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2.1

Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR), initially developed in Japan to treat early gastric cancer, has evolved into a minimally invasive alternative treatment approach for early cancers throughout the upper and lower gastrointestinal tract. This endoscopic technique involves removal of affected mucosal tissue, in most cases with the use of preresection saline injection lifting of the target lesion to separate it from the submucosal layer. The lesion is most often removed with an endoscopic snare that applies electrocautery. The advantage of EMR is the added information provided by deeper en-bloc resection specimens for histological analysis.

The standard treatment of Barrett's esophagus (BE) with high-grade dysplasia (HGD) has been esophagectomy, due to the previously estimated 40% pooled risk of harboring occult invasive adenocarcinoma (Ferguson and Naunheim 1997; Pellegrini and Pohl 2000). However, more recent analysis of the literature points toward a much lower rate of invasive cancer at 12% (Konda et al. 2008). Intramucosal cancer (IMC) in the setting of BE has also traditionally been treated by esophagectomy, despite a relatively low incidence of lymph node metastasis of less than 1%, associated with noninvasive, T1a disease (Buskens et al. 2004; Pech et al. 2008; Stein et al. 2005). The use of EMR to treat focal areas of BE with HGD/IMC has been reported in several prior studies. However, focal resection solely of neoplastic areas has been associated with a high rate of synchronous and recurrent lesions noted by various groups, ranging from 14 to 47%, and increasing with longer observation times (Ell et al. 2000; Nijhawan and Wang 2000; May et al. 2002a, b; Pech et al. 2003; Larghi et al. 2005; Mino-Kenudson et al. 2005). With these issues in mind, circumferential endoscopic resection of BE has been utilized with promising results by

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select groups with the curative intention to eradicate all Barrett's epithelium thereby reducing or eliminating metachronous lesion development (Peters et al. 2006; Seewald et al. 2003; Giovannini et al. 2004; Larghi et al. 2007). EMR is the only endoscopic modality which serves the dual function of curative potential and provision of more accurate histological staging. In our institution, EMR resulted in a 45% rate of upstaging or downstaging of final BE neoplasia histology when comparing pre-EMR biopsies with resection specimens (Chennat et al. 2009) (Figs. 2.1 and 2.2).

With respect to esophageal squamous cell carcinoma (SCC), EMR has been shown to have similar rates of survival in patients with m3 or sm1 disease as compared to those who underwent surgery (Kodama and Kakegawa 1998). Thus, EMR may be an acceptable alternative particularly in patients at higher surgical risk (Shimizu et al. 2002). Follow-up intervals for surveillance after esophageal EMR have not been clearly defined to date, and should be performed in a protocol fashion.

The absolute indications for gastric EMR include well or moderately differentiated mucosal adenocarcinoma without ulceration or with an ulcer scar smaller than 2 cm for



Fig. 2.1 Long segment Barrett's esophagus with high-grade dysplasia

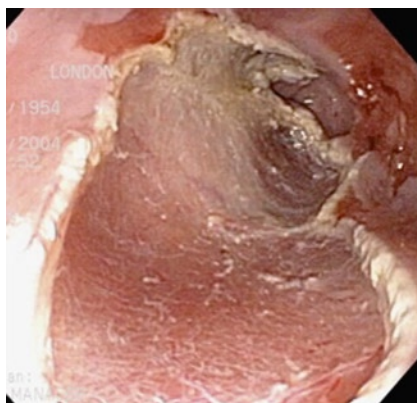


Fig. 2.2 Postendoscopic mucosal resection (EMR) of long segment Barrett's esophagus with high-grade dysplasia

superficially elevated lesions. These lesions have a negligible risk of lymph node metastasis. Poorly differentiated or signet ring cell morphology are contraindications to EMR regardless of lesion size (Larghi and Waxman 2007). EMR has also been applied to early neoplastic gastric lesions, with acceptable long-term outcomes, demonstrating a 1.9% recurrence rate in a pooled series analysis of documented complete resections (Kojima et al. 1998). However, the recurrence rate has been noted to be 18% in another series when incomplete resection occurred (Ono et al. 2001).

The use of EMR for neoplastic duodenal lesions has been reported with less frequency in the literature. Outcomes of larger series have demonstrated complete resection without major complications in the setting of duodenal nonampullary adenomas with HGD or carcinoma (Ahmad et al. 2002; Oka et al. 2003) (Figs. 2.3 and 2.4). The data on endoscopic removal of ampullary early neoplastic adenomatous lesions generally recommend the assessment of these lesions with endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography to exclude invasive or biliary/pancreatic ductal involvement (Binmoeller et al. 1993). Long-term success rates of EMR of these lesions have been documented in the range of 70–80%, but careful endoscopic surveillance is still mandated for follow-up (Catalano et al. 2004).

Colonic polypoid and nonpolypoid lesions with evidence of HGD or intramucosal carcinoma have been shown by various studies to be successfully treated by EMR technique, with recurrence rates ranging from zero to 15% (Caputi Iambrenghi et al. 2009; Kudo 1993;

Fig. 2.3 Duodenal adenoma

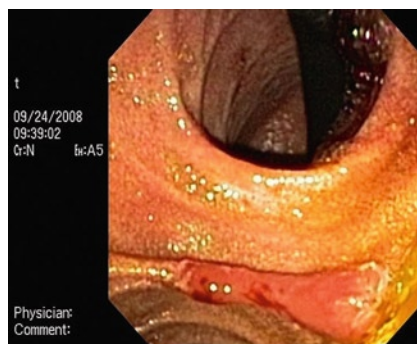


Fig. 2.4 Postendoscopic mucosal resection of duodenal adenoma

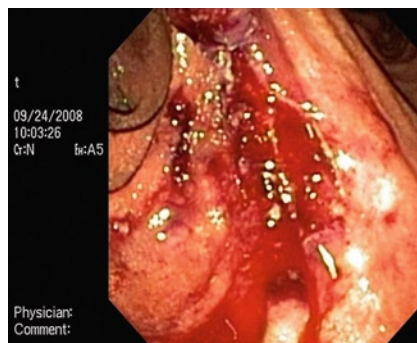
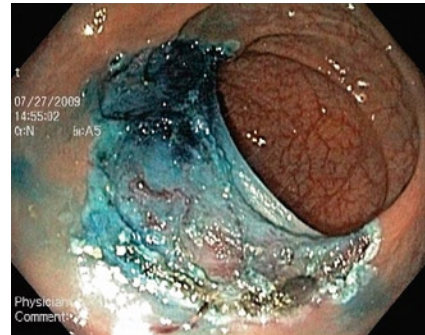


Fig. 2.5 Tubulo-villous adenoma in the rectum



Fig. 2.6 Postendoscopic mucosal resection of tubulo-villous adenoma in the rectum



Kudo et al. 2000) (Figs. 2.5 and 2.6). Lateral spreading tumors of the colorectum, which have different clinicopathologic features, have also been successfully addressed by EMR techniques (Hurlstone et al. 2004; Tanaka et al. 2001). Procedure-related complications such as bleeding and even perforation in certain cases can be successfully managed endoscopically (Raju 2009).

2.2

Endoscopic Submucosal Dissection

Due to concern about incomplete lesion resection via EMR, endoscopic submucosal dissection (ESD) has been developed and utilized particularly by the Japanese for more complete and extensive endoscopic resections (Figs. 2.7–2.10). Although the risk of perforation is higher with ESD vs. EMR, the safety profile and efficacy of ESD in patients with advanced age or poor performance status has been published (Hirasaki et al. 2005). ESD also has been utilized successfully in scenarios where prior EMR has been incomplete, leaving residual neoplasia in place. However, the use of ESD in locations where prior EMR has been attempted can be technically more challenging and less feasible due to tissue fibrosis formation (Yokoi et al. 2006).

Fig. 2.7 Intramucosal gastric cancer (T1) involving the pylorus

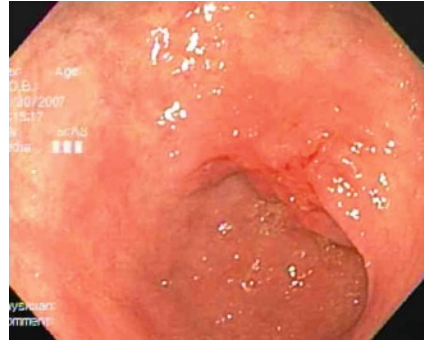


Fig. 2.8 Marking of desired endoscopic resection margins

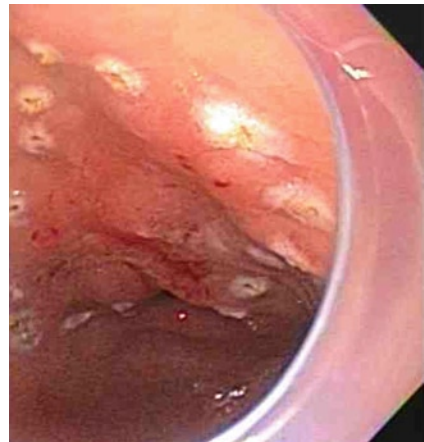


Fig. 2.9 Postendoscopic submucosal dissection (ESD) with pylorus preservation

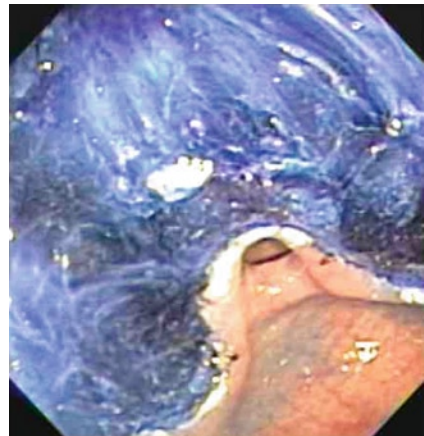
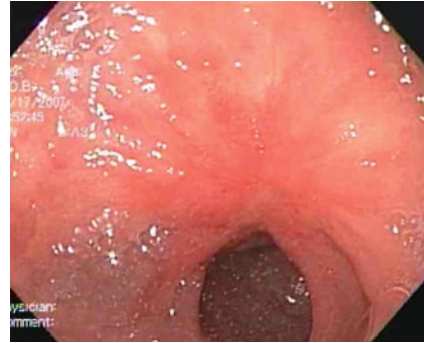


Fig. 2.10 Surveillance endoscopy 3 months after ESD with expectant scar and no residual cancer seen



2.3

Endoscopic Ultrasound

EUS and EUS-guided fine-needle aspiration (EUS-FNA) have together evolved into useful diagnostic and therapeutic modalities. Clinical management has been significantly affected by the addition of FNA technique to this procedure. The overall complication rate from EUS-FNA is less than 1% (Dye and Waxman 2002).

The accuracy and direct clinical impact of EUS-FNA is largely related to the availability of on-site cytopathology services. The clinical impact of on-site cytopathology in the evaluation of EUS-FNA for suspected malignancy cases has been previously studied by our center. A confirmatory diagnosis of positive or negative malignancy status was made more frequently if on-site cytopathology interpretation was present, decreasing the likelihood of an inadequate specimen or need for repeat procedure. Resources for on-site cytopathology evaluation should be allocated by all EUS centers (Klapman et al. 2003).

2.3.1 Pancreatic Adenocarcinoma

The role of EUS-FNA has become increasingly prominent in the diagnosis and treatment management of pancreatic adenocarcinoma (Figs. 2.11 and 2.12). Larger series have found that pancreatic adenocarcinoma EUS accuracy ranges from 78 to 94% for T stage disease and from 64 to 82% for N stage disease (Varadarajulu and Eloubeidi 2005). Chang et al. found that for pancreatic lesions, EUS-FNA had a sensitivity of 92%, specificity of 100%, and diagnostic accuracy of 95% for pancreatic lesions and 83, 100, and 88% for lymph nodes, respectively. Thus, with this level of accuracy, EUS-FNA peripancreatic N staging has had a direct impact on the reduction of unwarranted surgical procedures for these cancer patients, whom some authorities deem incurable by surgical resection (Chang et al. 1997).

EUS-FNA confers an added advantage over computed tomography (CT)-guided FNA of pancreatic lesions regarding two aspects. Through its direct ultrasound visualization,

Fig. 2.11 Pancreatic head mass measuring 5.1 cm visualized on endoscopic ultrasound (EUS) imaging



Fig. 2.12 EUS-guided fine needle aspiration (FNA) of pancreatic mass



EUS-FNA can safely target pancreatic lesions that are in close proximity to surrounding vascular structures. EUS also characterizes lesions considered too small to be detected by CT or magnetic resonance imaging (MRI) (Fig. 2.1). EUS-FNA offers a valuable role as a salvage diagnostic modality when CT-guided percutaneous FNA or endoscopic retrograde cholangiopancreatography (ERCP) cytology brushing samples are negative, but a strong clinical suspicion of pancreatic cancer persists (Fig. 2.2) (Gress et al. 2001).

2.3.2

Pancreatic Cystic Lesions

Pancreatic mucinous cystic neoplasms have malignant potential, and therefore require a differing management algorithm, often involving surgical resection. EUS-FNA derived

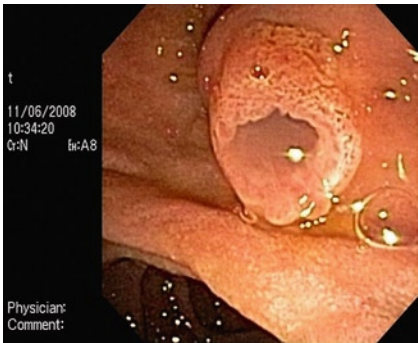
cytologic specimens in combination with cystic fluid tumor markers such as CEA (carcinoembryonic antigen) level help identify these lesions (Figs. 2.13 and 2.14). In a study which compared EUS-FNA diagnoses with final surgical pathology, FNA made an accurate diagnosis in 10/11 cases of pancreatic cystic lesions, with sensitivity and specificity for detection of malignancy of 100 and 89%, respectively, while the accuracy for identification of mucinous cystic neoplasms was 100% (Moparty et al. 2007).

EUS-FNA cystic CEA levels have been purported to be the most accurate (79%) diagnostic method for mucinous cystic lesions of the pancreas (Brugge et al. 2004). A multivariate analysis study found that the strongest predictor of mucinous neoplasia is the presence of identifiable mucin, followed by a CEA level greater than 300 ng/mL. Presence of extracellular mucin in cystic fluid. The determination of cystic fluid extracellular mucin presence has also been recommended in the work-up of mucinous lesions (Shami et al. 2007). Despite the ongoing controversies surrounding which type of marker is the optimal cystic diagnostic sample, EUS-FNA still serves an integral role in obtaining pancreatic cystic fluid for analysis.

Fig. 2.13 Intraductal papillary mucinous neoplasm (IPMN) seen on EUS



Fig. 2.14 Characteristic major papilla endoscopic “fish eye” appearance in the setting of IPMN



2.3.3

Hepatobiliary Neoplasms

Recent studies have shown that EUS-FNA may have an adjunctive diagnostic role in the work up of hepatobiliary cancers. In one study, 27 of 28 total patients had nondiagnostic or equivocal sampling of their biliary lesions via ERCP, percutaneous transhepatic cholangiogram (PTC), and/or CT-guided biopsy. EUS-FNA demonstrated a positive impact on management in 84% of total patients, by avoiding surgery for tissue diagnosis in patients with inoperable disease, facilitating surgery in patients with unidentifiable cancer by other modalities, and avoiding surgery in benign disease (Eloubeidi et al. 2004). In addition, EUS-FNA has an ancillary role in establishing M-stage disease in hepatic metastasis states. When a lesion, particularly in the left hepatic lobe, is not amenable to CT-guided or percutaneous biopsy, it oftentimes can be accessed transgastrically (Nguyen et al. 1999).

2.3.4

Submucosal Gastrointestinal Lesions

The ability of EUS to differentiate the five-layer gastrointestinal wall anatomy is the fundamentally unique aspect of this modality (Figs. 2.15 and 2.16). With the availability of miniprobe EUS, lesions in the right colon can be assessed also via a standard colonoscope. The accuracy rate for EUS-FNA of submucosal lesions is high (80%), and thus, potentially affects clinical decision making (Arantes et al. 2004). Distinguishing true leiomyomas from gastrointestinal stromal tumors (GISTs) has significant implications, as the two neoplasms have different prognoses and treatment options. Immunohistochemical findings that define these lesions can be derived readily from cell block material obtained by EUS-guided FNA (Stelow et al. 2003).



Fig. 2.15 Gastric gastrointestinal stromal tumor (GIST) seen in fundus on endoscopy exam

Fig. 2.16 Gastric GIST with characteristic submucosal splitting seen on EUS exam



2.3.5

Gastric Cancer

EUS has an overall 80% accuracy for T staging and 70% for N staging, and has been found to be superior to CT (Xi et al. 2003; Javaid et al. 2004). The major impact EUS-FNA has on gastric cancer management comes from the novel technique of endoscopic ultrasound guided paracentesis (EUS-P) of ascites to determine M staging. One study found that aspiration through EUS-FNA of a mean volume of 6.8 mL of ascites has a sensitivity, specificity, positive predictive value, and negative predictive value of 94, 100, 100, and 89%, respectively, for diagnosing malignant ascites. Accordingly, the finding of malignant ascites has significant impact on patient management, rendering a poorer prognosis (Kaushik et al. 2006).

2.3.6

Esophageal Neoplasms

As a complementary exam, EUS is used in conjunction with CT and positron emission tomography (PET) scanning in the staging of esophageal carcinoma. EUS vs. EUS-FNA for lymph node staging has been shown to have a sensitivity of 63 vs. 93% ($p=0.01$), specificity 81 vs. 100% (not significant), and accuracy 70 vs. 93% ($p=0.02$), respectively (Vazquez-Sequeiros et al. 2001). Celiac lymph node M1a disease confirmation via EUS-FNA has been found to be superior to CT scanning. As celiac lymph node involvement carries a poorer prognosis, and is usually treated with nonsurgical methods, this determination is critical (Parmar et al. 2002).

In cases of early-stage esophageal neoplastic disease, where minimally invasive procedures such as EMR can be considered for potentially curative treatment, EUS-FNA

has impacted management. Detecting unsuspected malignant lymphadenopathy via conventional endosonography and EUS-FNA dramatically changed the course of management in 20% of patients referred to our center for endoscopic therapy of BE with high-grade dysplasia or intramucosal carcinoma. Based on these results, we believe that conventional endosonography and EUS with FNA when nodal disease is suspected should be performed routinely in all patients referred for endoscopic therapy in this setting (Shami et al. 2006).

Subcarinal and supracarinal lymph node metastases proves critical in selection of transthoracic or transhiatal esophagectomy surgical strategy for distal esophageal carcinomas. In patients with a resectable distal esophageal carcinoma and subcarinal and/or supracarinal lymph nodes visualized on preoperative EUS, Fockens et al. prospectively studied the impact of EUS-FNA on surgical decision making. If EUS-FNA sampling of lymph nodes was positive for malignancy, then transthoracic resection was offered. Patients without demonstrated lymph node metastases were offered a transhiatal resection. Out of the 48 patients included in the study, lymph node metastases were found in 23% with EUS-FNA. Out of the 13 patients who had lymph nodes which were suspicious for malignancy on EUS, 31% had their diagnosis status changed to nonmalignant nodes with FNA confirmation. Conversely, EUS-FNA proved lymph node malignancy presence in 9% of 35 patients who had nonsuspicious-appearing nodes on EUS. Therefore, EUS-FNA has considerable impact on clinical decision management in distal esophageal carcinoma cases when transhiatal resection was presumptively planned (Marsman et al. 2006).

2.3.7

Colorectal Carcinoma

Recently, locoregional stage-focused colorectal cancer therapy has been given higher emphasis. EUS-FNA colorectal cancer N-staging, especially nonjuxtatumoral lymph nodes, has been shown to have clinical impact on decision making. This technique also aids in detecting disease recurrence (Shami et al. 2004). In the setting of re-staging after chemoradiation therapy, EUS has virtually no role, due to posttreatment induced local inflammation. However, when recurrence is not present intraluminally, and is suspected in the face of rising CEA levels, EUS-FNA can be helpful (Dye and Waxman 2002).

2.3.8

Lung Malignancy

The posterior mediastinum can be accessed for FNA through the esophageal wall, for staging of lung cancer. Sensitivity, specificity, and accuracy for EUS-FNA in mediastinal analysis have been reported as 91, 100, and 93%, respectively. Certain experts advocate EUS-FNA as the initial diagnostic procedure for suspected lung cancer with enlarged mediastinal lymphadenopathy, to possibly reduce the number of surgical staging procedures (Annema et al. 2005; Micames et al. 2007).

2.3.9

Therapeutic Applications of EUS-FNA

The following section will highlight EUS-FNA-based interventional applications with specific targeted therapies.

2.3.9.1

Celiac Plexus Blockade

Refractory pain management via celiac plexus neurolysis (CPN) through EUS guidance for inoperable pancreatic cancer has become an increasingly utilized modality. EUS utilizes an anterior approach to the celiac axis, so that the risk of resultant paraplegia is theoretically negligible, while posterior percutaneous approach confers a 1% risk (Raj and Chen 2006). In a large prospective study, 78% of patients had lower pain score at 2 weeks after EUS-CPN, with a sustained response of up to 24 weeks, independent of narcotic usage or adjuvant therapy (Gunaratnam et al. 2001).

2.3.9.2

EUS-Guided Pancreatico-Biliary Access/Drainage

When achieving selective ductal drainage through standard ERCP is unsuccessful, EUS-guided pancreatic or biliary access of the desired duct has been effectively performed as an alternative to surgery or percutaneous drainage (Figs. 2.17 and 2.18). EUS-FNA puncture is performed into an obstructed and dilated biliary or main pancreatic duct. After fluoroscopic guidewire access is established via the FNA needle, a transenteric fistula is created, through which stent placement in the desired duct can be performed, either directly or via a rendezvous ERCP. At qualified high-volume EUS/ERCP centers, this technique can



Fig. 2.17 EUS-guided pancreatic ductal access with contrast injection under fluoroscopy

Fig. 2.18 Pancreatic stent placed after EUS-guided pancreatic ductal access for rendezvous procedure



serve as an alternative salvage approach to difficult pancreatico-biliary access cases, with acceptable success and complication rates (Shami and Kahaleh 2007).

2.3.9.3

EUS-Guided Fine Needle Injection

A concept known as EUS-guided fine-needle injection (EUS-FNI) has evolved from using EUS-FNA as a portal to introduce various agents with therapeutic capabilities. Chang et al. have reported on injection of allogeneic mixed lymphocytic culture into unresectable pancreatic tumors. However, the study was terminated early when survival was determined to be less favorable in the lymphocytic culture recipients compared with the patient group receiving gemcitabine (Chang et al. 2000). Feasible injection of a replication-deficient adenovector into unresectable pancreatic tumors, with well-tolerated and fair responses has also been reported by the same investigator (Raju 2009).

2.4

Endoscopic Management of Malignant Gastrointestinal Obstruction

2.4.1

Malignant Esophageal Obstruction

The palliation of malignant esophageal obstruction has been enhanced by the development of self-expanding metallic covered or uncovered stents (SEMS) (Figs. 2.19 and 2.20). These devices offer relief from dysphagia, poor nutrition, and weight loss. A host of alternate nonstent therapies have been utilized such as argon plasma coagulation, photodynamic therapy, laser, brachytherapy, local injection of alcohol, and antineoplastic drugs. However, they have lost popularity due to lack of efficacy or expense, precluding logistical

Fig. 2.19 Nonoperable malignant esophageal stenotic obstruction

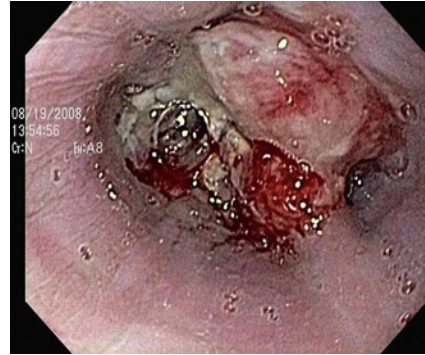
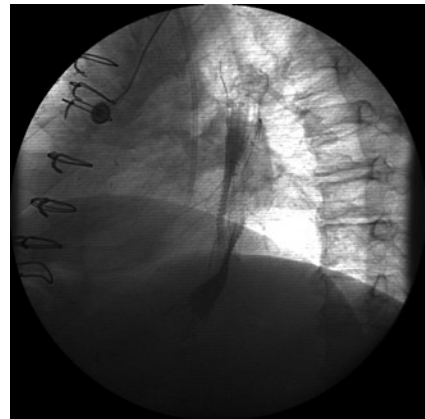


Fig. 2.20 Postesophageal stent prosthesis placement for relief of dysphagia



usage. The use of chemoradiation adjunctively with stent placement can be a strategy for malignant dysphagia relief, though the acute local inflammation from the chemoradiation can make tissue more friable and irritated temporarily (Fleischer and Sivak 1985; Christiaens et al. 2008; Okunaka et al. 1990; Homs et al. 2005; Wadleigh et al. 2006; Burris et al. 1998). It has been shown that covered metal stents help prevent tumor in growth without substantially raising migration rates, when compared to uncovered ones (Vakil et al. 2001). However, stent migration still presents itself as a significant complication particularly in distal esophageal obstructions (Verschuur et al. 2008).

The use of SEMS as sole therapy for patients with inoperable disease who have not already received, or are unfit for, chemoradiotherapy has been studied. Thousand stents were placed in 951 patients. Long-term follow-up was obtained for 35% with a median survival of 250 days (IQR 130–431, 95% CI 217–301). Mean dysphagia scores improved from 3.3 (SD 0.6) pre-SEMS to 1.0 (SD 1.3) for 78 patients still alive and 1.8 (SD 1.2) at

time of death of 165 patients. SEMS-related mortality was 0.3%, demonstrating that SEMS can effectively palliate inoperable esophageal cancer (White et al. 2009).

2.4.2

Malignant Gastro-Duodenal Obstruction

Endoscopic palliation of gastro-duodenal malignant obstruction can help obviate the need for otherwise invasive surgery in patients with limited life expectancy with unresectable cancer. In a study where 81 stents were inserted into 75 patients, the technical and clinical success rates were 98 and 87%, respectively. The median stent patency was 55 days (95% CI 40–70 days). The median survival was 79 days (95% CI 58–123 days). Stent occlusion caused by tumor ingrowth or overgrowth occurred in 31%. Use of covered stents (odds ratio 0.29, 95% CI 0.11–0.76; $p=0.01$) and chemotherapy after stent placement (odds ratio 0.34, 95% CI 0.13–0.91; $p=0.03$) were significant prognostic factors for ongoing stent patency after a multivariate analysis. This study found that endoscopic stenting is a safe and effective palliation treatment for malignant gastric outlet obstruction and a covered stent and chemotherapy are significant prognostic factors for stent patency (Cho et al. 2009). Successful stent placement in otherwise endoscopically inaccessible regions of the small bowel has been described for malignant obstruction using double-balloon-enteroscopy-assisted techniques (Ross et al. 2006).

2.4.3

Malignant Colorectal Obstruction

Colorectal obstruction expandable metallic stent placements for either palliation or preoperatively as a bridge to surgery have become mainstays of therapy (Figs. 2.21–2.23). Studies have shown that for acute colonic obstruction, outcomes of SEMS placement are more favorable to surgery with the respect of overall medical cost and mortality. Risks of stent placement include tumor ingrowth, migration, and tenesmus/pain if stent placement is close to the anal verge (Dekovich 2009; Siddiqui et al. 2007).



Fig. 2.21 Malignant obstruction at the ileocecal valve with guidewire for future stent placement

Fig. 2.22 Endoscopic view after ileocolonic stent placement across malignant stenosis

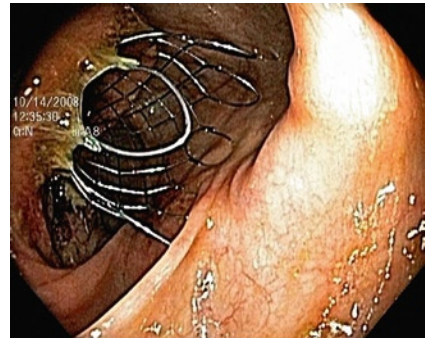
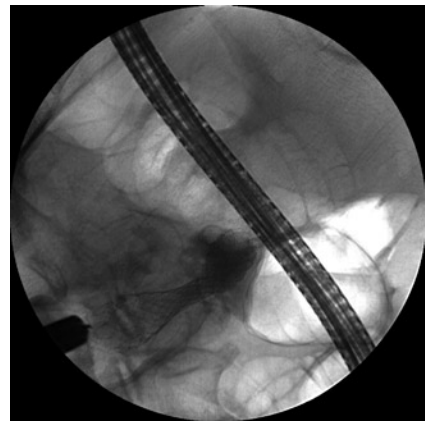


Fig. 2.23 Fluoroscopic view after ileocolonic stent placement across malignant stenosis



2.4.4

Malignant Biliary Obstruction

Malignant biliary obstructions often result from intrinsic biliary tract cancers or extrinsic compression from pancreatic tumors or surrounding lymphadenopathy. The onset of jaundice portends greater morbidity and mortality in these patient populations, who also may be immunosuppressed by adjuvant or palliative chemotherapy. In cases of operable disease, ERCP plastic biliary stenting will provide temporary therapeutic relief of jaundice prior to surgery. The plastic stent variety has a three-month patency as advocated by industry, and will require repeat future stent exchanges. In an effort to reduce the need for repeat procedures, and enhance longer stent patency, SEMS have been developed for the biliary tract for inoperable cases.

Cross-sectional imaging (preferably magnetic resonance cholangiopancreatography [MRCP]) is often utilized preprocedurally to determine the appropriateness of endoscopic stent therapy and to guide stent placement. Hilar cholangiocarcinomas particularly benefit from the preprocedure “mapping” provided by 3-D reconstructive MRCP imaging, so as to avoid “blind” contrast injection into otherwise undrainable hepatic systems.

Fig. 2.24 24 Hilar malignant biliary obstruction cholangiogram via endoscopic retrograde cholangio-pancreatography (ERCP)

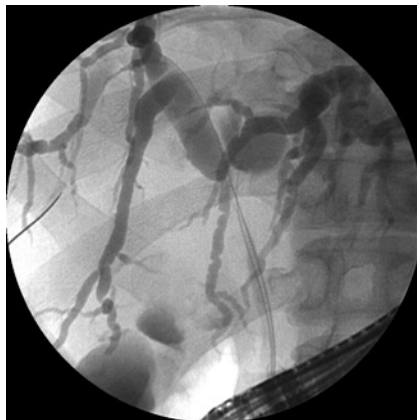
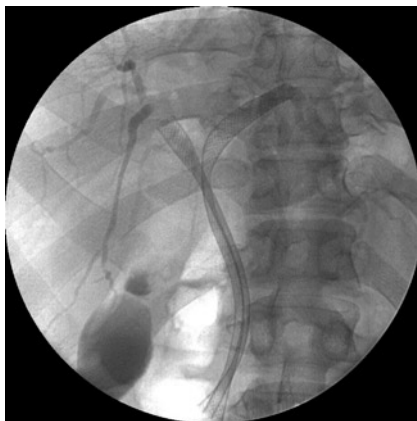


Fig. 2.25 Postbilateral self-expanding metal stent placement across malignant hilar biliary obstruction



Self-expanding metal stents are preferred over plastic stents for their cost effectiveness if patient survival is estimated to be greater than 6 months. Photodynamic therapy is a treatment option for local but inoperable cholangiocarcinoma which is capable of prolonging survival (Stern and Sturges 2008) (Figs. 2.24 and 2.25).

2.5 Conclusion

The field of interventional gastrointestinal endoscopy is transforming into a robust specialty that can offer a wide array of minimally invasive nonsurgical alternatives for diagnostic and therapeutic objectives in gastrointestinal oncology patients. The outcomes of these techniques are often favorable to surgical approaches. Development of improved endoscopic imaging and ancillary devices will enhance the field's progress and further enable physicians to accomplish previously incomprehensible techniques for hopefully better quality of patient care.

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