Endoscopic Management of Large Duodenal Adenomas

Duodenal adenomas are often incidentally detected during routine upper endoscopies, yet data regarding effective management are scarce. Owing to the potential for malignant transformation, duodenal adenomas should be excised whenever possible. Traditionally, surgical resection was the mainstay in removing duodenal adenomas. However, due to the anatomic location of the duodenal adenomas, surgeons often faced difficulties requiring extensive segmental resection or pancreaticoduodenectomy. With advances in endoscopic tools and techniques, duodenal adenomas are increasingly managed endoscopically. There are two main endoscopic resection techniques, endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). While most endoscopists are unfamiliar with the techniques of ESD, they are well acquainted with EMR, largely from frequent necessity during colon polyp removal. Compared to EMR during colonoscopy, however, EMR in the duodenum is much more arduous and complications are more problematic to manage. In this article, all practical points on how best to perform duodenal adenoma resection and data on follow-up are reviewed.

INTRODUCTION

Duodenal adenomas may occur sporadically or as a part of familial adenomatous polyposis (FAP) syndrome. FAP patients are more likely to present with multifocal disease than patients with sporadic adenomas. Adenomas in the duodenum may occur at the ampulla or non-ampullary locations. The strategy in managing ampullary adenomas is markedly different than that of non-ampullary duodenal adenomas (NADA). In this review, we will only focus on NADA.

Duodenal adenomas may progress to carcinomas, somewhat resembling the process of colon adenoma to carcinoma sequence. Cassani et al., in a retrospective study of 213 patients at a tertiary referral cancer center, reported while there was no difference between FAP and sporadic groups with progression to new dysplasia or cancer when observed without intervention, there was a significant difference in overall survival between the FAP and sporadic groups (P < 0.001). The range of time of progression to cancer was 3-161 months.
Therefore, observation is not ideal in managing duodenal adenomas, which leaves the affected patients with two alternate options: 1. Surgical resection 2. Endoscopic management with resection and/or ablation.

**Management of Large Non-Ampullary Adenomas**

Surgical resection of NADA often presents challenges mainly from location of the polyps in the duodenum. Compared to operations involving the stomach or colon, the surgical approach to the duodenum is demanding as it is bordered by other major organs in the retroperitoneal space.\textsuperscript{3}

The goal of surgical resection would be primary resection and anastomosis of the duodenum; however, it is often not possible to have such an outcome, either secondary to the particular location of the polyp and/or the extent of polyps, thus resulting in duodenal resection, combined with jejunal anastomosis. Furthermore, as the pancreatic duct and bile duct join at the ampulla, patients may face pancreaticoduodenectomy for NADA when the adenoma involves the medial wall near the papilla in the second portion of the duodenum. Therefore, patients and surgeons frequently choose or advocate endoscopic means of therapy for NADA.

While technically facile, endoscopic ablations by argon plasma coagulation (APC) or heater probe are not suitable in most cases, because the ablative attempt would not be able to cover the entire adenomatous area owing to the size of the adenoma(s). Consequently, patients and providers resort to endoscopic resection (ER) in managing NADA. In general, there are two ER techniques; endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). There are pros and cons in each technique. EMR is technically less challenging to perform than ESD, but provides multiple segmented specimens making it impossible to assess lateral-margin status. On the other hand, ESD provides the specimens in one piece allowing accurate evaluation of lateral-margins. Even though endoscopic resection has been successfully performed by EMR or ESD for benign mucosal and early malignant tumors in various locations of the gastrointestinal tract, ESD in the duodenum should be attempted only by experts with thorough preparation and discussion of the options with the patient and surgical colleagues; such discussions should consider technical difficulty, thinness of the duodenal wall, and the risk of immediate or delayed perforation.
Endoscopic Management of Large Non-Ampullary Duodenal Adenomas

1. Endoscopic Visualization of Duodenal Adenoma and Defining the Margins for Resection

To improve visualization of adenomas in the duodenum, one may use chromoendoscopy techniques by spraying diluted methylene blue or indigo carmine. However, preparation of the solution and spraying the dye necessitate additional steps in the resection procedure. With the advent of narrow band imaging (NBI) technology, the duodenal polyps can be better detected, obviating the need to employ the coloring agents. Once the margins are clearly visualized, the planned resection margin should be marked using a hot snare or ESD knife.

2. Preparation for Endoscopic Resection

Before the initiation of ER, intubation should be considered to protect the patient’s airway as the endoscope may be repeatedly advanced into the duodenum during the resection process. Regarding solutions to inject into the submucosal layer, there are multiple candidates with varying viscosity. The higher the viscosity, the longer the submucosal lift will last. Among the most viscous solutions are hyaluronic acid and hydroxypropyl methylcellulose, which are relatively inexpensive, but not readily available in the United States. Other viscous solutions include hypertonic solutions of sodium chloride (3.0%), dextrose (20, 30, or 50%), glycerol, and albumin. Albumin is ubiquitous in hospitals, yet expensive. Normal saline solution (0.9%) is inexpensive, available, and easy to inject. Though viscous solutions are often necessary for ESD, it is not imperative to have such solutions in EMR, where saline solution mixed with epinephrine may be readily used.

3. Techniques of Endoscopic Mucosal Resection

3a. Injection-assisted EMR

In this technique, a mixture of solution is prepared by injecting 10 cc of epinephrine (1:10,000) to either 250 mL or 500 mL of normal saline. Usually, a small amount of indigo carmine or methylene blue is added to provide blue color on the sub-adenomatous base after EMR. Once the solution is prepared, 10 cc aliquots can be made using syringes. Submucosal injection is performed by advancing the injection needle at the normal mucosa near the endoscopic edge of the polyp. To avoid transmural injection, the needle should be introduced as injection is being applied. Once the submucosal bleb is created, further injection of the solution should be carried out observing continuing elevation of the mucosal layer. There is no need to raise all areas of the edge before commencing on resection. Resection can be carried out using either cut or coagulation electrocautery with a preferred setting. Most endoscopists use blended cutting (more cutting than coagulation), rather than coagulation settings. This is because of the feared complication of delayed perforation from transmural thermal injury. There are no firm recommendations where EMR should begin in terms of location; EMR may be initiated
at the proximal or distal end, or right or left edges, whichever would be strategically advantageous for complete resection. In terms of snare size, 15 mm is sufficient. Use of a larger size snare increases the risk of grabbing too much tissue, including the muscularis propria layer, because the duodenal wall is quite thin and delicate. To ensure the muscularis propria layer is not involved in the resection, it is vital to loosen the snare slightly by shaking after grabbing the segment to be resected before applying electrocautery. Bleeding can usually be managed using a coagulation grasper while performing EMR. Before completing the EMR session, it is also essential to inspect the EMR base to ensure no adenomatous tissue is remaining and to prevent delayed bleeding. Any suspicious tissue or visible blood vessels in the resection base should be treated at the time of EMR. Experts of ER prefer using a coagulation grasper rather than APC for treatment of residual tissue or vessels. When APC is used, one may occasionally observe insufflation of submucosal tissue from emitted argon gas. The significance of treating the base after ER was well illustrated in the study by Lépilliez et al.; the authors reported that there was no delayed bleeding when the resected base was treated by endoscopic clipping or APC, in contrast to a 22% bleeding rate without the treatment.  

3b. Band Ligation-assisted EMR (EMR-L)  
Although EMR-L is minimally invasive and easy to perform in the esophagus, stomach, and rectum, EMR-L should not be employed in resecting duodenal adenomas. Different from the walls of the esophagus, stomach, or rectum, the duodenal wall is very pliable and thus suctioning of the polyp by applying a band can bring the entire wall into the banding cap, resulting in perforation when resected (Figure 1). EMR-L is based on the technique of variceal band ligation. When there is a sessile or flat polyp, suction is applied to the targeted area, and subsequently a band is applied to create a pseudopolyp. Once the pseudopolyp is created, it is resected using a snare with electrocautery. In general, there are two sizes available in EMR-L kit (Duette Multi-Band Mucosectomy device, Cook Medical Inc., Winston-Salem, NC), one for the diagnostic upper scope and the other for the therapeutic upper scope (one to fit endoscopes with outer diameters of 9.5 to 13 mm and the other 11 to 14 mm). It is important to select proper endoscope and the band ligation kit to ensure precise fitting of the device. It is recommended to place one band and immediately cut the segment, rather than placing multiple bands and cutting all banded areas in sequence. By slightly overlapping the cutting area, while avoiding injury to the muscle layer, one can avoid leaving slivers of adenomatous tissue in between the bands.

3c. Cap-assisted EMR (EMR-C)  
In this technique, an EMR cap is attached to the tip of the scope and submucosal injection is performed using an injection needle and the aforementioned solution mixture. Then, an EMR snare provided in the EMR kit (Olympus America Inc, Center Valley, Pa) is placed in the internal groove of the EMR cap, creating a loop. Next, the targeted lesion is suctioned into the cap and the snare is fastened while suction is still being applied. One caveat is, as mentioned under EMR-L section, suction should be applied with caution. Full suction is likely to bring the full thickness of the duodenal wall into the cap, resulting in perforations when resected. Therefore, it is paramount to apply a controlled suction; one-half or less of vacuum suction should be applied when EMR-C is performed in the duodenum. Furthermore, this technique should be reserved only for the experts with extensive experience in ER. Even then, a multidisciplinary approach should be employed alerting surgical colleagues before EMR-C is planned due to perforation risk.

4. Endoscopic Submucosal Dissection (ESD)  
While EMR provides multiple segmented specimens, ESD allows resection of the entire segment in one piece, thus allowing clear discernment of margin involvement. In ESD, following injection of one of the aforementioned solutions under the targeted lesion, the submucosa is dissected by an electrosurgical knife. Thus, ESD allows excision of larger and deeper lesions with curative intent than can be resected by EMR. ESD, however, requires an extensive dedicated training, including repetitive practice at ex-vivo and live animal lab as well as closely supervised attempts in human cases, in order to attain competency.

Data regarding the efficacy and safety of duodenal adenoma resection are scarce. Kim et al. reported the result of their retrospective observations of 64 lesions in 62 patients who underwent endoscopic resection of duodenal subepithelial tumors in an academic setting. Injection assisted EMR was performed in 38 lesions, EMR-L in 18, and ESD in 8. The overall en bloc
Endoscopic Management of Large Duodenal Adenomas

resection and complete ER rates were 96.9% (62/64) and 100% (64/64), respectively while complete pathologic resection was 76.6% (49/64). Ironically, ESD was independently associated with incomplete pathologic resection. Strikingly, the procedure-related bleeding and perforation rates were 6.3% and 4.7%, respectively. Follow-up data were promising showing no recurrence in patients who underwent complete ER at a median follow-up of 20 months (range 6-112 months). In the study reported by Cassani et al., 47/213 patients (14 FAPs and 33 sporadic adenomas) underwent EMR of their adenomas and 46/47 achieved endoscopically complete resection. The deep margin was positive in 4 resections (9%). Evidence of recurrence was seen in 3 patients (6%). All recurrences occurred within 1 year of EMR.

Hoteya et al. compared the outcomes of EMR and ESD in 129 endoscopic resections for NADA. The authors performed 74 ESD (49 lesions > 20 mm, and 25 lesions < 20 mm in diameter) and 55 EMR procedures. In terms of technical outcomes, the authors concluded that EMR was safer than ESD for small size NADA as perforation and delayed bleeding were significantly higher in both ESD groups than in the EMR group. The authors felt prophylactic endoscopic closure of large mucosal defects after ESD was useful in preventing the complications. Navaneethan et al. reported a systemic review on the efficacy and safety of endoscopic resection of duodenal polyps; in total, the meta-analysis included 440 patients (485 duodenal polyps) from 14 studies. The mean size of polyps ranged from 13 mm to 35 mm with 1.9% being adenocarcinoma. The majority of the polyps were sessile (92%) and located in the 2nd portion of the duodenum. EMR was successful in 93% (95%CI 89-97%) with immediate bleeding rate of 16% (95%CI 10-23%), delayed bleeding rate of 5% (95%CI 2-7%), and perforation rate of 1% (95% CI 1-3%). In addition, APC was applied post-EMR in 29% of the procedures to ensure complete eradication of the dysplastic tissue. Surgical intervention was required in 12 patients after initial EMR (3%); of which 8 cases of non-curative EMR and 4 for procedure related adverse events (3 perforations and 1 hemorrhage).

Follow-Up of Large Non-Ampullary Adenomas After Endoscopic Resection
In our hospital, we routinely keep patients for observation for 1-2 days post ER with follow-up blood counts the (continued on page 36)
morning after the procedure. To protect the ER site, proton pump inhibitor is given either intravenously or by mouth.

Regarding diet, the patient is kept fasting on the day of ER. On post-operative day 1, clear liquids are given, which are advanced to full liquids for the following 2 days, and then soft diet for the ensuing 3 days.

If the patient has abdominal pain or rebound tenderness, delayed perforation should be considered and excluded. If abdominal pain persists and/or increases, computed tomography (CT) of the abdomen with oral and intravenous contrast is indicated, along with surgical consultation. If CT is indeterminate, diagnostic and/or therapeutic upper endoscopic examination is warranted. If a small perforation is noted, attempts to close it endoscopically can be made along with urgent surgical consultation.

1. Delayed Perforation
Even after successful ER, monitoring for delayed perforation is advised, especially when the duodenal adenoma is large and located in the 2nd portion of the duodenum or distal to the ampulla. Ideally, leaving a thin submucosal layer over the muscularis propria would be ideal, but is not always possible. This is even more difficult to achieve when the ER base is tethered to the muscularis propria layer by fibrotic scar tissue. Scar tissue may form from previous vigorous biopsies and/or ablative therapy by heater probe, electrocautery, or APC treatment. Therefore, if ER is planned or considered, one or two small biopsies at the periphery of the lesion would be ideal.

The concern for delayed perforation should be heightened if the muscle layer is exposed and/or damaged during ER. The biliary and pancreatic enzymes may auto-digest the exposed muscle layer. Therefore, if endoscopic closure is possible, the application of clips should be attempted. However, as the duodenum is fixed in the retroperitoneum, opposing the mucosal/submucosal defect is not straightforward. Furthermore, if a clip is placed on the muscularis propria layer, it can cause immediate perforation or enlarge a perforation that had already occurred. To divert the pancreatic enzymes and bile, one may consider placing nasobiliary and/or naso-pancreatic tubes; but placing these tubes are technically challenging and uncomfortable to patients. To circumvent this enigma after EMR/ESD of NADA, Hochberger et al. recently introduced a novel approach of placing a vacuum sponge, 2.5 cm long and 1.8 cm wide (Endo-Vac; Braun, Melsungen Germany) in the duodenum through an overtube (US Endoscopy, Mentor, Ohio, USA).8

Using this technique, the drainage tube connected to the sponge was externalized via the nose, and suction of approximately 125 mmHg was applied. The authors also performed endoscopic closure using over-the-scope clip and endoclips immediately after EMR/ESD to reduce or eliminate the unprotected area. EGD on post-procedure day 4 showed no signs of perforation and excellent wound healing upon retrieving the sponge. Surgical management of perforations depends on the amount of time elapsed between the time of perforation and timing of surgery. Immediate surgical intervention would allow...
primary repair or resection of the perforated segment with primary anastomosis. However, when there is a delay in surgical management, a significant amount of bile and pancreatic secretions may collect in the retroperitoneal space, complicating the operation. At the operation, pus may be found in the retroperitoneal space during irrigation and aspiration (wash-out). In this situation, primary anastomosis is not possible; thus diverting surgical resection and anastomoses would be performed along with placement of multiple drainage tubes at the pockets of fluid collections in the retroperitoneum by consultation with interventional radiology. The recovery from this type of operation is lengthy and arduous, especially in the elderly where a long-term physical and occupational therapy would be needed.

2. Surveillance for Recurrence
In the aforementioned meta-analysis of EMR, the recurrence rate after EMR was 15% (95% CI 7-23%) over a median follow-up of 6-72 months, and endoscopic resection of recurrent polyps was successful in 62% (95% CI 37-87%). Therefore, it is crucial to provide a continuing endoscopic surveillance in this population after ER. The first esophagogastroduodenoscopy (EGD) post-EMR is usually performed in 3 months when the ER site is carefully examined for any residual lesions or early recurrence. If any residual polyp or recurrence is detected, endoscopic resection, biopsy, and/or ablative therapy may be performed. If EGD is unremarkable, it would be reasonable to perform a surveillance EGD in 1 year and then annually for several years; provided that the original adenoma(s) were absent of high-grade dysplasia or carcinoma.

**Future Management of Large Duodenal Adenomas**
Ichikawa et al. reported the safety and feasibility of laparoscopic and endoscopic cooperative surgery (LECS) for early non-ampullary duodenal tumors in 12 patients. In this study, 13 early duodenal lesions (10 adenocarcinomas, 2 neuroendocrine tumors, and 1 adenoma) in 12 patients were managed by LECS. All submucosal tumors were successfully resected en bloc and the defect in the duodenal wall was sutured after resection. For epithelial lesions, ESD was performed and the base of the ESD was reinforced via manual suturing. Notably, there were two intraoperative perforations in 2/11 epithelial lesions while ESD was being performed; these were successfully repaired via laparoscopic approach. The median procedure time was 322 minutes with no significant blood loss; 1 patient had minor leakage due to a pancreatic fistula.

The LECS technique emphasizes the importance of a multidisciplinary approach for this challenging task. As was previously emphasized, the most feared complication of duodenal adenoma resection is perforation. If the size of the perforation is small and surrounding mucosa and submucosal layers are available, it would be reasonable to attempt endoscopic closure using clips. However, when the size of perforation is greater than 2 cm, it would be difficult to close it by placing clips. Endoscopic suturing (ES) would be valuable in this situation, however ES is a difficult procedure to master and attain proficiency. While ES is being performed, more carbon dioxide can be introduced into the peritoneum, as well. It is imperative to ensure no pooling of fluid at the site of perforation, while ES is being attempted, by repositioning the patient as appropriate. Future research should focus on developing artificial tissue that can be sprayed to cover the perforation immediately (for example, such as fibrin glue or cyanoarylate); this material would adhere to the mucosa creating instantaneous cover at the perforation.

**CONCLUSION**
Duodenal adenoma resection is a daunting task, which requires careful planning prior to attempted resection. The patient and the family should be invited to partner with providers in discussing therapeutic options, risks involved, and potential complications with their consequences. It would be ideal to discuss the case at multidisciplinary conference, in order to find the best approach for effective treatment, and 2, seek early and active involvement of a surgeon as perforations are grave adverse events in a significant minority of patients. Following successful ER, the patient should be closely monitored for delayed complications and recurrence. Future endeavors should focus on development of effective and convenient diversion of biliary and pancreatic secretions in the duodenum, potential tissue covering/protectants and/or easier endoscopic suturing systems to solve the conundrum of endoscopic perforation management.
References


