

# Biliary drainage in pancreatic cancer: The endoscopic retrograde cholangiopancreatography perspective

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## INTRODUCTION

Biliary obstruction secondary to tumor infiltration of the bile duct is a very frequent complication of pancreatic cancer. Pancreatic cancer is actually responsible of jaundice in two out of three patients with malignant biliary obstruction in clinical trials.<sup>[1]</sup> In addition, obstructive jaundice is often the first clinical sign of the disease. Obstructive jaundice limits or even precludes the use of chemotherapy, both in a neoadjuvant and palliative settings. Biliary drainage becomes, therefore, one of the cornerstones in the management of patients with pancreatic cancer.

Transpapillary stenting is the approach of choice for biliary drainage in patients with pancreatic cancer and obstructive jaundice. The indications of preoperative biliary stenting, as well as relevant aspects of biliary drainage in the context of unresectable pancreatic cancer (metal or plastic stents, covered or uncovered metal stents, and new alternatives for the present and the future), are discussed in the present overview.

## PREOPERATIVE BILIARY DRAINAGE FOR RESECTABLE PANCREATIC CANCER

Preoperative biliary drainage increases complications compared with surgery without preoperative drainage.<sup>[2]</sup> Nevertheless, some patients may benefit from preoperative relief of jaundice; these include patients with untreatable pruritus, acute cholangitis, or renal dysfunction as a consequence of obstructive jaundice. In addition, patients in whom the surgical procedure is delayed due to neoadjuvant therapy, need of nutritional support in cases of high risk of malnourishment, or due to logistic issues, also require a preoperative biliary stenting.

The endoscopic transpapillary approach is generally preferred for biliary drainage in this preoperative setting, but complications should not be underestimated.<sup>[2]</sup> In fact, complications such as post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis, cholangitis, or hemorrhage may preclude patients from further curative surgical resection of the tumor. In this context, the use of maneuvers aiming at reducing

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the risk of post-ERCP complications (*e.g.*, rectal indomethacin or diclofenac, pancreatic duct stenting, adequate hydration, early precut in difficult cannulation or antibiotics) should be maximized.

For preoperative biliary drainage, the use of self-expandable metal stents (SEMS) should be preferred over plastic stents since they are associated with significantly lower complication rate and stent dysfunction, with a similar surgical complication rate.<sup>[3,4]</sup>

## **BILIARY DRAINAGE FOR UNRESECTABLE PANCREATIC CANCER**

### *Palliative surgical or endoscopic transpapillary drainage?*

Endoscopic and surgical biliary drainage in patients with unresectable pancreatic cancer show similar technical success rate and long-term efficacy.<sup>[5]</sup> Endoscopic biliary drainage is associated with less complications (risk ratio [RR] 0.60; 95% confidence interval [CI] 0.45–0.81), shorter hospital stay, better quality of life, and lower cost than the surgical palliative approach.<sup>[5]</sup> Based on these results, a minimally invasive transpapillary approach is preferred for biliary drainage in patients with unresectable pancreatic cancer.

### *Transpapillary biliary stenting for unresectable pancreatic cancer*

Although new devices and recent development of therapeutic endoscopic ultrasound have opened new minimally invasive options for biliary drainage, endoscopic transpapillary biliary stenting continues to be the therapy of choice for obstructive jaundice in the majority of patients with unresectable pancreatic cancer. Endoscopic transpapillary stenting is feasible in >90% of the cases in experienced hands. In addition, short-term efficacy, defined as jaundice and pruritus relief, is higher than 80%.<sup>[6-9]</sup> Different studies have shown however that jaundice and pruritus relief is lower in patients with very high hyperbilirubinemia (in whom symptom relief takes frequently longer), liver metastasis (due to a lesser role of common bile duct obstruction in the pathogenesis of hyperbilirubinemia) and atypical biliary obstruction.<sup>[6-9]</sup>

### *Self-expandable metal stents or plastic stents for unresectable pancreatic cancer?*

Both SEMS and plastic stents are commercially available for endoscopic biliary drainage. Choosing one over the other should be based on aspects such as dysfunction

rate and need of reinterventions, complication rate, patient survival and cost.

A large number of studies have reported on the dysfunction rate of SEMS and plastic stents in patients with malignant distal biliary obstruction. These studies have been included in a recent meta-analysis showing a lower dysfunction rate for SEMS (21.9%) compared to plastic stents (48.9%), with a relevant risk difference of 27%.<sup>[1]</sup> Time to stent dysfunction is also significantly longer for SEMS (250 ± 104 days) than for plastic stents (124 ± 104 days) ( $P < 0.001$ ). This superiority of SEMS over plastic stents is associated with a lower need of reintervention rate (21.4% *vs.* 56.6%, risk difference 35%).<sup>[1]</sup>

As with any other ERCP procedure, complications associated with endoscopic transpapillary biliary drainage in patients with unresectable pancreatic cancer include mainly pancreatitis, cholangitis, bleeding, perforation, cholecystitis, and liver abscess. The complication rate is of about 13% after both SEMS and plastic stents.<sup>[1]</sup> As mentioned above, the use of any maneuver aiming at reducing the risk of post-ERCP complications should be maximized specifically in patients with unresectable pancreatic cancer, in whom severe complications may prevent any further oncological therapy.

The question of whether sphincterotomy before SEMS placement is useful to reduce the risk of post-ERCP pancreatitis is a matter of debate. The risk of pancreatitis (7%–9%), cholangitis, stent migration, and stent dysfunction appears to be similar in patients undergoing or not undergoing sphincterotomy before SEMS.<sup>[10]</sup> The risk of bleeding is significantly higher after sphincterotomy, and thus sphincterotomy before SEMS placement cannot be generally recommended.<sup>[10]</sup> New multicenter, randomized clinical trials are currently ongoing aiming at definitively answering this question.

Pancreatic cancer is a disease with dismal prognosis. Survival of patients with unresectable pancreatic cancer is short. The choice of SEMS or plastic stents for biliary drainage in these patients has probably not a major impact, but a recently published meta-analysis has reported on a statistically significant longer survival after SEMS compared to plastic stent (median survival 187 d *vs.* 162 d,  $P < 0.001$ ).<sup>[1]</sup>

Finally, cost analysis in this setting is not an easy task. This is mainly due to different factors included in

the cost analysis in different studies (full treatment or stent cost and number of stents exchanged). Taking this limitation into account, cost evaluation generally supports SEMS over plastic stents due to a lower full treatment cost.

*What is the optimal self-expandable metal stents (uncovered, partially covered or fully covered)?* Similarly to what it has been described for SEMS and plastic stents, choosing among uncovered, partially covered, and fully covered stents depend on factors such as stent patency and dysfunction, as well as complications and patient survival. All these factors appear to be similar with all these SEMS, with the exception of the cause of stent dysfunction. Compared to uncovered stents, dysfunction of covered stents is more often due to sludge formation (RR 2.47; 95% CI 1.36–4.50), stent migration (RR 9.33; 95% CI 2.54–34.24), and tumor overgrowth (RR 1.76; 95% CI 1.03–3.02), but less often due to tumor ingrowth (RR 0.25; 95% CI 0.12–0.52).<sup>[11]</sup>

## ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY - GUIDED INTRADUCTAL ENDOSCOPIC ABLATION

The development of new devices and probes to apply radiofrequency ablation (RFA) into the bile duct in patients with malignant biliary obstruction may change in the future the way obstructive jaundice is managed in patients with pancreatic cancer today. Preliminary studies have reported on the use of ERCP-guided intraductal RFA before SEMS insertion.<sup>[12-14]</sup> These studies show that ERCP-guided RFA does not significantly influence stent patency, but it appears to be an independent predictor of longer survival in patients with unresectable pancreatic cancer. These promising results should encourage us to further evaluate the role of ERCP-guided RFA for malignant obstructive

jaundice in large, properly designed, and multicenter clinical trials.

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