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What can the Interventional Endoscopist Offer in the Management of Upper Gastrointestinal Malignancies?

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Abstract

The therapeutic possibilities of endoscopy have rapidly increased in the last decades and now allow organ-sparing treatment of early upper gastrointestinal malignancy as well as an increasing number of options for symptom palliation. This review contains an overview of the interventional endoscopic procedures in upper gastrointestinal malignancies. It describes endoscopic treatment of early oesophageal and gastric cancers, and the palliative options in managing dysphagia and gastric outlet obstruction. It also provides an overview of the therapeutic possibilities of biliary endoscopy, such as retrograde stenting and radiofrequency biliary ablation. Endoscopic ultrasound-guided therapeutic options are discussed, including biliary drainage, gastrojejunostomy and coeliac axis block. To aid in clinical decision making, the procedures are described in the context of their indication, efficacy, risks and limitations.

Keywords: Endoscopic resection; malignant obstruction; oesophageal cancer; palliation; pancreatic cancer; stenting

Introduction

Endoscopy is an indispensable tool in the diagnosis of upper gastrointestinal malignancies. Technological developments have enabled endoscopy to go beyond diagnosis to allow for interventions aimed at curative treatments of early cancers or provide effective symptom relief. The therapeutic endoscopic options have rapidly increased in the last decades within a constantly expanding field of indications. This review is intended as a summary of the therapeutic endoscopic techniques for upper gastrointestinal malignancies. It covers different anatomical locations (oesophagus, stomach, duodenum/pancreatobiliary tract) and both curative and palliative indications.

Oesophagus

Endoscopic Treatment Options for Oesophageal Adenocarcinoma

Oesophageal adenocarcinoma (OAC) generally occurs in the context of Barrett's oesophagus. Early OAC is commonly detected during endoscopic surveillance of Barrett's oesophagus or is diagnosed incidentally during an endoscopy for a variety of indications. The mainstay of treatment for early OAC is endoscopic eradication therapy, consisting of either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) combined with endoscopic ablation of the remaining Barrett's oesophagus [1]. EMR is the preferred method of choice for flat or superficially elevated lesions with no suspicion of submucosal invasion. The procedure can be carried out under either conscious sedation or general anaesthesia. Oesophageal EMR is best performed with a cap-assisted technique, such as a multiband mucosectomy device or a cap-and-snare technique.

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Typically, after delineation, the lesion is sucked into the cap and resected with the help of the snare (Figure 1).

Compared with EMR, ESD is a technically more challenging and time-consuming procedure with a higher rate of serious complications [2–5], but it has the advantage of en-bloc resection of the tumour with improved pathological assessment of lateral and deep margins [2]. Current guidelines recommend ESD for lesions with suspicion of submucosal invasion, diameter larger than 2 cm or associated extensive fibrosis or stricture [6]. Surgical treatment for early Barrett's oesophagus-associated neoplasia has similar success rates as endoscopic eradication therapy but a higher risk of serious adverse events [7]. EMR/ESD also offer precise histopathological staging. pT1a OAC has a very small risk of lymph node metastasis (<2%). Therefore, endoscopic treatment is usually considered curative and preferred to oesophagectomy [1,5]. In case of submucosal invasion (pT1b), endoscopic resection allows the presence of high-risk factors for lymph node metastasis to be determined, such as deep submucosal invasion, poor differentiation and the presence of lymphovascular invasion. Patients with one or more of the above risk factors are generally advised to undergo an esophagectomy as the risk of lymph node metastasis is significant. Historical surgical series reported that the risk of lymph node metastasis in cases of high-risk T1b OAC can be as high as 15–40% [8], although more recent series suggest that the risk of lymph node metastasis may be as low as 3% [9].

After EMR/ESD, ablation of the remaining Barrett's metaplasia is recommended, as the remaining Barrett's segment has an estimated risk of neoplastic progression of 15% at 5 years [1]. The ablation method with the largest body of evidence is radiofrequency ablation (RFA), which uses thermal energy to ablate the superficial mucosal layer. Several randomised controlled trials have shown its efficacy and safety as primary treatment of the dysplastic Barrett's segment, as well as for eradication of residual intestinal metaplasia following EMR/ESD. Complications include post-procedural pain, a low risk of bleeding and perforation (<1%) and a 5–10% risk of stricture [5,10]. Other ablation modalities include argon plasma coagulation (APC) and cryotherapy. The level of evidence of these techniques is lower compared with RFA, although emerging data indicate that in the near future they may represent a valid cost-effective alternative to RFA [11–13]. In particular, a pilot study suggested that APC may be more cost-effective compared with RFA [13].

Endoscopic Treatment Options for Oesophageal Squamous Cell Carcinoma

Early oesophageal squamous cell carcinoma treatment slightly differs from OAC treatment in that ESD is the preferred modality for endoscopic resection and no ablation is required, as the aim of the resection is to eradicate all neoplastic epithelium. There is evidence that ESD has higher curative resection rates (73.5% versus 21.3%) and lower 5-year recurrence-free survival (95.2% versus 73.4%) compared with EMR, as well as lower recurrence rate (2.9% versus 23.7%) [14]. The rationale behind this might be that early oesophageal squamous cell carcinoma extends more frequently into the submucosal layer [6,15].

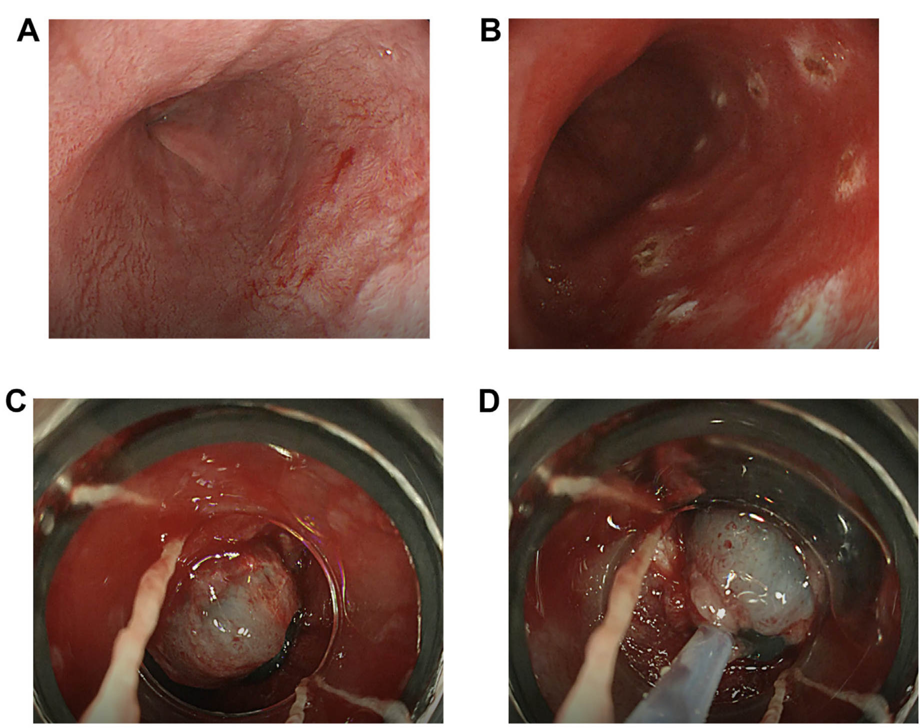

Fig 1. Endoscopic mucosal resection of a flat lesion on the right wall of the oesophagus using a multiband mucosectomy device. (A) White light image, (B) demarcation of the lesion, (C) band placement creating a pseudopolyp, (D) snare resection of the lesion.

Treatment of Dysphagia due to Malignant Oesophageal Obstruction

In the palliative treatment of advanced oesophageal cancer, several options for dysphagia relief are available: external beam radiotherapy, brachytherapy and oesophageal stenting [15]. In patients with an expected short life expectancy, oesophageal stents cause rapid dysphagia relief in 1–2 days in 90% of the patients, but long-term results for dysphagia improvement are higher after brachytherapy [16]. However, the availability and experience with brachytherapy differ between centres. Therefore, current European guidelines recommend an oesophageal stent for palliative treatment of dysphagia, with brachytherapy as a valid alternative option with or without a stent. The second choice is represented by laser therapy, photodynamic therapy or oesophageal bypass [15].

Self-expandable metal stents are recommended for use in malignant strictures (Figure 2). There is no difference between fully or partially covered stents in terms of outcome (technical success and stent obstruction) or adverse events [17,18]. The most common complications of stent placement are stent obstruction (15%), migration (6–30%), bleeding (3–12%), pain (9–15%) and reflux (9–15%) [18,19]. Both endoscopic suturing and over the stent clips have shown promise in reducing stent migration, although it is currently unclear which technique is superior and cost-effective [20,21].

In case of stent obstruction, stent in stent placement is the method of choice for removal of the stent, which induces pressure necrosis of the tissue at the site of ingrowth.

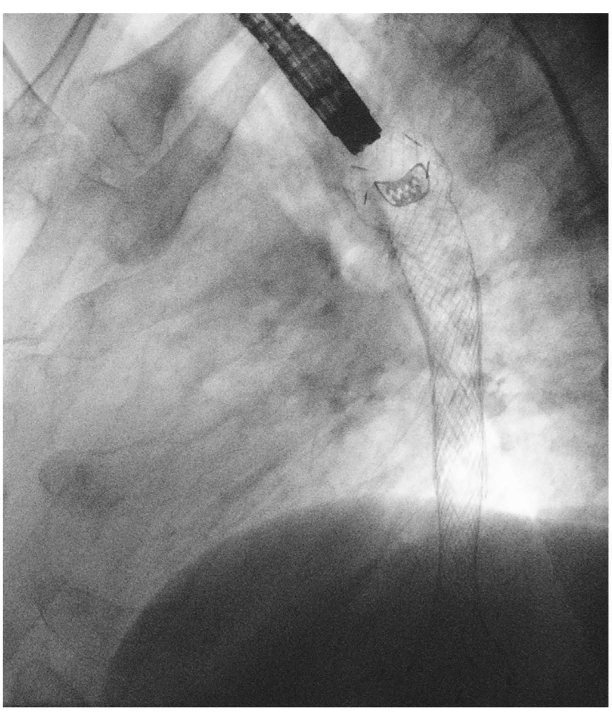

Fig 2. Lateral fluoroscopic image of the thorax showing a self-expanding metal stent in the oesophagus, anchored with a stent fixation clip. The endoscope is visible at the superior end of the stent.

Stomach

Both histological subtypes of early gastric cancer, the intestinal and the diffuse type, can be treated with endoscopic eradication therapy. In gastric cancer, EMR is only recommended for lesions ≤10 mm. ESD is the method of choice.

The following gastric lesions are deemed curable by endoscopic resection [6]:

- Early dysplastic lesions
- Intramucosal lesions of any size without ulceration
- Intramucosal lesions ≤30 mm with ulceration
- Submucosal lesions ≤30 mm, with at most sm1 involvement (<500 micron) and well-differentiated histology

ESD has high rates of en-bloc resection (>90%) with low rates of recurrence (<5%). However, due to the higher rate of metachronous lesions compared with surgery (5.2% versus 0.4%), disease-specific survival is lower for ESD, despite a comparable overall survival [6]. However, there is evidence that the quality of life is higher after ESD compared with surgery [16].

An exception to the recommendations above should be made for patients with hereditary diffuse gastric cancer syndrome, an autosomal dominant disease with a cancer penetrance of 60–70%. These patients have multifocal signet cell carcinoma, and cancer foci can remain dormant for several years before progressing to invasive cancer in early adulthood. Therefore, although endoscopic surveillance in expert centres can be offered in selected individuals, the definitive treatment is prophylactic total gastrectomy and there is no place for endoscopic resection.

Following endoscopic eradication therapy for early oesophageal and gastric cancer it is essential to initiate a surveillance programme to detect local recurrence and/or metachronous lesions arising from the background condition. The frequency of post-treatment surveillance is dependent on the final histology of the lesion, but generally consists of an endoscopy 3–6 months after resection and then annually [6,22].

Duodenum and Pancreatobiliary Tract

Endoscopic Intervention for Malignant Gastric Outflow Obstruction/Proximal Duodenal Obstruction

Gastric outflow obstruction is a common symptom in patients with malignancy of the distal stomach, duodenum and pancreas. The most common malignancy that results in gastric outflow obstruction is pancreatic cancer, with 15–20% of people presenting in this way [23]. The median survival in these patients is often limited and measured in months [24,25]. The classical symptoms of nausea, vomiting, dehydration and malnutrition leave patients in a weakened state and result in a poor prognosis if left untreated. Due to the short timeframe, the ideal procedure that would alleviate these symptoms would restore oral intake swiftly with minimal complications. Historically, the treatment options consisted of a surgical gastroenterostomy or a duodenal stent. Duodenal stenting has the advantage of providing quick symptomatic relief, but recurrence of obstructive symptoms is more common after stent placement than after surgery. A surgical approach provides more durable symptom relief [24] but requires postoperative recovery and may be obviated by the presence of extensive peritoneal disease or patient fitness. Moreover, there is an increased risk of complications if additional surgical biliary bypass is required. Overall, the consensus is that endoscopic stent placement is best suited for patients with a short life expectancy, whereas patients with a longer prognosis (several months or more) should undergo an alternative procedure [24,26,27].

Endoscopic ultrasound (EUS)-guided gastroenterostomy is a recent development used to treat gastric outflow obstruction. Under EUS guidance a small bowel loop close to the gastric wall is located and a lumen-apposing metal stent (LAMS) is positioned between the two lumens. Similar to duodenal stenting, EUS-guided gastroenterostomy can be carried out as an outpatient procedure. Compared with duodenal stenting, EUS-guided gastroenterostomy has a higher clinical success rate and a lower rate of stent dysfunction while having a comparable adverse event rate of around 10% [28,29]. Compared with a surgical gastroenterostomy, EUS-guided gastroenterostomy has a slightly lower technical success rate but a comparable or superior clinical success rate, with a shorter procedure time and a comparable adverse event rate [30]. Although the data on EUS-guided gastroenterostomy are encouraging, they are mostly based on limited patient numbers and retrospective data. There are ongoing prospective studies comparing EUS-guided gastroenterostomy with surgical gastroenterostomy and duodenal stenting. The main limitation of EUS-guided gastroenterostomy is its limited availability, although this will probable improve as the technique becomes more widely used. Also, significant ascites precludes EUS-guided placement of a LAMS using diathermy in the tip of the deploying mechanism (such as the Hot Axios™ system), as fluid acts as a heat sink.

Retrograde Biliary Stenting

Malignant biliary obstruction if often seen in primary pancreatic cancer and cholangiocarcinoma, but also encountered due to hepatic OR lymph node metastasis of cancer from other primaries, or lymphoma. The question of whether biliary decompression is necessary and the best way to achieve this requires careful consideration. Cholangitis is one of the few true indications for emergency biliary decompression. In most other cases there is time to consider the optimal drainage strategy, and in the case of complex biliary structuring, to transfer the patient to a specialised centre if needed. The optimal drainage strategy is determined by the aetiology and location of the malignant obstruction. Pancreatic cancer is a common cause of malignant obstruction and there is good evidence that biliary drainage in patients with resectable disease whose bilirubin is <250 μmol/l is associated with more complications compared with a straight to surgery approach [31]. The benefit for preoperative drainage in patients with a bilirubin >250 μmol/l is conflicting, and requires a case by case discussion [32,33]. In unresectable malignant distal common bile duct obstruction, an uncovered self-expanding metal stent should be placed, preferably via an endoscopic retrograde cholangiopancreatography (ERCP) [34].

Current guidelines advise against routine stenting of resectable malignant hilar strictures [34]. In unresectable intrahepatic biliary strictures, uncovered self-expanding metal or plastic stents can be used; the choice will depend on the anatomy of the stricture and the diameter of the involved bile ducts. It is crucial that before placement of uncovered metal stents, the diagnosis of malignancy is established with a high degree of certainty, preferentially with a tissue diagnosis. Biliary strictures are not always thought to be malignant, and placing an uncovered stent in a benign stricture can have significant subsequent complications.

Endoscopic Ultrasound-guided Biliary Drainage

ERCP is the preferred method for obtaining biliary drainage for malignant extrahepatic biliary obstruction (using either plastic or metallic stents). Where ERCP is unsuccessful or not possible due to tumour infiltration of the major papilla or proximal duodenum, the traditional approach has been to carry out percutaneous transhepatic biliary drainage (PTBD). Where possible, a self-expanding metal stent is deployed across the stricture to enable removal of the external drain.

EUS-guided choledochoduodenostomy and EUS-guided hepaticogastrostomy are emerging as alternative methods for biliary drainage where ERCP is not possible. EUS-guided choledochoduodenostomy involves the creation of a fistula from the duodenum to the common bile duct, with subsequent placement of a stent (most commonly a LAMS) to keep the tract open (Figure 3). It is a particularly attractive

Fig 3. Axial contrast-enhanced computed tomography image of the upper abdomen showing a lumen-apposing metal stent between the first part of the duodenum and the bile duct following endoscopic ultrasound-guided choledochoduodenostomy.

option for patients in whom ERCP is not possible and who also have ascites, given the increased risks of PTBD in the presence of ascites. EUS-guided choledochoduodenostomy can be used after failed ERCP in any patient who has a bile duct diameter of at least 12 mm. EUS-guided hepaticogastrostomy is where a tract is created (and stented) from the stomach to one of the bile ducts in the left lobe of the liver. It is technically more demanding than EUS-guided choledochoduodenostomy, but it is used where ERCP or EUS-guided choledochoduodenostomy are not anatomically possible (e.g. if a patient has an obstructing distal gastric tumour). EUS-guided hepaticogastrostomy has the advantage over PTBD that there is no need for an external drainage catheter in all rather than some cases. Given the transperitoneal route used for EUS-guided hepaticogastrostomy, this technique is less/not suitable for patients with ascites. Whether EUS-guided choledochoduodenostomy or EUS-guided hepaticogastrostomy should be considered as the first-choice technique for biliary drainage given the risks of ERCP (particularly acute pancreatitis) and PTBD is an area of current investigation [35,36]. Although the introduction of LAMS has simplified the technique of EUS-guided choledochoduodenostomy in particular, both EUS-guided choledochoduodenostomy and EUS-guided hepaticogastrostomy are still generally only an option in high-volume EUS centres (in contrast to PTBD), although data from case series and retrospective cohorts suggest that EUS-guided biliary drainage may be superior to PTBD [37–40].

Endoscopic Ultrasound-guided Radiofrequency Ablation of Malignant Pancreatic Lesions

EUS-guided RFA is a technique gaining interest in both benign and malignant pancreatic lesions [41]. EUS-guided RFA of pancreatic neuroendocrine tumours and unresectable pancreatic adenocarcinoma has been shown to be fairly safe and effective, with a high technical and clinical success rate [42–44]. Two small studies have reported an increased median overall survival (20.5–24.03 months) for patients with unresectable pancreatic adenocarcinoma when EUS-guided RFA was performed with concurrent palliative chemotherapy [45,46]. However, given the small number of patients, more studies are needed to confirm these promising results and to evaluate further the potential adverse events before making a recommendation for EUS-guided RFA to be widely utilised.

Intrabiliary Radiofrequency Ablation

Intrabiliary RFA is an emerging tool in the palliative management of malignant biliary obstruction, in particular cholangiocarcinoma. It allows for image-guided local delivery of thermal energy and can be used as either the primary treatment for malignant biliary strictures (often in combination with stent placement) or to help clear biliary stents occluded by ingrowth of malignant tissue [47–49]. Several studies also suggest that RFA can prolong patient survival [47,50,51], but these data are based on small studies and as such need to be interpreted with caution. Intrabiliary RFA has also been used to treat biliary bleeding from hepatobiliary tumours, although the evidence in support of this application is still limited [52]. Adverse effects of intrabiliary RFA include abdominal pain, pancreatitis, haemobilia, cholangitis and cholecystitis, all with an incidence of 1–2% [39,53].

Endoscopic Ultrasound Pancreatic Brachytherapy

Predominantly in the setting of locally advanced pancreatic cancer, EUS has been used to deliver brachytherapy as an alternative to external beam radiotherapy. A range of radiopharmaceuticals have been used, including a gel containing P-32 (a beta-emitter) [54] and seeds containing I-125 (a gamma-emitter) [55]. In a single-arm pilot study of EUS delivered P-32 gel in 50 patients with locally advanced pancreatic cancer, there was a reduction in tumour size, Ca19-9 level and fluorodeoxyglucose (FDG) uptake at 12 weeks after injection. The median survival was 15 months [56]. Compared with traditional external beam radiotherapy treatment for locally advanced pancreatic cancer of 25 fractions, a single treatment with EUS-delivered brachytherapy would have the advantage of significantly reducing the number of hospital attendances required (if shown to have equal or better efficacy). Newer external beam regimens typically involve only five fractions [57–59], so this difference would now be much smaller. Further research into this technique is needed before widespread adoption – particularly important would be to determine if it confers a survival advantage over standard treatment.

Endoscopic Ultrasound-guided Coeliac Plexus Interventions in Pancreatic Malignancy

Uncontrolled abdominal pain is frequently reported in patients with advanced pancreatic cancer [60,61] and is undertreated in up to 60% of patients [62]. Given the poor prognosis with inoperable pancreatic cancer, adequate pain control plays a vital role in the management of these patients.

The coeliac plexus is composed of paired ganglia located close to the coeliac trunk and transmits pain sensation from the pancreas. Coeliac plexus neurolysis (CPN) involves the ablation of neural pathways involved in pain transmission by injecting a local anaesthetic followed by a neurolytic agent, like absolute alcohol, into the area of coeliac plexus. CPN has been shown to be a useful adjunct in pain management regardless of the route of administration (percutaneous or EUS-guided). It is still a matter of debate as to which technique is superior, as there are no head-to-head comparison studies. However, given easy visualisation of the coeliac axis with EUS, which leads to precise injection (Figure 4), EUS-guided CPN is the preferred technique if available [63].

Two recent meta-analyses have concluded that EUS-guided CPN provides pain relief in over two-third of patients [64,65]. Studies have reported as high as 44% of

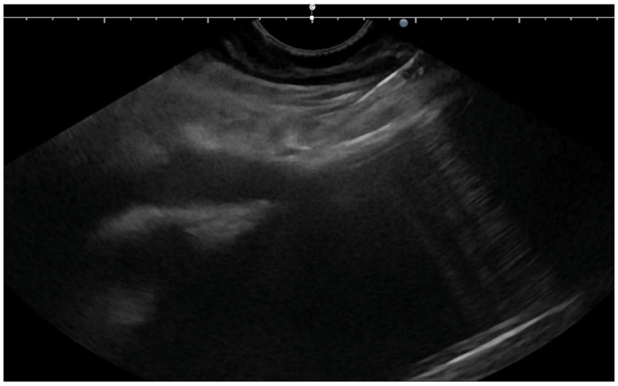

Fig 4. Endoscopic ultrasound image during endoscopic ultrasound-guided coeliac plexus neurolysis. The needle tip is at the origin of the coeliac trunk, prior to instillation of local anaesthetic and absolute alcohol.

adverse events with EUS-guided CPN, but most of these are minor and transient-like exacerbation of pain, diarrhoea and transient hypotension. Less than 1% of patients have a serious adverse event, including infection, bleeding, paraplegia or death [66]. There are still insufficient studies to recommend the appropriate timing of EUS-guided CPN – whether it should be done early at the diagnosis of pancreatic cancer or be kept as a treatment for intractable pain.

Overall, EUS-guided CPN is an effective modality in the management of pain in pancreatic cancer, but more well-designed studies are needed to recommend the optimal technique, ascertain the predictors of response, guide better patient selection and the timing of the procedure.

Endoscopic Ultrasound-guided Gallbladder Drainage

Similar to acute calculous cholecystitis, malignant obstruction of the cystic duct can lead to acute cholecystitis or symptomatic mucoele (hydrops) of the gallbladder. Surgical removal of the gallbladder (cholecystectomy) is the treatment of choice in such cases. EUS-guided gallbladder drainage is a promising modality for gallbladder drainage in patients who are unfit for surgery and is preferred over percutaneous transhepatic gallbladder drainage due to inherent risks of bleeding, bile leakage and pain at the site of insertion [67,68]. Moreover, percutaneous transhepatic gallbladder drainage is contraindicated in patients with ascites [69]. ERCP and transpapillary stent placement in cystic duct can be technically challenging, especially in malignant biliary obstruction and has a risk of pancreatitis [70]. EUS-guided gallbladder drainage facilitates an internal drain from the gallbladder to the duodenum or stomach. A review of 221 cases performed with conventional drainage devices, such as plastic pigtail stents, nasobiliary drainage tubes and self-expanding metal stents, showed an overall technical success of 83.7% (185/221) and clinical success in 92.3% (204/221) patients, with procedure-related adverse events in 7.2% of patients [71]. EUS-guided gallbladder drainage using LAMS is increasingly popular as it has the advantage of anchoring the gallbladder wall to the duodenal or gastric wall, thereby reducing the risk of bile leakage and stent displacement [72]. Data from eight retrospective studies of EUS-guided gallbladder drainage using LAMS with a total of 287 patients showed an overall technical success in 90.2% and clinical success in 93% of patients, with 8% reported adverse events [71]. Further prospective randomised studies are needed to establish EUS-guided gallbladder drainage as the procedure of choice for gallbladder drainage in patients unfit for surgery.

Conclusion

Recent technological developments have enabled a multitude of endoscopic therapeutic interventions that have changed the management of upper gastrointestinal cancers, allowing effective treatment of early malignant lesions and effective symptom palliation. Some of these techniques still have limited availability, but it is often possible to have access to them via multidisciplinary discussion involving an interventional endoscopist. Most of these procedures can be carried out as an outpatient day case or a day transfer. The overview of the endoscopic possibilities outlined in this review will hopefully facilitate this discussion and enable patients with an upper gastrointestinal malignancy to optimally benefit from the treatments interventional endoscopy has to offer.

Author contributions

EMG is the guarantor of integrity of the entire study. KB and EMG were responsible for study concepts and design. KB, EMG, PP, JH, MdiP, SV, GC and NRC carried out the literature research. KB, EMG, PP, JH, MdiP, SV, EG, GC and NRC prepared the manuscript. KB and EMG edited the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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