Endoscopic biliary drainage
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Citation for published version (APA):

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Palliation of malignant pancreaticobiliary obstruction

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INTRODUCTION

Pancreaticobiliary malignancies include pancreatic head cancer, gallbladder carcinomas and proximal cholangiocarcinomas also referred to as Klatskin tumors. Pancreatic head carcinoma comprise of tumors which may originate from various tissues and include pancreatic adenocarcinoma, distal cholangiocarcinoma, carcinoma of the ampulla of Vater and duodenal carcinoma. Although there are marked differences in biological behaviour and clinical outcome between these tumors, the overall prognosis is dismal. At the time of presentation more than 90% of patients have local irresectable disease or distant metastases which leaves only a minority of patients suitable candidates for curative resection. Other treatment modalities such as chemotherapy and radiotherapy have only little to no effect on survival. Unfortunately, the majority of these patients can only be offered palliative treatment. More than 85% of patients with pancreaticobiliary malignancies will develop obstructive jaundice in the course of their disease and often it is a presenting symptom. Relieve of jaundice, besides pain management, is the mainstay of palliative therapy. In the past, the golden standard treatment was surgical biliary diversion. Because of associated morbidity and mortality, surgical treatment has been challenged by endoscopic stent placement since the introduction of endoscopic retrograde cholangiopancreatography (ERCP) in 1980. Nowadays, endoscopic biliary drainage has become the palliative treatment of choice to relieve biliary obstruction in pancreaticobiliary malignancies.

EPIDEMIOLOGY

Of all pancreaticobiliary malignancies, pancreatic adenocarcinoma has the highest incidence with around 30,000 new cases annually in the United States. It ranks fifth among the leading cause of cancer related deaths (1,2). Only 10% of patients are suitable candidates for resection and the overall 5 year survival rate is less than 4% (3,4). The incidence of gallbladder carcinomas is 1 per 100,000 person-years. The survival rate is only slightly higher than that of pancreatic carcinoma (2). Most likely only the patients who will survive are those in whom an early cancer was detected in a postcholecystectomy specimen. Klatskin tumors also have a poor prognosis with less than 10% of patients surviving 5 years after being diagnosed and with the vast majority of patients dying in the first year (5). The number of tumors that are potentially resectable is low, ranging from 5-20%. In ampullary carcinoma biliary obstruction usually develops relatively early in the course of the disease. Therefore, tumors are usually small and radical resection is possible in the majority of cases with an overall 5 year survival rate up to 50% (6).
PATHOGENESIS

Although a detailed discussion of the pathogenesis of pancreaticobiliary malignancies is beyond the scope of this chapter it is interesting to note that several epidemiological studies have identified risk factors for the development of pancreaticobiliary malignancies.

Tobacco smoking doubles the risk of pancreatic cancer (7,8). Patients with chronic pancreatitis have an increased risk for developing pancreatic cancer which is estimated at 4% per 20 years (9). The risk of developing pancreatic cancer in patients with hereditary pancreatitis is as high as 50% with smoking being an important risk modifier (10,11). Etiological factors for cholangiocarcinoma include primary sclerosing cholangitis and hepatolithiasis (12,13). Gallstone disease is the most important risk factor for gallbladder cancer (14).

CLINICAL FEATURES

The most common presenting symptoms of pancreaticobiliary malignancies are painless jaundice with anorexia and weight loss, which are seen in the majority of patients. If pain occurs, it is often located in the epigastric region or right upper quadrant and may radiate to the back. Back pain usually indicates retroperitoneal infiltration with tumor and therefore irresectability. Other symptoms may include dark urine, pale stools and pruritus. As much as 80% of patients with pancreatic cancer have an impaired glucose tolerance or frank diabetes mellitus at the time of presentation. Carcinoma of the body and tail of the pancreas presents with similar features although jaundice is usually absent or develop very late in the course of the disease.

PATHOLOGY

About 90% of pancreaticobiliary malignancies are ductal adenocarcinoma. Most of these tumors arise from the pancreatic head. Other exocrine malignancies are mucinous cyst adenocarcinoma and acinar cell carcinomas. Endocrine tumors include gastrinoma and insulinoma. Metastases of a primary tumor (mamma, lung, melanoma) and a lymphoma should be considered because of important treatment implications (e.g. chemotherapy). Mesenchymal tumors are extremely rare.

The definitive diagnosis of malignancy depends on obtaining a tissue diagnosis. Although a number of patients are palliated without definite confirmation of the tumor, in cases of adjuvant therapies such as radiotherapy or chemotherapy, a cytological or histological biopsy proven malignancy is a prerequisite. In order to lower
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The number of costly and cumbersome ultrasound or CT guided punctures, it is advisable to attempt obtaining a tissue diagnosis during the same ERCP procedure in which a biliary endoprosthesis is inserted for palliation of jaundice. Various techniques can be used to obtain tissue specimens during ERCP including cytologic brushings, forceps biopsy, needle aspiration cytology and fluid collection from the bile and/or pancreas.

Cytologic brushings are relatively easy to obtain and widely used. Specificity approaches 100% but sensitivity is as low as 30-60% (15,16). The sensitivity in cholangiocarcinoma is higher compared to pancreatic carcinoma. Forceps biopsy or needle aspiration cytology requires endoscopic sphincterotomy and therefore carries an increased risk of complications. Ampullary tumours can be directly biopsied. FNA is superior to brush cytology and endobiliary forceps biopsy with a cancer detection rate of 65% (17-19). Sampling of ductal fluid is a simple method, but its sensitivity is very low and therefore it is not used very often. Several studies have shown that sensitivity can be increased by combining different techniques of tissue sampling (16). Endosonographic fine needle aspiration biopsy results in an excellent sensitivity of 85-90% and specificity of virtually 100% (20). Although these tests may be useful in making the diagnosis of carcinoma, a negative test cannot rule out malignant disease. Percutaneous fine needle aspiration biopsy is another accurate method for confirmation of malignancy with a sensitivity of 60-90% (21). However, needle track seeding has been described and this technique should only be used for tissue confirmation in the case of irresectable disease.

Differential Diagnosis

The most important discrimination is the differential diagnosis between benign and malignant lesions. In the case of the former, surgery may not be indicated and may even cause harm to the patient while in the latter case it is the treatment of choice if a lesion is resectable.

An enlarged pancreatic head may either be caused by pancreatitis or by carcinoma. The patients' history and clinical presentation contribute to making a diagnosis. Cystic lesions of the pancreas may either be benign (pancreatic pseudocyst or serous cystadenoma), pre-malignant (mucinous cystadenoma), or malignant (cystadenocarcinoma). Radiological imaging is used to characterize these lesions. Endoscopic ultrasound may further increase accuracy of the diagnosis in combination with fine needle aspiration and fluid analysis.

In the case of a suspicious mid or proximal bile duct stricture a gallbladder carcinoma should be included in the differential diagnosis. It is important to exclude benign causes of strictures such as Mirizzi's syndrome, primary and secondary sclerosing cholangitis, and postoperative conditions. An algorithm of the diagnosis of pancreaticobiliary cancer is presented in Figure 1.
TREATMENT

Since the introduction of endoscopic biliary stenting in 1980, the palliative treatment of pancreaticobiliary malignancies has changed considerably. Nowadays, endoscopic stenting to relieve jaundice is well established and is considered the preferred treatment (Figure 2). Compared to percutaneous and surgical drainage it is associated with lower morbidity and mortality rates (22-24). The main problem of endoscopic biliary drainage is late stent occlusion which necessitates stent exchange. The technical success rate of endoscopic biliary drainage is between 70-90% and is higher for distal tumors compared to more proximal malignancies involving the bifurcation. The complication rate of therapeutic ERCP ranges between 5-10% (25,26).

INDICATIONS/CONTRAINDICATIONS

The indications for an ERCP with a drainage procedure by stent placement are jaundice and/or fever and/or pruritus. Biliary stenting has also been shown to improve symptoms of anorexia and quality of life (27,28). It has been suggested that preoperative biliary drainage may improve surgical outcome after pancreaticoduodenectomy. This however, has not been substantiated in clinical trials (29-31). If preoperative drainage is indicated because of cholangitis, drainage should be performed using plastic stents. In this setting metal expandable stents are too expensive and might cause technical problems for the surgeon during the resection. There are no absolute contraindications. Coagulation disorders are a relative contraindication and should be corrected before ERCP.

OVERVIEW OF STENTS FOR BILIARY DRAINAGE

Plastic Stents

The median patency of a conventional 10 Fr plastic stent ranges between 3-6 months. The incidence of stent occlusion varies between 20-50% (32-34). The initial event in stent blockage is adherence of proteins and bacteria to the inner wall of the stent and subsequent formation of a biofilm. Bacteria are introduced into the biliary system during transpapillary placement of the stent. Sludge then forms from the accumulation of bacteria which produce β-glucuronidase and form calcium bilirubinate and calcium palmitate (35-37). Many efforts have been made to prolong stent patency some of which are discussed in the following paragraphs.

Stent Diameter

The first biliary stents which were placed were only 7 Fr or 8 Fr in diameter due to limitations of the diameter of the working channel of the endoscope (2.8 mm). When side viewing endoscopes with large diameter working channels (4.2 mm) were introduced in 1980 it became possible to insert large bore plastic stents (38). Larger stents (10 Fr) perform better than smaller diameter stents (7 Fr) (39). This
appears to be due to the higher flow rate, as predicted by Poiseuille's law and less stasis with larger diameter stents. Theoretically, bile flow rate is proportional to the internal diameter raised to the fourth power, so even a small increase in diameter results in a substantial increase in flow capacity (40). Somewhat in contrast to this hypothesis, use of larger diameter plastic stents of 11.5 Fr or 12 Fr did not result in further improvement of stent patency (41-43).

**Stent Design**

The first biliary stents had a pigtail configuration at the proximal end to provide better anchorage. Straight stents were then developed because of their improved bile flow characteristics compared to pigtail stents (40,44,45) (Figure 3). Huibregtse developed the Amsterdam type stent: a straight design with two side holes to facilitate biliary drainage and two side flaps to prevent dislocation which has become the standard type stent design since 1980 (46).

Sludge in plastic stents mainly accumulates around side holes (35,47). This seems due to higher intraluminal flow turbulence and decreased flow rates (40). Soehendra postulated that elimination of side holes might improve patency rates and designed the so-called teflon Tannenbaum stent: a straight stent without side holes and multiple proximal and distal side flaps to prevent dislocation (48,49). First uncontrolled results were encouraging with patency rates comparable to metal stents but randomized trials could not confirm these initial results (50-52). Omitting side holes in standard designed polyethylene stent also did not show improvement in stent patency (53).

**Stent Material**

Different materials have been used for stent construction: polyethylene, polyurethane and teflon. In vitro studies have shown a direct relation between the coefficient of friction and the amount of encrusted material. Teflon has the lowest friction coefficient and therefore the best potential for preventing stent clogging (35). Initially, teflon Tannenbaum stents showed a favourable patency rate (48,49). A randomized study comparing Amsterdam type stents made from polyethylene and teflon did not show a difference in stent patency (54). Other controlled clinical trials could also not confirm the superiority of teflon material in a Tannenbaum designed stent (50-52).

Scanning electron microscopy of out-of-package biliary stents has shown that the inner surface smoothness of plastic stents is highly variable. This is possibly due to the manufacturing process of plastic stents by extrusion. Only the polyurethane stent was found to have an extremely smooth surface (53).

Two new polymers were introduced with an ultrasmooth surface: Vivathane and Hydromer. Both materials have been shown to reduce bacterial adherence in vitro (56,57). In addition, the Hydromer stent not only has a smooth texture but also a
coating that absorbs water and provides a hydrophilic sheath. Because bacteria initially attach by hydrophobic interactions, this coating could potentially lower bacterial adhesion and therefore increase stent patency. However, the encouraging results of in vitro studies could not be confirmed in prospective clinical trials (58,59).

**Stent Coating**

Priming the inner surface of a stent with a coating with some form of anti-adhesion property may reduce biofilm formation and hence stent clogging. Antibiotics, antitrombotics, silver and hydrophilic coating were all effective in reducing bacterial colonisation in vitro (57,60,61). Clinical studies however, using antibiotic-coated or hydrophilic-coated stents did not show any benefit (59).

**Stent Position**

Placing the stent entirely within the common bile duct has the theoretical advantage of preserving the barrier function of the sphincter of Oddi. This prevents duodenal reflux of food and bacteria into the stent and biliary tree. This so-called ‘inside stent’ approach can only be performed when a free margin of 1 to 2 cm is maintained between the distal end of the stricture and the papilla. With this in mind, about one third of patients with malignant obstructive jaundice are potential candidates for such treatment (62). However, in a randomized trial no difference in stent performance was found. In fact, in the ‘inside stent group’, stent migration occurred significantly more frequent (63).

**Antibiotics**

Bacteria can enter the bile duct through the portal circulation but more easily directly from the duodenum. When an endoprosthesis is placed, the barrier function of the sphincter of Oddi is lost and bacteria enter the biliary tract freely. Sludge may then form because these bacteria produce \( \beta \)-glucuronidase and form calcium bilirubinate and calcium palmitate. In order to prolong stent patency, prophylactic treatment with antibiotics seemed a logical step. _In vitro_ studies showed that antibiotic treatment reduced bacterial adherence to plastic stents (64). In a prospective randomized study with ciproxin no difference in stent patency was found (65). In another study rotating antibiotics (cycles of 2 weeks ampicillin, metronidazol and ciprofloxacin) were combined with ursodeoxycholic acid and no difference in stent patency was shown (66). Only one small pilot study showed a reduced rate of stent blockage with norfloxacain plus ursodeoxycholic acid (67). Other studies combining antibiotics and bile salts (ofloxacin and ursodeoxycholic, ciprofloxacin and Rowachol) did not show a longer duration of stent patency (68,69). In summary, at this point in time there is no compelling evidence that stent patency benefits from antibiotic prophylaxis.
Aspirin
Animal studies with prairie dogs have shown that aspirin inhibits mucous glycoprotein secretion by blocking prostaglandin synthesis (70). In a clinical study, the use of aspirin reduced the content of all sludge components although no effect on stent patency was shown (71). No further studies using aspirin have been performed.

Bile Salts
Bile salts have a potent antibacterial effect and may also stimulate bile flow. Because bacteria attach by hydrophobic interactions, hydrophobic bile salts (deoxycholate, taurodeoxycholate) inhibit initial bacterial attachment as was shown in experimental studies (72). However, hydrophobic bile salts are not well tolerated. Unfortunately, hydrophilic bile salts like ursodeoxycholate, which are better tolerated, have minimal effect on bacterial adhesion. Except for one small pilot study, different prospective clinical studies using ursodeoxycholic acid alone or combining ursodeoxycholic acid with antibiotics could not show a difference in stent patency (66-69).

Stent Exchange
Some endoscopists prefer to schedule patients for elective stent exchange every 3-4 months. The optimal time interval remains an unanswered question (73,74). Prophylactic stent exchange requires a repeat (clinically not indicated) endoscopy and has to be compared to the risks of watchful waiting and the risk of (severe) cholangitis. As the majority of patients will not develop stent occlusion before dieing of the underlying disease, most endoscopists favour an expectant management strategy.

Stent Cleaning
Some endoscopists have proposed to leave an occluded stent in situ and clean the obstructed lumen with a cytology brush or by flushing with saline instead of performing stent replacement (75). This however, carries the risk of inducing biliary sepsis by actively introducing the biofilm of the stent and bacteria from the duodenum into the biliary tract. Therefore, stent cleaning is not recommended.

Metal Expandable Stents
The diameter of biliary stents was restricted by the size of the instrumentation channel of the endoscope until the development of the expandable metal stents. All currently available expandable stents are made of metal. They differ in the way they are braided, the size of the meshes, the type of metal and their rigidity. Presently, many different types of self expandable metal stents are available from different manufacturers (Figure 4). There are two expansion types: self-expandable stents with an intrinsic expanding force and balloon expanding stents deployed by inflation of a balloon.
To date, the most experience has been gained with the self-expandable Wallstent. This stent is delivered in a collapsed configuration on an 8 Fr delivery system. When deployed it expands to a final diameter of 30 Fr (approximately 10 mm) and shortens about 30% in length. The final diameter will be achieved after one week, when an equilibrium is achieved between the dilating force of the stent and the resistance of the bile duct wall/tumor.

These large calibre metal expandable stents of 30 Fr provide a longer patency rate compared to plastic stents, but they do not prevent blockage indefinitely. Due to their design, these metal expandable stents have much less surface upon which bacteria may adhere. The mechanism of stent blockage differs from plastic stents and include tumor ingrowth through the interstices of the stent or overgrowth of the end of the stent and intima hyperplasia.

Several studies have shown a median stent patency of about 6-9 months (33,34,74,76,77) (Figure 5). Self-expandable stents are more difficult to insert, they cannot be removed after deployment and initial costs are high (about $1000). Various types of self expandable metal stents have been introduced, these are summarized below. Randomized trials with large groups of patients and long term follow-up are only available for the Wallstent.

**Wallstent®**

The initial endoscopic placement experience was reported in 1989 (78). Wallstents (Boston Scientific, Boston, MN, USA) are made from stainless steel alloy filaments braided in a tubular mesh configuration. In the early phase of development, technical problems were mainly the restraining membrane failing to completely retract but this is rarely seen nowadays (79). The first randomized trial comparing plastic stents and Wallstents was performed by Davids et al. Wallstent patency was superior to plastic stents with median duration of 9 months (33). These results have been confirmed in several other studies (34,74,80).

**Ultrajelx Diamond Stent®**

Compared to the Wallstent, this stent is more flexible, employs a larger mesh design, has less radial expandable force and is constructed from nitinol. The name of this stent relates to the appearance of its mesh pattern. Non randomized studies comparing the Ultrajelx Diamond stent (Boston Scientific, Boston, MA, USA) to the Wallstent suggested an equal or less durable patency (81,82). One prospective uncontrolled multicenter study showed a stent patency of the Diamond stent of almost 16 months, a result which has never been documented with any type of biliary stent (83). This exceptional outcome should be confirmed in a prospective randomized trial, preferably in comparison to the Wallstent.
**Endocoil Instent®**
This 'removable' self-expanding stent is made of a coil spring of nickel-titanium alloy that expands radially (Instent, Eden Prairie, MN, USA). It can only be used for distal stenosis because apposing coils prevent drainage of segmental ducts. Theoretically, the problem of tumor ingrowth should be prevented by the apposing coils. However, stent dysfunction by tumor ingrowth remains a problem and removal of the stent is not without risk (84,85). No long term follow-up or comparative data are available.

**Gianturco Z-Stent®**
The Gianturco Z-stent (Wilson Cook, Winston Salem, NC, USA) has wide gaps between the zigzag bands, with greater potential for tumor ingrowth. Advantages of this stent are the fact that it does not shorten upon expansion and has no sharp edges at the ends. The Gianturco Z-stent is the second most used expandable stent and it is mostly inserted via the percutaneous route. Patency rates are comparable to the Wallstent (86-89).

**Strecker Stent®**
This is a balloon expandable stent and there are only a few reported studies (90,91). Technical failures occur in up to 27%. The main disadvantage of this stent is its diameter of only 21 Fr and the absence of an intrinsic radial force (34,92). These unfavourable features have prohibited the general use of the Strecker stent (Boston Scientific, Boston, MA, USA). This stent is not commercially available any more.

**Covered Self Expandable Stent**
Tissue ingrowth through the meshes of the stent is responsible for stent occlusion in about 22-33% of patients (33,34). To overcome this problem, self-expanding metal stents have been covered with a polyurethane or silicone membrane, except for the proximal and distal 5 mm. Results of various stents (M.I. Tech Corporation, Seoul, South Korea; Wilson Cook, Winston Salem, NC, USA; Boston Scientific, Boston, MA, USA) in various studies are contradictory (92-94). Major concerns are the risk of stent migration, cholecystitis and pancreatitis, although these complications have not been reported with any significant frequency. Furthermore, these stent should not be used intrahepatically because of occlusion of hepatic side branches by the covering membrane. The exact role of covered self expandable stent is still under investigation.

**Plastic or Metal Stent?**
Self expandable metal stents have a longer duration of patency compared to plastic stents and ideally should be placed in all patients. The high initial costs have limited their use in different health care settings worldwide.
Therefore in a cost effective approach the choice between a plastic or metal stent depends mainly on an estimate of patient survival. Tumor size seems a reliable predictor of survival. Prat et al. claim that in the case of a tumor greater than 30 mm a polyethylene stent should be placed because of shorter expected survival (95). The presence and number of liver metastases have also been shown to be independently related to prognosis (96,97). Comparative studies did not show any benefit of self expandable metal stents compared to polyethylene stents in the first three months after insertion (33,74). Therefore, it seems reasonable to insert a polyethylene stent in patients with a life expectancy less than 3 months (Figure 6). If expected survival extends 3 to 6 months an expandable metal stents should be considered (Figure 7). Different authors have shown this strategy as cost-effective (33,98,99). Patients who present with early clogging of a polyethylene stent (within one month after insertion) should also receive a self expandable stent, irrespective of their life expectancy although this has not been proven in prospective studies (100).

**PROCEDURE OF STENT PLACEMENT**

**Sedation**

ERCP is usually performed under conscious sedation. This is achieved with intravenous administration of diazepam or midazolam. Fentanyl or pethidine may be used for control of pain. For reasons of safety, oxygen saturation is monitored by pulse oximetry and heart rate and blood pressure are also registered. In some centers more sophisticated sedating agents are used such as propofol. In most cases the use of propofol is supervised by an anaesthesiologist although recently some reports suggest that its use by a non-specialist anaesthesiologist such as endoscopists or nursing staff is safe (101). Prior to sedation the pharynx is anesthetized with xylocaine spray.

**Antibiotics**

Drainage of the biliary tree is the mainstay of therapy for patients with cholangitis. There is controversy about routine use of pre-procedure antibiotic prophylaxis (102-104).

Pre-operative administration of antibiotics should definitively be started in a patient with fever. Since failure to drain the entire biliary tree is the most important risk factor associated with cholangitis after ERCP, antibiotic prophylaxis should also be administered in a highly selective group of patients in whom incomplete drainage is anticipated such as patients with a hilar malignancy or primary sclerosing cholangitis (105,106). Prophylaxis can be given as a single, adequate dose shortly before the procedure. If contrast is injected in the biliary tract but obstruction cannot be relieved, antibiotic therapy should be continued (or started) until drainage is established. Gram negative bacteria are consistently the most common organisms in bile: Escherichia coli and to a lesser extent Klebsiella spp. and gram positive Enterococcus spp. Therefore antibiotics in these cases should be bactericidal, aimed at gram-neg-
ative bacteria, with good penetration in liver tissue and bile. Ciprofloxacin is currently the first choice of antibiotic in our unit with the caveat that is does not cover Enterococci. In case of fever despite ciprofloxacin, the addition of amoxicillin or switch to piperacillin/tazobactam is advisable.

**TECHNIQUE OF STENT PLACEMENT**

The procedure starts with the introduction of a large channel (4.2 mm) side viewing therapeutic endoscope into the second portion of the duodenum. Standard cannulation of the papilla of Vater is performed by a ball-tip or cone-tip catheter; eventually cannulation can be attempted with a guidewire inserted in the ball-tip catheter. If this approach fails, a double lumen sphincterotome with a guide wire (cannulotome) should be used. Use of this device may aid in achieving an optimal angle for bile duct cannulation. When this is also not successful a precut sphincterotomy is performed to obtain biliary access (107). With the use of all these different techniques, deep cannulation is achieved in up to 95% of patients.

Once a diagnostic cathether is inserted into the bile duct, contrast is injected. It is essential to define the exact anatomy, location and nature of the stenosis. To avoid post procedural cholangitis in patients with complex hilar strictures, contrast filling of segments that will not be drained should be avoided. The next step is to pass a guidewire through the stricture in order to facilitate introduction of the catheter and enable exchange for other instruments. When passage of a guidewire through the stricture cannot be accomplished, the direction of the guidewire can be changed by manipulating its position with movements of the endoscope similar to those made for standard cannulation. The assistant can help to cross the stricture by moving the guidewire in and out the catheter. The endoscopist can manipulate the guidewire by moving the guiding catheter.

A variety of guidewires are available with different flexibility, diameter and shape of the tip. On the one hand, rigid guidewires facilitate introduction of instruments (such as an IDUS probe) and small diameter stents. On the other hand, very slippery guidewires with a hydropolymer coating which follows bends easily and are used to pass asymmetric strictures. Once the guidewire is passed through the stricture a catheter can be advanced and more complete filling can be obtained.

A sphincterotomy is not routinely necessary for introduction of one biliary stent. Previously it was believed that a sphincterotomy was necessary to facilitate introduction of different devices and also to avoid occlusion of the pancreatic duct by the endoprosthesis. In clinical practice however, this did not prove to be a problem. Only in cases when more then one prosthesis is placed, a sphincterotomy is indicated.

**Plastic Stents**

Once the stricture is passed with a guidewire a stent can usually be inserted. First, a catheter is introduced over the guidewire through the stricture to ensure a more rigid introductory system in order to facilitate stent placement. If appropriate the
guidewire can be exchanged for a cytology brush to obtain tissue samples.

The endoprosthesis is positioned over the guiding catheter and inserted into the instrumentation channel. With a pusher tube the stent is further advanced towards the tip of the endoscope with the elevator bridge closed. When the prosthesis reaches the tip of the instrumentation channel, the elevator bridge is opened and the stent is pushed out of the endoscope by the pusher tube under endoscopic and fluoroscopic control. During further advancement of the stent it is important to keep the endoscope tip close to the papilla. The stent should be advanced one step at a time by pushing it a little bit further each time into the duodenum. The stent is raised by closing the elevator bridge, and the tip of the endoscope is moved closer to the papilla with the up-down knob hereby introducing the stent. These steps are repeated until the distal side flap has reached the papilla. Finally, the assistant pulls out the catheter and guidewire while the endoscopist keeps the prosthesis in position with the pusher tube.

In most distal and mid common bile duct strictures it is usually possible to insert a 10 Fr endoprosthesis without prior dilatation. In proximal strictures however, it is not rare that strictures have to be dilated in order to allow stent placement. This can be achieved with the use of progressive dilating catheters which are introduced over a rigid guidewire. Balloon catheters can be used as well to accomplish this goal. If it is still not possible to insert a 10 Fr stent, a smaller calibre prosthesis (7 Fr) should be inserted which can be exchanged for a 10 Fr prosthesis a few days later. When both right and left liver lobes have to be drained it is usually more convenient to place the endoprosthesis draining the left side first, followed by the right side.

The required length of the endoprosthesis can be measured by using guidewire as a measuring device. First, under fluoroscopic control the proximal tip of the guidewire is positioned at the level where the proximal tip of the endoprosthesis is projected. Then, the endoscopy nurse fixes the guidewire between finger and thumb just where it exits the catheter. Subsequently, under fluoroscopic control the guidewire is withdrawn from the catheter until the proximal tip reaches the duodenum. The distance between finger and thumb and the distal margin of the catheter is the required length of the endoprosthesis.

Plastic stents are available various widths (ranging from 5 to 12 Fr) and lengths (ranging from 5 to 19 cm).

**Management of Plastic Stent Occlusion**

A clogged plastic stent can be removed by means of a snare or dormia basket. It is important to keep the position of the endoscope in line with the common bile duct. When a snare is used, the stent is caught in the snare and removed through the instrumentation channel of the endoscope. When a dormia is used, the stent is pulled close to the endoscope and both the endoscope and stent are withdrawn.

When massive tumor invasion is present in the duodenum and difficult stent
exchange is anticipated because of a non-optimal scope position, it can be helpful to leave the occluded stent in place and use it as a guidance for common bile duct cannulation and introduction of a second stent.

Soehendra described a technique which enables removing a clogged stent while maintaining the original pathway to the bile duct (108). A ball tip catheter is positioned at the distal end of the stent and the stent is cannulated with the guidewire. A Soehendra retriever is introduced over the guidewire and the tip is screwed into the distal end of the stent. Then the retriever with along the stent is pulled out while leaving the guidewire in place.

Self Expandable Stents
For introduction of a self-expandable stent a stiff guidewire is positioned through the stricture by standard techniques. The insertion device with the constrained stent is then inserted through the instrumentation channel over the guidewire. When the insertion device is in position with the help of radio-opaque markers, the prosthesis can be released by removing the outer catheter while keeping the inner catheter in place. Deployment follows gradually as the outer catheter is withdrawn and can be followed fluoroscopically. If deployment is not according to plan and repositioning is required, the expandable stent may be constrained again by pushing the outer catheter inwards whenever the point of no return has not yet been passed. This point may vary with stent type but may extent to 83% of total stent deployment and is indicated by a marker. Deployment reduces the length of the self expandable metal Wallstent by about 30%. Therefore, it is important to constantly correct the position of the expandable stent under fluoroscopic control which usually means that one has to pull the insertion device outwards while deploying the stent.

When the expandable metal stent bridges the papilla in the case of a distal stenosis, the endoscopic image is used to keep a fixed distance of about 1 cm between the papillary orifice and the distal margin of the stent.
Stent diameter expands to 8-10 mm and the available deployed lengths are 40, 60, 80 and 100 mm.

In case of a complex hilar stricture when both liver lobes are drained by two or more self expandable endoprostheses the procedure is as follows (109). The procedure begins with the introduction of two stiff guidewires, one in each liver lobe. If appropriate, dilation of a stricture is performed over one of the guidewires. Then, a expandable metal stent is inserted over the guidewire into the left system and deployed. Finally, an expandable metal stent is inserted into the right system alongside the first stent and deployed under fluoroscopic control (Figure 8).

Although technically difficult, it is also possible to insert a second self expandable stent through the meshes of a former placed self expandable stent (110). In that case a guidewire is introduced and the mesh is dilated using a balloon catheter before passing the second constrained stent and deploying it.
Management of Self Expandable Stent Metal Occlusion
Self expandable stents can be removed within the first 2 to 3 days after deployment by grasping it with forceps or a snare. After this time, the stent becomes embedded in the tumor tissue and cannot be extracted. Stent obstruction is mainly due to tumor ingrowth through the interstices of the stent or overgrowth of the ends of the stent. Management of stent occlusion consists of placement of a polyethylene stent or a second self-expandable stent through the occluded self-expandable stent. Another strategy is mechanical cleaning by using a balloon and flushing, but this is only effective in case of sludge formation.

INTRAHEPATIC BILIARY OBSTRUCTION
Strictures at the level of the hepatic confluence account for about 20% of malignant bile duct obstruction and mainly consist of primary cholangiocarcinoma, gallbladder neoplasms and metastatic spread to hilar nodes. Cholangiocarcinoma arising at the hilar level is also referred to as a Klatskin tumor and is classified according to the degree of involvement of the intrahepatic bile ducts (111) (Figure 9). Stenting the proximal biliary tree is more challenging and associated with lower success rates than stenting distal common bile duct stenosis. Drainage can be achieved either endoscopically (retrograde) or percutaneously (antegrade). Procedure induced cholangitis caused by contrast injection in undrained biliary branches is the main complication and occurs in up to 30% (112-114). The current management strategy (depending on local services available) is first to attempt endoscopic drainage; when this strategy is not successful percutaneous drainage offers additional opportunities (115,116). When internal drainage fails, an external drain can be left in situ minimizing the risk of cholangitis.

Uni- or Bilateral Drainage?
There is controversy whether to drain one or both liver lobes in Bismuth type II, III and IV strictures. In Bismuth type I, one stent always suffices because the left and right ducts communicate and drainage will be complete. Theoretically, at least 25% of the liver volume must be drained to achieve biochemical improvement and relief of symptoms (117). Concerns about unilateral drainage include the inability to relief jaundice, as well as the potential for bacterial contamination in the undrained lobe. Indeed, the worst treatment results seem to be obtained in patients with cholangiographic opification of both lobes but drainage of only one (118). Recently, a prospective randomized trial compared unilateral to bilateral hepatic duct drainage (119). Unilateral drainage was associated with a significantly higher rate of successful endoscopic stent insertion. Bilateral stent placement was associated with a significantly higher rate of complications because of the higher rate of early cholangitis. In per-protocol analysis the rate of successful drainage, complications, and mortality did not differ between the two groups. MRCP-guided endoscopic stent placement in
Bismuth III and IV malignancies was associated with a low morbidity and mortality in an uncontrolled study (120). The intention was to place an unilateral stent in one of both lobes guided by the MRCP picture avoiding entry and contrast injection in the contralateral lobe. In those patients in whom, by accident, guidewire entry (50%) or contrast injection (20%) occurred in the contralateral liver lobe, stents were placed bilaterally. This treatment strategy resulted in a very low cholangitis rate of only 6%. A recent study evaluated selective unilateral MRCP or CT-targeted drainage and no episodes of cholangitis were observed (121). The message seems to emerge that unilateral drainage is appropriate when unilateral cannulation and opacification has been achieved. If the contralateral lobe is (unintentionally) opacified or probed, it should also be drained to avoid cholangitis.

**Plastic or Self Expandable Metal Stent?**

By design, expandable stents may be more suitable than plastic stents for draining hilar tumors. The stent lumen is much wider and more importantly intrahepatic side branches can drain through the metal meshes. Indeed, self expandable stents which were inserted via the percutaneous route, showed a higher treatment efficacy compared to plastic stents (115,122). There are no randomized studies available comparing endoscopic and percutaneous insertions of self expandable metal stents in hilar strictures. Additional proof of the superiority of self expandable stents over plastic stents is suggested from a retrospective series of patients with non resectable hilar cholangiocarcinoma by whom during stent treatment, plastic stents were replaced by metal expandable stents(123). Successful palliation without the need for further biliary reintervention was achieved in the majority of patients (69%). A potential drawback of the placement of a metal stent is that, in the case of treatment failure, introduction of additional stents may become difficult. However, a technique of introducing a second stent through the wire mesh of the first stent has been described (110).

**DUODENAL STENOSIS**

Duodenal stenosis due to pancreaticobiliary malignancies occurs in 10-20% of patients (124). Presenting symptoms include nausea and vomiting due to gastric outlet obstruction. Usually this is a late event and occurs in patients in poor general condition who have already received a biliary endoprosthesis (125). Surgical bypass has a significant procedure related mortality of up to 10% as well as related morbidity and prolonged hospital stay (24,126,127). Endoscopic stenting for duodenal obstruction together with bile duct stenting may be an effective alternative. Placement of duodenal stents has a high technical success rate without major procedure related complications (128-130). Stenting is carried out under simultaneous endoscopic and fluoroscopic control. Preliminary dilatation of the duodenal stenosis can be performed by balloon dilatation if necessary. Patients are usually able to tolerate a liquid diet immediately after stent placement. Full stent deployment may take a few days during which time soft foods are allowed.
One study reported about simultaneous decompression of biliary and duodenal obstruction with similar success rates as to duodenal stenting alone (131). Because of the difficulty to endoscopically access the biliary tree through the mesh wall of a duodenal stent, preferably an expandable metal biliary stent should be placed before the duodenal stent is introduced (Figure 10). If endoscopic biliary stenting fails the remaining treatment options are percutaneous stenting, combined percutaneous and endoscopic management or surgical bypass.

**POSTPROCEDURAL CARE**

General measures after conscious sedation include observation in a day care unit for several hours with monitoring of blood pressure and oxygen saturation.

When a patient develops fever post-ERCP, efforts should be made to obtain specimens for culture and administration of antibiotics should be started. If fever does not subside, the accuracy of biliary drainage should be reassessed and migration and early stent occlusion should be excluded. In the case of a complex malignant hilar stricture it is important to check for undrained dilated intrahepatic segments and rule out abscesses by transabdominal ultrasound or CT. Depending on the findings, ERCP should be reattempted or percutaneous drainage achieved.

**COMPLICATIONS**

**Early Complications**

Early complications are defined as those which occur less than 1 week after the conclusion of the procedure. The complications range between 5 and 10% for therapeutic ERCP with a mortality rate of up to 1% (25,26,132). Cotton introduced a complication grading system in which complications are graded in mild, moderate and severe and these guidelines are still widely used (25).

The most frequent early complication is cholangitis, probably due to introduction of bacteria into the biliary tract during the procedure. This is reported in approximately 10-15% of patients in most series. It occurs more often following endoscopic procedures for complex hilar strictures when incomplete drainage is achieved. The same holds true for patients with primary sclerosing cholangitis. In these 'high risk' procedures antibiotics should be administered prophylactically and continued for a few days after the procedure.

Post ERCP-pancreatitis occurs in about 5-7% of patients. It is defined as new onset or increased abdominal pain, lasting at least 24 hours after ERCP, with associated elevation in serum amylase or lipase of at least 3-5 fold above normal (25,26,133). Most cases are mild, self-limited, and only require intravenous fluids and gut rest. Serious cases may evolve into (infected) necrotizing pancreatitis with multi organ failure.

The rate of post sphincterotomy bleeding is about 0.2-5% with an associated mortality rate less than 1% (134). Bleeding is usually obvious immediately after sphinctero-
tomography but can be delayed for hours or even several days. Most episodes of delayed bleeding are managed successfully by conservative measures and blood transfusions if the haemoglobin level drops significantly. Post sphincterotomy bleeding usually occurs at the apex of the sphincterotomy site and can be managed endoscopically with injection of adrenaline.

Retroperitoneal perforation occurs in less than 1% in most series. It may be caused by standard sphincterotomy, precut sphincterotomy or by guide wire manipulation. Most cases are diagnosed or suspected during ERCP. These perforations mostly heal with conservative measures and usually do not result in clinical symptoms (135). Conservative treatment measures consist of nil by mouth, antibiotic treatment and nasogastric suction. It is estimated that about 20-30% of these patients will require surgery.

In cases of peritoneal perforation caused by the duodenoscope, prompt exploratory laparotomy, with repair or oversewing of the defect in the duodenal wall, is mandatory (136).

Late Complications
The primary late complication of stent placement is occlusion of the endoprosthesis, occurring in up to 50% of cases (33,34). Clinically these patients present with a flu-like syndrome with cholestasis, frank cholangitis or jaundice. Treatment consists of exchange of the occluded stent or, in case of an occluded self expanding metal stent, insertion of a polyethylene stent or second self expandable stent (see management of plastic stent occlusion and management of self expandable metal stent occlusion) through the obstructed expandable stent. Plastic stent migration, either proximally or distally, may occur in up to 10% of cases (137).

FUTURE TRENDS

PHOTODYNAMIC THERAPY
Photodynamic therapy (PDT) involves the administration of a photosensitizer which is activated with a laser light and causes necrosis of the exposed tissue. Preliminary results suggest prolonged survival and stent patency for PDT in cholangiocarcinoma at the hilum (138-140). Controlled trials are in progress. PDT cannot be combined with uncovered expandable stents, since PDT generates necrotic tumor tissue, which sloughs into and occludes the lumen (141). However, replacement of plastic stent by a self-expandable stent one month after PDT could be promising (138).

DRUG COATED BILIARY STENTS
Future prospects include development of chemotherapy impregnated expandable stents. Covering biliary stents with chemotherapeutic agents, delivering chemother-
apy directly to the tumor tissue, at least in theory, should give protection against tumor ingrowth, overgrowth, or both. For optimal therapeutic effects these drugs should be released over a longer period of time with good penetration in tissue and without systemic toxicity.

Carboplatin and paclitaxel have shown to inhibit cell proliferation in *in vitro* studies (142,143). Carboplatin coated plastic stents have been used with promising preliminary results in a limited number of patients (143). Further controlled trials are warranted.

**EUS GUIDED PLEXUS NEUROLYSIS**

Celiac plexus neurolysis can improve pain control in patients with pancreatic cancer. The injected agent usually includes a local anaesthetic (bupivacaine or lidocaine) and a neurolytic (phenol or alcohol). A meta-analysis showed long-lasting benefit for 70-90% of patients and adverse effects were common but generally transient and mild (144). For best results it is recommended to perform celiac plexus neurolysis not too late in the course of the disease when pain becomes unbearable. This may be explained by central effects of chronic pain leading to hypersensitization and unresponsiveness to anti pain treatments. EUS may reduce neurological complications (because of the anterior approach) compared to the percutaneous technique although no comparative studies have been performed (145). Side effects of celiac plexus neurolysis are usually mild and include postprocedural pain and transient diarrhoea.
Figure 1. Algorithm of diagnosis of pancreaticobiliary cancer.

Figure 2. Stenosis of both common bile duct and pancreatic duct, also called a double duct sign (A), caused by a pancreatic adenocarcinoma and a 10 Fr 9 cm plastic endoprosthesis inserted through a distal bile duct sticture (B).
Figure 3. Different types of plastic endoprosthesis (from top downwards): a double pigtail stent, an Amsterdam type stent (one side hole and one side flap at each end) and a Tannenbaum type stent (without side holes and multiple side flaps at each end).

Figure 4. Different types of self expanding metal stents (from top downwards): Wallstent (Boston Scientific, Boston, MA, USA), Gianturco Z-stent (Wilson Cook, Winston Salem, NC, USA), Hanaro stent and covered Hanaro stent (M.I. Tech Corporation, Seoul, South Korea).
**Table:**

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* Mean

PE: polyethylene stent, SEMS: selfexpandable metal stent

**Figure 5.** Results of trials comparing self expandable stents with plastic stents.

**Figure 6.** Mid common bile duct stricture caused by gallbladder carcinoma (A) with an 11 cm 10 Fr plastic endoprosthesis inserted (B).
Figure 7. Distal common bile duct stricture caused by a pancreatic adenocarcinoma (A) with a self-expandable metal stent inserted (B).
Figure 8.
A. Klatskin type II tumor (irresectable because of vascular involvement)
B. Guidewires inserted to both the left and right biliary system.
C. A self expandable metal stent has been inserted into the left system and deployed.
D. Two sided self expandable metal stent drainage.
**Figure 9.** Bismuth classification:

- **I** Stricture involving the common hepatic duct
- **II** Stricture involving both right and left hepatic ducts
- **III A** Stricture extending proximally to the right secondary intrahepatic ducts
- **III B** Stricture extending proximally to the left secondary intrahepatic ducts
- **IV** Stricture involving secondary intrahepatic ducts bilaterally

**Figure 10.** Pancreatic adenocarcinoma growing into the duodenum with a self expandable metal stent (not yet fully deployed) in the biliary tract and a self expandable metal stent in the duodenum.
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