Scientific Research Publishing

Open Journal of Gastroenterology, 2022, 12, 249-262
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Advanced Endoscopic Palliation of Unresectable Periampullary Carcinoma: A Systematic Review

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How to cite this paper: Simkhada, S., Aryal, S., Osei, A.D., Pokharel, A., Matar, R. and Maitar, M. (2022) Advanced Endoscopic Palliation of Unresectable Periampullary Carcinoma: A Systematic Review. *Open Journal of Gastroenterology*, **12**, 249-262.
https://doi.org/10.4236/ojgas.2022.1210025

Received: August 23, 2022
Accepted: September 24, 2022
Published: September 27, 2022

Abstract

Background and Aims: Periampullary malignancies often present at an advanced unresectable stage requiring palliation of symptoms for the better quality of life. Though they require multispecialty support; role of endoscopic interventions in palliation is paramount because of the advancement in technology and increase experience of Gastroenterologist. **Methods:** We did extensive review of articles regarding endoscopic advances in the management of Unresectable Periampullary Malignancies. Several systematic reviews, Meta analysis, and Randomized controlled trials published over the last 2 decades were thoroughly searched on PUBMED and GOOGLE SCHOLAR. **Results:** Advanced Endoscopic procedures have been emerging as a superior modality than conventional measures because of minimal invasiveness and greater clinical and technical success. **Conclusion:** Periampullary malignancies often present at an advanced unresectable stage requiring palliation of symptoms for the better quality of life. Several endoscopic interventions have already been established as the standard of care in palliation of symptoms of unresectable periampullary malignancies, we can say with confidence that with growing advances in EUS, advancement in technologies and increasing experiences, the role of gastroenterologist will be pivotal in these groups of patients.

Keywords

Periampullary Malignancies, Endoscopic Ultrasound, Celiac Plexus Neurolysis, ERCP, EUS-BD, EUS-GE

1. Introduction

Periampullary cancer comprises 4 entities, because they share similar presentation, location and intervention, it is worthwhile discussing their intervention together. Traditionally any tumor within 2 cm of Ampulla of vater, Carcinoma of Head of Pancreas, Distal Cholangiocarcinoma, Carcinoma of 2ND part of Duodenum and Carcinoma arising from Ampulla of Vater itself are considered Periampullary Cancer.

They comprise 5% of gastrointestinal malignancies, of which Pancreatic cancers are the most common. Pancreatic cancer is the fourth leading cause of cancer-related death in men and the first leading cause in women, with an approximate incidence of 10 per 100,000 populations per year [1] [2].

Due to anatomical proximity and similar presentation, preoperative differentiation on imaging is challenging hence endoscopic interventions definitely aid in localizing and even help in staging therefore guide timely intervention and increase overall survival. Pancreatoduodenectomy and segmental resection along with neoadjuvant and adjuvant therapy are the only potentially curative options for all periampullary carcinomas, role of endoscopic interventions in diagnosis, staging and palliation is paramount and with the advancement in technology role of Gastroenterologist is pivotal.

The commonality of all periampullary cancers advanced presentation is gastric outlet obstruction, intractable pain and obstructive Jaundice. We are going to discuss in depth the role of gastroenterologist to palliate the suffering of the patients of periampullary tumors and improve the quality of life.

Periampullary malignancies especially pancreatic adenocarcinomas are the leading cause of cancer related mortality. The majority of these malignancies are unresectable at the time of presentation. Therefore, palliation of symptoms including pain, jaundice, and pruritus is the main objective in these patients. Endoscopic palliation in pancreatobiliary malignancies includes biliary drainage, enteral stenting for gastric outlet obstruction, and celiac plexus neurolysis for relief of pain.

Over the last decade, the role of endoscopy as a palliative modality has broadened with the availability of novel tools and techniques. The development of endoscopic ultrasound (EUS) as a therapeutic modality has allowed a wide array of remedial procedures to be performed endoscopically and with confidence we can say that this is going to bring the revolution in the field of medicine.

2. Methods

We did extensive review of articles regarding endoscopic advances in the management of Unresectable Periampullary Malignancies. Several systematic review, Meta analysis, and Randomized controlled trials published over the last 2 decades were thoroughly searched on PUBMED and GOOGLE SCHOLAR.

3. Endoscopic Intervention for Intractable Pain

EUS Guided Celiac Plexus Neurolysis, Review of several studies

Pain is one of the most prevalent symptoms in periampullary cancer at presentation (75%) and its incidence increases as the disease advances to more than 90% of patients [3]. Pain control is the main therapeutic goal for clinicians in palliative care of pancreatic cancer patients and the conventional management with high doses of narcotics and the inherent adverse effects may further impair quality of life [4] [5] [6].

Severe abdominal and back pain is one of the most common clinical manifestations of advanced periampullary cancer and the occurrence and severity of pain directly correlates with cancer progression [7].

First reported in 1914 as an intraoperative procedure, celiac plexus neurolysis has proved to be an alternative or adjunctive intervention for pain management. Traditionally, CPN has been performed under fluoroscopic, ultrasonographic or computed tomography imaging guidance [8]. In 1996, a relatively safer, accurate and convenient technique was introduced by Faigal *et al.* and Wiersema and Wiersema, in the form of endoscopic ultrasonography guided celiac plexus neurolysis (EUS-CPN) [9] [10]. Utilizing real-time imaging and Doppler assessment of intervening blood vessels provides the EUS-guided CPN an edge over other techniques [8].

The indication for EUS-CPN/CGN is intractable pain in advanced periampullary cancer not relieved by medical management or in patients having the adverse effects of higher doses of Opiates impairing the quality of life. Absolute contraindications are Resectable tumors, Coagulopathy (INR > 1.5) and thrombocytopenia (Platelets < 50,000/microliter).

EUS-CPN usually uses a combination of a local anesthetic such as bupivacaine and a neurolytic agent in the form of absolute ethanol or phenol. It can be performed in several ways: central approach; bilateral approach, broad approach and direct approach.

In the central technique, the neurolytic agent is injected at the base of the celiac artery;

In the bilateral technique, the neurolytic agent is injected on both sides of the celiac artery [11].

Broad approach/technique was first described in 2010 by Sakamoto *et al.* [12], and this approach is based on the injection of the substances above and on both sides of the origin of the superior mesenteric artery, without losing the longitudinal axis of the aorta, and by aiming for a broader diffusion of the neurolytic agent.

Direct approach/technique [13] is based on the direct injection of each celiac ganglia to distribute the alcohol and anesthetic doses.

In the recent review by Perez-Aguado *et al.* [14] the efficacy of EUS-CPN varies from 50% to 94% in the different studies, and EUS-CPN has a pain relief duration of 4 - 8 weeks. Any of the 4 different techniques could be used to perform

EUS-CPN effectively with no differences in terms of complications between the techniques.

Likewise a metaanalysis and systematic review done by Asif *et al.* [15] who compared several studies for the last decade who found, with bilateral injection technique, the pooled proportion of patients with pain relief was 57% (95% CI = 48 - 67). On the other hand, with the central injection technique, the pooled proportion of patients with pain relief was higher at 66% (95% CI = 61 - 71).

Most of the studies showed the comparable pain control however a prospective study by, Sahai *et al.* [16] found better pain control with Bilateral technique compared to central.

A randomized multi centre trail by Doi *et al.* [17] demonstrated significant pain relief with the injection directly into the ganglia compared to the central approach, (73.5% *vs.* 45.5%). This study also demonstrated the complete response rate was higher in direct ganglia injection. However this was just compared at 7th postoperative day which clearly showed it was for short term relief.

A recent multicentre prospective trial by Kamata *et al.* [18] study evaluated the efficacy of endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) in combination with EUS-guided celiac ganglia neurolysis (EUS-CGN) for pancreatic cancer-associated pain. This study showed better short term response, efficacy with the combination group compared to EUS-CPN however addition of EUS-CGN did not improve the average length of pain relief period.

A randomized double blind trial by Levy *et al.* [19] interestingly found increased mortality in the EUS-CGN compared to EUS-CPN even in patients with non metastatic disease with no significant difference in improving the quality of life and pain response rate. The median survival time was significantly shorter for patients receiving CGN (5.59 months) compared to (10.46 months) (hazard ratio for CGN, 1.49; 95% CI, 1.02 - 2.19; P = 0.042), particularly for patients with non-metastatic disease (hazard ratio for CGN, 2.95; 95% CI, 1.61 - 5.45; P < 0.001). Rates of survival at 12 months were 42% for patients who underwent CPN vs. 26% for patients who underwent CGN.

To conclude, it is established that EUS-CPN regardless of approach has a great role in relieving the intractable pain bypassing the adverse effects of higher dosage of Opiates and improving the quality of life. Though EUS-CGN has been considered for greater short term pain relief, a recent study showed increased mortality hence further studies are required to validate its use.

4. Endoscopic Palliation of Biliary and Enteral Obstruction

Surgical bypass, Gastrojejuonsotomy and hepaticojejunostomy, historically were the only modalties for the treatment of Duodenal obstruction and Biliary obstruction in patients with unresectable periampullary cancer. [20] [21] [22]. With the advances in technology, Endoscopic double stenting, transpaillary stenting and enteral stenting has become the standard treatment to provide better quality of life in patients fighting in their terminal stages being minimally in-

vasive and having shorter recovery time [23].

In patients, where transpapillary approach is not feasible, Percutaneous transhepatic biliary drainage has been a method of palliation to relieve pruritus, jaundice, pain and a rescue measure for cholangitis but it is very discomforting with regards to pain, skin infection and decreased quality of life.

Various EUS guided procedures have emerged as a novel platform and have been more popular in the management of biliary and duodenal obstruction.

In this review, we are going to explore recent advances and the role of gastroenterologists in the endoscopic palliation of biliary and enteral obstruction in advanced unresectable periampullary cancers.

5. Endoscopic Biliary Drainage

Endoscopic biliary drainage has favourable (80% - 90%) short term < 90 day success rate in the setting of distal bile duct obstruction though it carries complications up to 10% which include Cholangitis, bleeding and ERCP pancreatitis. [24].

Either plastic or metallic stents can be used. Plastic stents are comparatively inexpensive and can be easily removed in the future if needed but more prone for obstruction whereas Self expandable Metallic stents (SEMS) are less likely to occlude though they are expensive and cannot be removed easily.

Self Expandable Metallic Stent (SEMS) placement is an established procedure for unresectable distal malignant biliary obstruction [25] [26] [27] [28]

Endoscopic sphincterotomy is generally done as a routine procedure during SEMS placement for advanced periampullary carcinoma to prevent pancreatitis since SEMS expansion causes the compression of pancreatic duct opening. However a randomized control study done by Hayashi *et al.* [29] showed endoscopic sphincterotomy did not affect the outcome of SEMS placement complications including pancreatitis probably because of prior blockage of pancreatic duct by the cancer.

There are two types of SEMS;

Covered SEMS are considered to prevent tumor in growth and easy to remove. Uncovered SEMS do not migrate and prevent acute pancreatitis [30] [31] [32] [33].

Recent extensive review done by Tanisak *et al.* [34] did not find clinically and statistically significant procedure related complications (cholangitis, pancreatitis, cholecystitis, bleeding) in covered versus uncovered SEMS [30] [31] [35] [36] [37]. The rate of recurrent biliary obstruction was clinically and statistically significant in uncovered SEMS was only shown by prospective randomised study done by Isayama *et al.* [30] wheras all other studies [31] [35] [36] [37] did not show significant differences. Two studies, however showed covered SEMS delay the time to recurrent biliary obstruction compared to uncovered SEMS [30] [31], the later was a randomised muticenter trial by Kitano *et al.* [31].

In cases of endoscopic retrograde cholangiopancreatography-biliary drainage,

self-expandable metal stent placement is a good indication for patients whose prognosis is expected to be over 2 months. The superiority of one type over the other has varied from studies to studies hence comparable prospective clinical trials are needed to establish a standard guideline.

6. Endoscopic Palliation of Malignant Gastric Outlet Obstruction (MGOO) Caused by Periampullary Cancers

The most frequent cause of MGOO in the Western countries is pancreatic adenocarcinoma, which lead to obstructive symptoms in about 15% - 20% of patients during the disease course, while gastric adenocarcinoma is the most common cause in Asiatic population [38]-[43]. Less common causes are duodenal or ampullary neoplasms, biliary cancers, lymphomas or adenopathies from other malignancies [44].

Surgical gastrojejunostomy holds more durable relief of symptoms with fewer re-interventions at the cost of higher procedure related risk and prolonged hospital stay. Enteral stenting provides rapid improvement but have higher rate of stent dysfuction due to tumor overgrowth requiring frequent reinterventions. Recently EUS Gastroenterostomy with lumen apposing metal stents (LAMS) is emerging as a promising alternative though several prospective comparative trial is ongoing.

Currently, the endoscopic deployment using through-the scope stents is the most used technique, and requires therapeutic endoscopes with a large working channel (*i.e.*, ≥3.7 mm). Most cases are managed with therapeutic gastroscopes, but cases of dilated stomachs or strictures in the distal duodenum could be better managed with a colonoscope or a duodenoscope [45] [46].

Currently, available enteral SEMS are made of nitinol, an alloy of nickel and titanium, which confers high flexibility useful for sharply angulated strictures, even if with a weaker expansive radial force compared to other metal stents [47].

Several studies on enteral SEMS for MGOO have shown a high rate of technical success (defined as the successful deployment of the stent across the stricture), which is usually above 90%, and a good rate of clinical success, which ranges from 63% to 97% [48]. Clinical success is generally defined as the relief of obstructive symptoms and the improvement of food oral intake. Adler *et al.* developed a clinical score aimed at providing an objective measure of the oral intake before and after the treatment for MGOO [49].

The Gastric Outlet Obstruction Scoring System (GOOSS) assigns a score of 0 in case of no oral intake, 1 for only liquids, 2 for soft solids and 3 for low-residues or full diet, and currently is the most used score to quantify the clinical improvement after treatment for MGOO [49].

A recent systematic review from van Halsema *et al.* included 19 prospective studies from 2009 to 2016 and analyzed outcomes of more than 1200 patients with MGOO treated with SEMS. The overall pooled technical success rate was 97.3% and the clinical success rate was 85.7%, thus confirming the high efficacy

of this technique [48].

The presence of carcinomatosis, number of duodenal obstruction and patients poor performance scale have been associated with poor outcome and stent failure [50] [51] [52].

Enteral stenting has been established as a great palliative measure to relieve the gastric outlet obstruction obviating the procedural complications and prolonged hospital stay of surgical bypass.

7. Concomitant Biliary and Gastric Outlet Obstruction and Role of Endoscopic Ultrasound in the Palliation of Unresectable Periampullary Cancer

Unresectable periampullary malignancies frequently cause biliary obstruction which is estimated to affect 70% - 90% of pancreatic cancer patients during the course of the disease and may appear before, concomitantly or after the onset of MGOO [38].

Classification of combined malignant biliary and duodenal obstruction.

Transpapillary biliary stenting is the most challenging in type II obstruction if the scope can be negotiated with type 1 obstruction after the dilatation, transpapillary biliary stenting can still be done with great success [53] [54] [55] (**Table 1**). Though major papilla can be easily stented in Type III, they are more prone for the duodenal-biliary reflux because of distal obstruction [53] [56] (**Table 1**).

Although technically challenging, ERCP through an indwelling duodenal stent is feasible and effective, as reported in a recent multicenter retrospective studies on 71 patients, with an overall technical success rate of 85%, which was reduced to 76% in case of duodenal obstruction at the level of the ampulla [55]. The recent progress of interventional EUS, and the possibility to perform EUS-guided biliary drainage (EUS-BD) from the stomach (*i.e.*, EUS-guided hepato-gastrostomy) or from the bulb (EUS-guided choledocho-duodenostomy) has radically changed the approach to the patients with concomitant MGOO and biliary obstruction [57].

EUS-BD in patients with MGOO is safe and effective, even when performed in the same session or with an indwelling duodenal stent, and probably could be

Table 1. Mutignani *et al.* [53].

	Location
Type I	Duodenal obstruction proximal to the major papilla
Type II	Duodenal obstruction involving the major papilla
Type III	Duodenal obstruction distal to the major papilla
	Timing
Group 1	Biliary obstruction occurring before the onset of duodenal obstruction
Group 2	Biliary and duodenal obstruction occurring simultaneously
Group 3	Biliary obstruction occurring after the onset of duodenal obstruction

considered the first-line strategy to achieve biliary drainage in this setting of patients [58] [50] [60].

A systematic review and meta analysis by Han *et al.* regarding EUS-guided biliary drainage versus ERCP for first-line palliation of malignant distal biliary obstruction revealed similar technical and clinical success rates for EUS-BD and ERCP (technical: 94.8% vs. 96.5%, clinical: 93.8% vs. 95.7%). The results were similar and highly homogeneous in RCTs and retrospective studies. EUS-BD was associated with higher incidence of biliary peritonitis of 2.4% whereas ERCP is associated with much higher incidence of pancreatitis (7.3%) [61]

Increased success rates and decreased adverse events were observed in studies published after 2015. These findings may be due to improvements of EUS-BD accessories, better procedure organization, and greater endoscopist experience [61].

A recent multicenter study revealed that EUS-BD has longer stent patency, fewer reinterventions, shorter procedure times than ERCP and better quality of life for the primary palliation of malignant distal bowel obstruction [62].

PTBD and precut papillotomy has been the conventional method in difficult canulation however EUS-BD is emerging to have more technically success rate and less complication [63].

8. Endoscopic Ultrasound-Gastroenterostomy (EUS-GE)

EUS-GE has been a new invention in the field of gastroenterology for the effective palliation of malignant gastric outlet obstruction. Use of Lumen Apposing Metallic stent (LAMS) between the stomach and small intestine distal to the obstruction is done under EUS and Flouroscopic guidance. It bypasses the risk of procedural complications and Stent occlusion associated with Surgical and Enteral stenting respectively.

Two systematic reviews and meta-analysis comparing EUS-GE and enteral stenting and surgical Gastro-enterostomy showed that EUS-GE was associated with a significantly lower rate of reintervention despite a comparable technical/clinical success and safety profile [64].

Currently there is an ongoing trial 'EUS guided Gastroenterostomy versus Enteral Stenting for Palliation of Gastric Outlet Obstruction: A Randomzed Clinical Trial, which is being done at Johns Hopkins University by Khasab, M., Sanaei, O. which is estimated to be completed in January 2023.

9. Summary

Periampullary malignancies often present at an advanced unresectable stage requiring palliation of symptoms for the better quality of life. Role of endoscopic interventions in palliation is paramount and with the advancement in technology role of Gastroenterologist is pivotal. Endoscopic palliation in pancreatobiliary malignancies includes biliary drainage, enteral stenting for gastric outlet obstruction, celiac plexus neurolysis for relief of pain and more recently EUS

guided biliary drainage and gastric bypass. All these modalities have been getting better year after year with greater technical and clinical success due to advancement in technology and greater endoscopist experiences.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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