × 60-mm silicone-covered stent (Nitinella Plus; ELLA-CS, Hradec Kralove, Czech Republic) (*arrows*) was deployed in the region of the distal stenosis caudally to the origin of the cystic duct. (**C**) A 10 × 100-mm noncovered stent (Niti-S; TaeWoong Medical, Gyeonggi-do, Korea) was deployed as a proximal and distal extension of the covered stent to treat the hilar stenosis and prevent overgrowth and stent migration. (**D**) Cholangiogram shows satisfactory expansion of both stents

occurred within the first 30 days, with a mean stent patency of 305 ± 183.96 (range 95–600) and a mean survival of 310 ± 192.68 days (range 95–615). In another study, Aggrawal et al. [50] used high dose rate intraluminal brachytherapy by way of percutaneous access. Initial percutaneous drainage was performed, and 1 week later patients underwent brachytherapy with 800 cGy applied 1 cm from the central axis of the source. Another session followed 1 week later. The investigators did not report any major complications, and good response regarding pruritus and jaundice was achieved. Brachytherapy with the use of iridium-192, which is a γ-emitter, appears particularly suitable for treatment of inoperable tumours of the bile tree with satisfactory results; however, it is limited to few specialized centers; therefore, no large series have been reported.

Intraductal RFA

RFA is based on the interaction between biological tissue and high-frequency rapidly alternating electric current causing vibrational movement of tissue's water molecules; movement transmission results in frictional energy loss,

which is deposited as heat in the biological tissue [51]. RFA is a well-established percutaneous and intraoperative heat energy-delivery method leading to tumour necrosis in primary and secondary hepatic cancers [52].

Steel et al. [53] reported the first human trial in 22 patients using a biliary intraductal RFA device after two initial published studies, one with in vivo [54] and one with ex vivo animal experiments [55]. Investigators included patients with unresectable pancreatic or bile duct cancer with Karnosky score >60 %. They inserted endoscopically the Habib EndoHPB (EMcision UK, London, UK) catheter, which is a bipolar RFA probe that is 8F in diameter and is advanced over on 0.035-in. guidewire. The catheter has two ring electrodes 8 mm apart with the distal electrode 5 mm from the leading edge and provides coagulation necrosis for a length of 2.5 cm. The generator used was a 1500 RF (RITA Medical Systems Inc., Fremont, CA), which delivers energy at 400 kHz at 7–10 W for 2 min. There is a rest period of 1 min before moving the catheter. After treatment, the investigators deployed a bare self-expandable metallic stent (Wallstent). In a relative short follow-up period of 90 days, one case of pancreatitis and two of cholecystitis occurred, whereas three cases of biliary obstruction had already been noticed. The results of the percutaneous application of this device were recently published in CVIR from the multicentre retrospective analysis of Mizandari et al. [56]. Thirty-nine patients with malignant biliary stricture were treated. RFA was performed 1 week after initial biliary decompression; immediately after 2 min at 10 W treatment, a stent was deployed. Patients subsequently received a bare metallic stent, and chemotherapy was also administered where required. No major complications were noticed, thus indicating that use of intraductal RFA is a safe new tool for the management of malignant biliary obstruction. In one case, stent blockage occurred 42 days after the procedure. Mean patency was 92 days (range 14–260), which is not better than conventional stent patency.

BSIR Registry

A concerning factor after the recent BSIR registry, which is the largest reported series on the outcomes of percutaneous biliary drainage and stenting for obstructive jaundice in the literature [10], is the fact that in a cohort of 610 inpatients who received percutaneous biliary drainage for malignant jaundice, the total mortality was 19.8 % (121 of 610 patients). Mortality for the subgroup that received drainage only was 29.5 % (28 of 95) and of the subgroup that received a combination of drainage and stenting was 17.9 % (92 of 515). The presence of mild to moderate ascites was significantly correlated with mortality for both subgroups ($p = 0.0002$ for the drainage subgroup, and $p < 0.001$ for the drainage/stenting subgroup). None of the other factors examined—including age, level of obstruction, sex, bilirubin level before the procedure, presence of sepsis, international normalized ratio (INR), platelet count, number of needle passes, or side of approach—were correlated significantly with mortality for the two subgroups. Survival rates were 48 % at 90 days, 32 % at 180 days, and <20 % at 1 year. The low survival rate is in contention with the high technical (98.7 %) and clinical success in both transhepatic drainage and stenting. The high mortality rate (21.7 %) reported is one of the highest among interventional procedures. There was no clear indication on what led to such a result; the investigators suggested that the overall state of health of the patients at the time of treatment is the most crucial factor for survival after drainage and/or stenting. One additional factor must be taken into consideration: A large registry may include results from various departments with a different level of experience according to the number of cases performed.

Conclusion

Minimally invasive treatment of malignant biliary disease is still an exciting area of research and development. The question on how to increase stent patency has not yet been completely resolved. From current evidence, the use of covered stents is justified and appears to be the first line of treatment despite their greater cost. According to the current evidence, it appears that presence of lateral barbs in necessary to prevent stent migration and that an uncovered proximal stent extension could be an improvement to prevent overgrowth. Drug release from the covering membrane, particularly gemcitabine, as well as intraductal implementation of RFA in the malignant stricture could be alternative options for better palliative treatment of these patients.

Conflict of interest The authors declare that they have no conflict of interest.

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