ANNALS OF GASTROENTEROLOGY 2000, 13(3):217-220

Special topic by C. Dervenis

Endoscopic Palliation for Unresectable Adenocarcinoma of the Pancreas

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INTRODUCTION

Pancreatic cancer is the fourth and the fifth most common cancer in men and women respectively and has the lowest 5-year survival rate of any cancer.[1,2] The dismal prognosis of patients with pancreatic cancer is mainly due to the late diagnosis and, consequently, the low curative resection rates. While curative resection offers the only chance for long- term survival, 85-90% of the patients are staged as unresectable at the time of the diagnosis. Of the minority of patients undergoing surgical exploration with curative intent, up to 25% are found to be unresectable in the operating room.[3,4]

The patient with unresectable pancreatic cancer has a limited life expectancy (<12 months), often complicated by obstructive jaundice, duodenal obstruction and pain. In these patients palliation of symptoms is the only relief which can be offered. Optimal palliation will relieve the symptoms of the disease, improve the quality and maybe, marginally prolong life expectancy.

PALLIATION OF JAUNDICE

Obstructive jaundice due to extrahepatic bile duct compression and/or infiltration is the commonest symptom of patients with pancreatic carcinoma and is the commonest presenting symptom in approximately 70% of cases at the time of diagnosis.

In patients with unresectable pancreatic tumour the choice of palliation is between endoscopic stent placement or a surgical by pass procedure. Percutaneous transhepatic management is inferior to endoscopic approach for billiary drainage because of complications associated with liver puncture, particularly bleeding and bile leakage. It is applied as an alternative method if endoscopic approach fails or as complimentary to endoscopy for a rendez-vous procedure.[5]

If the tumour is proven unresectable in what is preoperatively considered a radical operation, it is reasonable for the surgeon to palliate jaundice by performing a biliary bypass, with or without a prophylactic gastroenteroanastomosis.

In patients with high operative risk due to severe concurrent diseases, endoscopic palliation with stent insertion is definitely the treatment of choice.

For the rest of the patients, comprising the majority of cases with pancreatic cancer, the choice as to the optimal non-operative palliation is usually not clear-cut.

There are only a few prospective randomized controlled studies comparing endoscopic stenting with surgical bypass.[6-11] None of them used metallic expandable stents and the size of plastic stents used varied in the different studies. All of these studies have shown that while both techniques have an equally high technical and therapeutic success rate, endoscopic stenting has lower early morbidity and mortality rates which, on the other hand, are counterbalanced by the higher rate of late complications.

In one of the largest randomized prospective studies[6] using only 10 Fr plastic stents, technical success approached 98% for surgical and 97% for endoscopic (stenting) palliation with effective functional biliary decompression in about 90% of the patients in both groups. However, in stented patients, there was a lower proce-

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dure-related mortality rate (3% versus 14%, p=0,01) and a major complication rate of 11% versus 29%, (p=0,02) with a median hospital stay of 20 days versus 26 days (p=0,001). Recurrence of jaundice was noticed in 39% of the patients after a median time interval of 4.4 months (due to stent blockage), while in the surgical group, only 2% of the patients experienced recurrent extrahepatic common bile duct obstruction with jaundice. Late gastric outlet obstruction occurred in 17% of the stented patients but only in 7% of those treated surgically. Despite the early benefits of stenting, there was no significant difference in overall survival between the two groups (median survival 26 weeks for the operated and 21 weeks for the stented patients).

In other words, endoscopic stent insertion offers effective biliary patency with lower complication rate than open surgery, but at a cost of an increased incidence of late obstruction, which is undesirable in a terminally ill patient.

A stent that would remain patent and functional for the rest of a patient's life would fulfill the criteria of optimum palliation for inoperable patients with pancreatic cancer, but to date such an "ideal" stent is not available.

Multiple studies from many endoscopy centres have identified the principles which rule the function of newer, high quality stents and describe the strategies to prolong stent patency. The sequence of plastic stent occlusion begins with the intraluminar coating of the stent by deposition of host proteins, which promote bacterial attachment, followed by bacterial production of glucoproteins, which lead to biofilm formation consisting of bacteria and bacterial by-products and subsequently to sludge formation that inevitably leads to stent occlusion.[12,13] Stents of larger diameter have longer patency rate because it takes longer for this process to obstruct the lumen. On the other hand, duodenoscope design limits the maximal stent diameter to about 12 Fr, but even these larger stents occlude at a median time interval of 3 to 6 months.[6,14,15] Ten Fr stents clearly have a patency advantage over smaller stents,[16,17] but further increase in stent diameter does not appear to offer a significant advantage.[18,19]

Although in vitro experiments have shown that stents without side holes or those made from materials with a low coefficient of friction (such as Teflon or with a hydrophyllic coating) clog more slowly, this was not proven in clinical trials.[20-23] Oral use of ursodeoxycholic acid plus broad spectrum antibiotics were found to be beneficial in prolonging stent patency but this was reported in only one study and needs further confirmation.[24]

In search of a more effective approach to overcome the continuing problem of plastic stent occlusion, self-expandable metal stents have been developed. These stents are made of steel or nitinol and come in a compressed and sheathed form so that they can pass through the working channel of the endoscope and, after insertion in the bile duct, they expand to a diameter of up to 10mm (32Fr). Comparative studies between metallic and plastic stents clearly show the superiority of metal stents, in terms of both more effective bile duct drainage and lower stent occlusion rate with subsequent longer patency, thus limiting the need for repeated endoscopic procedures. A relative disadvantage of these stents is their high initial cost (about tenfold that of plastic ones).[25-29] They remain patent about twice as long as conventional plastic stents and they occlude at an average of 8 to 12 months. They become obstructed mainly either by tumour ingrowth through the meshes of the stent or tumour overgrowth at either end, while sludge-related occlusion is relatively rare. In these cases, since metallic stents cannot be extracted, recanalization can be achieved with the insertion of either a plastic or a second metallic stent through the lumen of the occluded stent. In order to overcome the above mentioned mechanisms of metallic stent occlusion, membrane-covered stents have been developed, but they can still become occluded due to either tumour ingrowth at the level of the partially coated ends or to sludge encrustation as in the plastic stents.[30,31] The problem with the coated stents is that they tend to migrate, which in a way cancels out their advantage over occlusion. Whereas uncovered metallic endoprostheses cannot be extracted, it is possible to remove an occluded coated stent.

Despite the significant patency advantages of metal stents no clear increase in patient survival has been proven in relevant studies.[28,32]

At present, self-expandable metallic stents are an excellent palliation choice in patients with a definite diagnosis of pancreatic cancer, staged as unresectable but with a life expectancy of more than 6 months.[26,33]

In the rest of the patients the use of a plastic stent with prophylactic stent exchange every three months seems to be preferable to stent exchange after symptomatic occlusion.[28] If the patient has a good performance status and a low tumour burden about 3 months following initial plastic stent insertion, exchange with a metallic stent is a reasonable approach.

PANCREATIC PAIN

Pain in end–stage pancreatic carcinoma patients may be the most intractable and incapacitating symptom. The main causes are considered to be neoplastic infiltration of the local nervous bed and obstruction of the main pancreatic duct with secondary upstream ductal hypertension.[34] Endoscopic pancreatic stenting has proven beneficial for relief of pain in patients who suffer from postprandial pain because of neoplastic obstruction of the main pancreatic duct.[35,36] Pancreatic stenting is a very demanding endoscopic procedure because of the angulation and the narrowing of the duct proximally to the stricture. The largest inserted stents are plastic stents sized 5 to 7 Fr. Bile and pancreatic drainage can be carried out during the same ERCP session, following biliary sphincterotomy with the pancreatic stent being placed first. This technique has been reported to be helpful in selected patients with "obstructive" pain, but it needs further evaluation with larger randomized trials.

DUODENAL OBSTRUCTION

Duodenal obstruction due to infiltration from pancreatic carcinoma is usually a terminal event occurring in about 5-9% of the patients.[37] Obstructive symptoms, including nausea, vomiting and abdominal distension may be devastating, leading to considerable deterioration of patient's quality of life. Surgical gastroenterostomy is the preferred palliation for these patients. However, in terminally ill patients and those with a very limited life expectancy, the operative procedure is probably not the treatment of choice. There is increasing evidence suggesting that in these patients palliation of duodenal obstruction can be achieved by endoscopic placement of an uncoated self- expandable metallic stent, in order to establish lumen patency.[38,39] These stents have a large diameter of 18,20 or 22 mm and a length of 60 to 90 mm when fully expanded, but their effectiveness is somehow limited by occlusion, mainly because of external compression or infiltration from the tumour. Covered enteric stents are not yet available in the market. A relative disadvantage of enteric stents is that, after placed, they preempt access to the biliary tract. In a patient with duodenal infiltration who needs biliary stent exchange, balloon dilatation of the duodenal lumen may offer an alternative palliative approach, allowing access for stent replacement or exchange. However, the dilatation effect is usually quite temporary compared with that of enteric stenting.

In conclusion, endoscopy can offer a variety of palliative options in patients with unresectable pancreatic cancer, but further technical improvements are required to solve the problem of long-term stent occlusion. Expandable metallic stents have already been proven to have a significant patency advantage over plastic stents and their use is expanding in relieving obstruction of both the biliary tree and duodenal lumen. The management of such patients is a complicated one and is better judged by a multidisciplinary team approach including expert endoscopists, surgeons, oncologists and radiologists.

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