



Palliative therapy in pancreatic cancer—palliative surgery

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Abstract: Pancreatic cancer is a highly lethal disease with a dismal prognosis. It will probably become the second leading cause of cancer-related death within the next decade in Western countries. Over 80% of patients undergo palliative treatment for unresectable pancreatic cancer due to locally advanced disease or metastases. Those patients often develop gastric outlet obstruction (GOO), obstructive jaundice and pain during the course of their disease. Symptoms such as vomiting, anorexia, pruritus and jaundice will impact the quality of life (QOL) and could delay the administration of the chemotherapy. Palliative therapy in pancreatic cancer aims to relieve the symptoms durably and to improve the QOL. Palliative surgery was traditionally considered as a gold standard with the “double by-pass” including biliary-digestive and gastro-jejunal anastomosis. However, since the development of endoscopic stenting and minimally invasive surgery, the choice of the best modalities remains debated. While there is still a place for surgical gastrojejunostomy (GJ) in case of duodenal or GOO, endoscopic biliary stenting during endoscopic retrograde cholangiopancreatography (ERCP) is now accepted as the gold standard in case of obstructive jaundice. In pain management, endoscopic ultrasound guided or percutaneous celiac plexus neurolysis is recommended. The selection of the best technique should consider the effectiveness and the morbidity of the treatment, the performance status of the patient and the disease stage. While endoscopic stenting is associated with earlier recovery and shorter length of stay, recurrence of symptoms and reintervention are less frequent after palliative surgery. Finally, controversy exists on whether to perform prophylactic palliative surgery in the absence of symptoms when unresectable disease is discovered during surgical exploration.

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Pancreatic cancer is still associated with poor prognosis. Median survival rates are approximately 22 to 26 months after curative surgery followed by adjuvant treatment (1-3), and 11 to 15 months in patients who receive treatment with chemoradiation (4-7). Surgery remains the only chance for potential cure. However, at the time of diagnosis, 50% of the patient had concomitant metastases, up to 25% had locally advanced disease and only 15–20% of the remaining patients are eligible for potentially curative resection (8). Indeed, at diagnosis, up to 80% of patients are unresectable

due to locally advanced disease or metastases and will undergo palliative treatment. Historically, palliative surgery with the “double by-pass” was the standard treatment for unresectable pancreatic cancer. However, since the 1990s, endoscopic approach was developed with good results.

Palliative care is defined by the World Health Organization (WHO) as “The total active care of patients whose disease is not responsive to curative treatment. Control of pain, other symptoms, and psychological, social, and spiritual problems, is paramount. The goal of palliative

care is achievement of the best quality of life (QOL) for patients and their families” (9). The most frequent complications in patients with unresectable pancreatic cancer are: duodenal or gastric outlet obstruction (GOO), obstructive jaundice, and pain due to invasion of the celiac plexus. Palliative care should be started as soon as possible to provide durable symptom relief and to improve the QOL. Palliative open surgery was historically the standard to treat duodenal and biliary complications. Meanwhile minimally invasive procedure and endoscopic stenting have been introduced as alternatives. The choice between the different modalities should consider the balance between their effectiveness and their morbidity or mortality. The “palliative care triangle” approach is also very useful to involve the patient’s and the family’s concerns in the choice of the best palliative treatment (10).

Treatment of GOO

Approximately 10% to 25% of patients with pancreatic cancer will develop malignant duodenal or GOO in the course of the disease (11). Nausea and vomiting are the predominant symptoms. Over time, dehydration and significant weight loss with malnutrition will occur. In the majority of patients, GOO will impaired the QOL and could result in a significant delay in the treatment of cancer (12,13). The aim of the palliative treatment is to re-establish oral feeding by restoring gastrointestinal continuity and to improve the QOL. Traditionally, GOO is treated surgically with an open gastrojejunostomy (GJ). It is associated with good functional outcomes. However, the morbidity remains significant. Endoscopic placement of a duodenal stent has been suggested to be less invasive than surgery with faster relief of symptoms. More recently, minimally invasive procedures with laparoscopic GJ have been also introduced. To date, there is actually no gold standard.

Historically, GOO is treated with an open GJ through an upper midline incision. A side-to-side anastomosis is performed between the posterior surface of the stomach and the small bowel below the level of the obstruction, approximately 20 to 30 cm distal to the ligament of Treitz and the duodenojejunal angle. The anastomosis can be performed antecolic or retrocolic through the transverse colon mesentery, hand sewn or stapled. To date, there is no evidence favoring either technique (14). Surgical palliation is associated with good functional outcomes but with a significant morbidity of 25% to 35% and a perioperative mortality rate of 2% (15-17). The main complication

remains delayed gastric emptying that occurs in 15 to 30% of cases (18,19). More recently, laparoscopic GJ (LGJ) has been developed. There are only two controlled trials and both included a small number of patients (20,21). Navarra *et al.* reported in a RCT including 24 patients that laparoscopic GJ performed in patients with malignant GOO was safe, feasible and efficient. When compared to open GJ, LGJ was associated with an earlier recovery of oral feeding and a lower rate of delayed gastric emptying (20). Guzman *et al.* reported no significant difference between LGJ and OGJ in a retrospective study with 20 patients (21). LGJ seems to be safe and feasible. However given the limited studies and the low level of evidence, further RCT with adequate sample sizes are warranted.

Palliative endoscopic stent for GOO was first described in the 1990s. A guide wire is passed through the stenosis or the obstruction and with fluoroscopic guidance, a stent is deployed to cover the obstruction. Several stents are available. They are self-expanding metal stent (SEMS) that can be covered or uncovered. Covered stent are associated with less obstruction and then less reintervention, while uncovered stent was associated with less migration (22). Stents design continues to advance and partially covered stent are being investigated. Endoscopic palliation is a well-tolerated and less invasive procedure when compared to palliative surgery. Nonetheless, complications can occur in 2% to 12% of cases including hemorrhage, perforation, aspiration pneumonia, occlusion by tumor ingrowth or food bolus, and migration. The most common adverse event following endoscopic stent is prosthetic occlusion. It has been shown that a new procedure can be performed to insert an additional stent trough the original one (23). It is feasible, less invasive and effective management (24).

They are only three RCTs assessing the benefits and the harms of palliative endoscopic stent and palliative surgery (25-27). While two of them favored endoscopic stent (25,27), the RCT of Jeurink *et al.* reported better results of GJ on long term. Indeed, this multicenter RCT found that although stent placement resulted in earlier recovery of oral feeding and a shorter hospital stay, the surgical group had finally better food intake, less recurrent obstructive symptoms and less reintervention after a follow up of two months (26). The authors conclude that palliative surgery should be the treatment of choice for patients with a life expectancy of two months or more. Two systematic reviews and meta-analysis have demonstrated comparable technical success and clinical outcomes between endoscopic stent and palliative surgery. While endoscopic stent was associated

with shorter length of stay and faster oral intake, surgery was associated with lower reintervention rate (22,28). No difference in median survival was found (28). The results of the Cochrane Review published in 2018 are in line with the previous studies (14). Endoscopic stenting is associated with a quicker resumption of oral intake and a shorter hospital stay. However, the reintervention rate is increased due to the high rate of stent obstruction or migration. The authors also recommended preferring palliative surgery in patients with prolonged survival.

According to this data, the choice of the best palliative treatment will depend on the life expectancy and also the performance status of the patient. Surgical GJ appears to be the best option for patients with good performance status and a life expectancy greater than 2 months, while endoscopic stenting is more indicated in patients with shorter life expectancy and who are poor surgical candidates. Besides, it is also important to consider the stage of the disease. Presence of carcinomatosis and ascites is an independent risk factor for poor clinical success after stent placement (29).

Two recent retrospective studies have compared the efficacy and the safety of palliative surgery versus endoscopic stenting for treating GOO specifically in patients with unresectable pancreatic cancer (30,31). Yoshida *et al.* reported in 53 patients comparable results in term of morbidity, clinical and technical success. Endoscopic stenting was associated with shorter length of stay but significantly more reintervention. Most importantly, in this group, the proportion of patients who could receive planned chemotherapy was higher and the interval between the treatment and the chemotherapy was shorter (30). The authors recommend then endoscopic stenting to treat GOO in patients with unresectable pancreatic cancer in whom chemotherapy is planned. Uemura *et al.* reported in a Japanese multicenter retrospective study the management of malignant GOO caused by advanced pancreatic cancer in 99 patients. The technical success was respectively 98% in the stent group and 100% in the surgical group. The time to resumption of oral intake, the length of hospital stay, and the time to start chemotherapy were significantly shorter in the stent group than those in the surgical group. There was no difference in survival between the two groups (31).

Nevertheless, the debate is still open on the best approach for malignant GOO due to the low level of evidence. Considering the small of number of RCTs and the small sample size in each study, the overall applicability of meta-analysis is limited. Besides, the studies included

patients with different types of cancer including pancreatic cancer but also gastric or duodenal cancer. It is well known that the survival is dependent on the underlying disease, with pancreatic cancer having the shorter median survival. Further RCT comparing endoscopic stenting, open GJ and LGJ in patients with unresectable pancreatic cancer are required with larger sample size.

Treatment of obstructive jaundice

Obstructive jaundice is the most common symptom in patients with unresectable pancreatic head malignancies and has important consequences on QOL. Up to 80% of the patients will develop jaundice during the natural history of their disease. Obstructive jaundice is associated with a proinflammatory state, impaired immune function and disturbances in coagulation. Patients with jaundice are at high risk to develop renal dysfunction, bacteriobilia and hemorrhage. Clinically, patients will develop pruritus, diarrhea and malnutrition due to fat malabsorption (11).

Historically, in jaundiced patients, surgery was the gold standard and a biliary digestive anastomosis was performed. A choledocoduodenal anastomosis was performed unless in case of tumor extension to the duodenum or the distal bile duct. In this context, a hepaticojejunostomy on-a-Roux en Y loop should be performed to avoid recurrence of symptoms due to tumor ingrowth. Besides, the Roux-en-Y reconstruction is preferable in patients with long life expectancy as it reduces the risk of cholangitis from enteric reflux into the biliary duct (32). In both situations, cholecystectomy is always performed. The distal portion of the bile duct is transected and anastomosed end-to-side to the duodenum or the jejunum with continuous 4-0 resorbable monofilament. In case of narrow bile duct (less than 1 cm), interrupted stitches could be performed and a biliary drain could be placed to avoid stenosis. Minimally invasive procedures have been developed. Berti *et al.* performed laparoscopic palliative biliary by pass in 12 patients with obstructive jaundice and unresectable periampullary adenocarcinoma. The technical success was 100% with no conversion to open surgery. Mean length of stay was 4.5 days and only two patients developed postoperative complications (16.6%) (33). Lai *et al.* also reported an experience of robot assisted laparoscopic hepaticojejunostomy in 9 patients with malignant biliary obstruction. Five patients received Roux-en-Y hepaticojejunostomy and four patients underwent double bypass. The morbidity was 22.2% while there was no

mortality. The mean length of stay was 13.3 days (34). To date, the level of evidence is insufficient to recommend laparoscopic procedures over open surgery. Further RCTs are needed.

Currently, endoscopic biliary stent is now accepted as the gold standard for palliation of obstructive jaundice in patients with unresectable pancreatic cancer. Biliary stent is placed during endoscopic retrograde cholangiopancreatography (ERCP) after cannulation of the bile duct and guidewire placement. A sphincterotomy is often associated to facilitate the insertion of the stent. Although biliary stents are less invasive than surgery, they can be associated with complications such as cholangitis or acute pancreatitis due to the obstruction of the stent, hemorrhage, perforation, and early stent migration. The Cochrane review has shown that endoscopic biliary stenting is feasible in over 90% of patients with malignant biliary obstruction, with a morbidity of 5% (35). Three meta-analyses have compared specifically endoscopic biliary stenting versus palliative surgery for malignant biliary obstruction (36-38). Biliary stenting was associated with lower morbidity, mortality and shorter length of stay. However, recurrent biliary obstruction was more frequent after biliary stenting. In a large multicenter retrospective study that included 622 patients, 20.3% of endoscopic and 4.5% of surgical patients underwent reintervention ($P < 0.0001$). Endoscopic procedure was associated with shorter length of stay, increased discharge home and lower total costs (39).

Different types of stent can be used for the endoscopic drainage of malignant biliary obstruction: plastic stent, covered self expandable metal stent (SEMS) or uncovered SEMS. The type of prosthesis does not influence the success rate of stent insertion (35). Compared with plastic stent, SEMS are associated with lower rate of reintervention, stent dysfunction and a better patient survival (40). In a multicenter RCT including 129 patients, Walter *et al.* reported that SEMS have longer functional time. The initial placement of SEMS was more expensive than plastic stent, but at long term the total costs did not differ between the two groups even in patients with a short survival duration (≤ 3 months) or those with metastatic disease (41). There was no significant difference between covered and uncovered SEMS in term of morbidity and patient survival. Covered SEMS were associated with a lower risk of obstruction due to tumor ingrowth but a higher risk of stent migration (40).

If endoscopic biliary stent placement is unsuccessful or technically not feasible, palliative biliary drainage can be

performed percutaneously. Percutaneous access also allows for internal metal stent or drain placement. However, sometimes it is necessary to maintain an external drain requiring routine changes during hospitalization. When compared to ERCP, percutaneous drainage is associated with higher adverse event rate, longer hospitalization and higher total cost. Endoscopic ultrasonography-guided biliary drainage (EUSBD) has been more recently developed and could be used as a serious alternative following failed ERCP (40).

To date, endoscopic biliary stent placed during an ERCP is the favored method for palliation of obstructive jaundice in patients with unresectable pancreatic cancer. It is less invasive, with lower morbidity, and less expensive than surgery. Besides, the length of stay is shorter. Nevertheless, there is still a place for palliative surgery if endoscopic or percutaneous treatments are not feasible due to contra-indication or technical difficulty. In case of recurrent obstruction of the stent in patients with good functional status and long life expectancy, biliary enteric bypass will provide effective palliation. Finally, considering the improvement of survival with newer chemotherapeutic agents, the palliative surgery could be more indicated considering the higher rate of recurrence after endoscopic stenting. The decision should consider the functional status of the patient but also the stage of the disease.

Pain management

Approximately, 80% of patients with advanced pancreatic cancer will experience abdominal or back pain commonly associated with malignant invasion of the mesenteric or celiac nerve plexus. The management of the pain is a major goal of palliative care to improve the QOL of the patient. Initially, pain is controlled with multimodal drug therapy including non-steroids anti-inflammatory agents and/or opioids analgesics, following the three-step analgesic ladder pain management strategy recommended by the WHO (42). Historically, celiac plexus neurolysis was performed during open surgery or percutaneously to reduce the pain. Intraoperative celiac block was performed by injecting ethanol or a local anesthetic at the level of celiac axis (43). To date, laparoscopic or open approach is only performed in symptomatic patients found unresectable during exploratory surgery. Endoscopic ultrasound guided celiac plexus neurolysis is favored as a minimally invasive intervention with an efficacy of approximately 80%. However, this approach should be used carefully considering the risk of

serious adverse events including ischemic and infectious complications (44).

Prophylactic palliative surgery

Despite improvements in preoperative imaging, 8% to 33% of patients are found to have unresectable disease at the time of surgery (45). Historically, in case of locally advanced or metastatic disease discovered intraoperatively, a double by pass was performed including a hepaticojejunostomy and a GJ.

The management of the obstructed biliary duct in the setting of unresectable disease found at the time of surgery is still debated. There is no specific data on the subject. In patients with good functional status and good prognosis, biliary digestive anastomosis is the best option. Endoscopic biliary stent should be favored in patients with poor functional status, shorter life expectancy and carcinomatosis (46).

It remains unclear whether prophylactic GJ is indicated in case of unresectable disease discovered intra-operatively in asymptomatic patients. Two RCT assessed the benefits of prophylactic GJ in patients found at exploratory laparotomy to have unresectable periampullary carcinoma (18,47). Lillemoe *et al.* in 1999 randomized 87 patients to compare prophylactic GJ with no surgery. While there was no significant difference regarding morbidity, length of stays and mean survival, prophylactic GJ significantly decreases the incidence of late GOO (18). The authors recommend then performing routinely retrocolic GJ when a patient is found unresectable during exploratory surgery. In 2003, Van Heek *et al.* demonstrate in a multicenter RCT that a double by pass is preferable to a simple by-pass with hepaticojejunostomy. Double by pass significantly decreases the incidence of GOO without increasing complication rates. The trial was terminated early due to the superiority of the double bypass (47). Similarly, the Cochrane review in 2013 reported a significant lower rate of GOO in the GJ group compared with control group, (respectively 2.5% *vs.* 27.8%). There was no difference regarding morbidity, survival and length of stay. The authors concluded that routine prophylactic GJ is indicated in patients with unresectable periampullary cancer undergoing exploratory laparotomy (48). However, these recommendations are based on studies published ten years ago. Since then, endoscopic stenting and chemotherapy options have been developed. More recently, studies supported exploratory laparotomy rather than palliative

surgery. Williamsson *et al.* compared in a retrospective study 73 patients undergoing double by-pass and 70 patients undergoing a wait and see strategy (endoscopic treatment in case of symptoms). Double by-pass was associated with increased morbidity and longer length of stay. The readmission rate for biliary or gastric outlet symptoms was similar between the two groups such as the survival. The results support a wait and see strategy. Indeed, they demonstrated that surgical by pass does not prevent future GOO (49). Insulander *et al.* reported in a retrospective study that prophylactic double by pass and exploratory laparotomy alone were comparable in term of mortality and initiation of chemotherapy. However, patients undergoing chemotherapy following double by pass had a shorter median overall survival when compared to patients undergoing exploratory laparotomy followed by chemotherapy (respectively 16.3 *vs.* 10.3 months; $P=0.04$) (50). One of the main limitations, in all the previous studies, is the absence of the impact on the QOL. Indeed, palliative treatment had to relieve the symptoms but also to improve the QOL with minimal recovery time.

Further RCTs are necessary to define the best indication of prophylactic palliative surgery in patients found to be unresectable during the surgery, especially in asymptomatic patients (51).

Is there a place for debulking surgery?

Only 20% of patients with pancreatic adenocarcinoma will be eligible for a potential curative resection (8). Complete macroscopic resection is considered an essential prerequisite for favorable survival in pancreatic cancer (2). In 2012, considering the lack of effective non-surgical treatment in pancreatic cancer, Gillen *et al.* published a systematic review to assess the benefits of tumor debulking or R2 resection compared to palliative surgery (bypass procedures) in patients with unresectable pancreatic and periampullary cancer. R2 resections were associated with increased morbidity, mortality and longer hospital stays. The survival benefit was not significant, respectively 8.2 months for palliative resection and 6.7 months for double loop bypass. In this context, the authors concluded that planned R2 resections couldn't be recommended (52). Two years later, the international study group of pancreatic surgery (ISGPS) suggests that extended pancreatectomy in locally advanced disease can be performed if macroscopic clearance can be achieved. Although extended pancreatectomy is associated with increased perioperative morbidity, the long-term

survival will be better compared with palliative surgery or palliative chemo or chemoradiotherapy (53). Tol *et al.* compared bypass surgery to R1 and R2 resection in a retrospective study including 402 patients with a pancreatic adenocarcinoma who underwent surgical exploration with a curative intent for resection (54). While the overall morbidity was increased in the R1 and R2 procedures, the mortality was comparable. Overall morbidity was 52% in R1 resection, 73% in R2 resection and 34% in bypass procedure. Survival curves showed a significant difference between R1 and R2 resections ($P=0.009$) and R1 and bypass patients ($P<0.001$). No difference in survival was seen between R2 resections and bypass surgery ($P=0.35$). Finally, the authors suggest that R1 resection could be performed considering the survival benefit and despite increased postoperative morbidity, but only in highly selected patients. R2 resection is not recommended.

Conclusions

For patients with unresectable disease, palliative management of GOO, obstructive jaundice and pain remains challenging. Physicians have different modalities, including surgery or endoscopy, to relieve symptoms durably and to improve the QOL. The choice between the different techniques should consider the balance benefits/risks, the performance status of the patient, the disease stage and the estimated life expectancy. In case of GOO, surgical GJ is the best option for patients with good performance status and a life expectancy of greater than 2 months. Laparoscopic GJ seems to be safe and feasible, however further RCT are necessary to conclude. On the contrary, endoscopic stenting is recommended for patients with poor functional status and shorter life expectancy. Both techniques have comparable technical success. While endoscopic treatment allows earlier recovery of oral feeding, surgical GJ is associated with less reintervention. To treat obstructive jaundice, endoscopic biliary stent is now accepted as the gold standard. The European Society of Gastrointestinal Endoscopy recommends insertion of SEMS during ERCP. Palliative surgery is no longer recommended in first intention and should be considered only in case of recurrent stent obstruction or in case of unsuccessful stenting due to technical difficulties. For pain management, when indicated, endoscopic ultrasound guided or percutaneous celiac plexus neurolysis is preferred over surgical approach. Finally, for patients found unresectable at the time of surgery, double bypass can be performed if

they were symptomatic preoperatively. However, the level of evidence is too low to recommend prophylactic bypass in asymptomatic patients.

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Footnote

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