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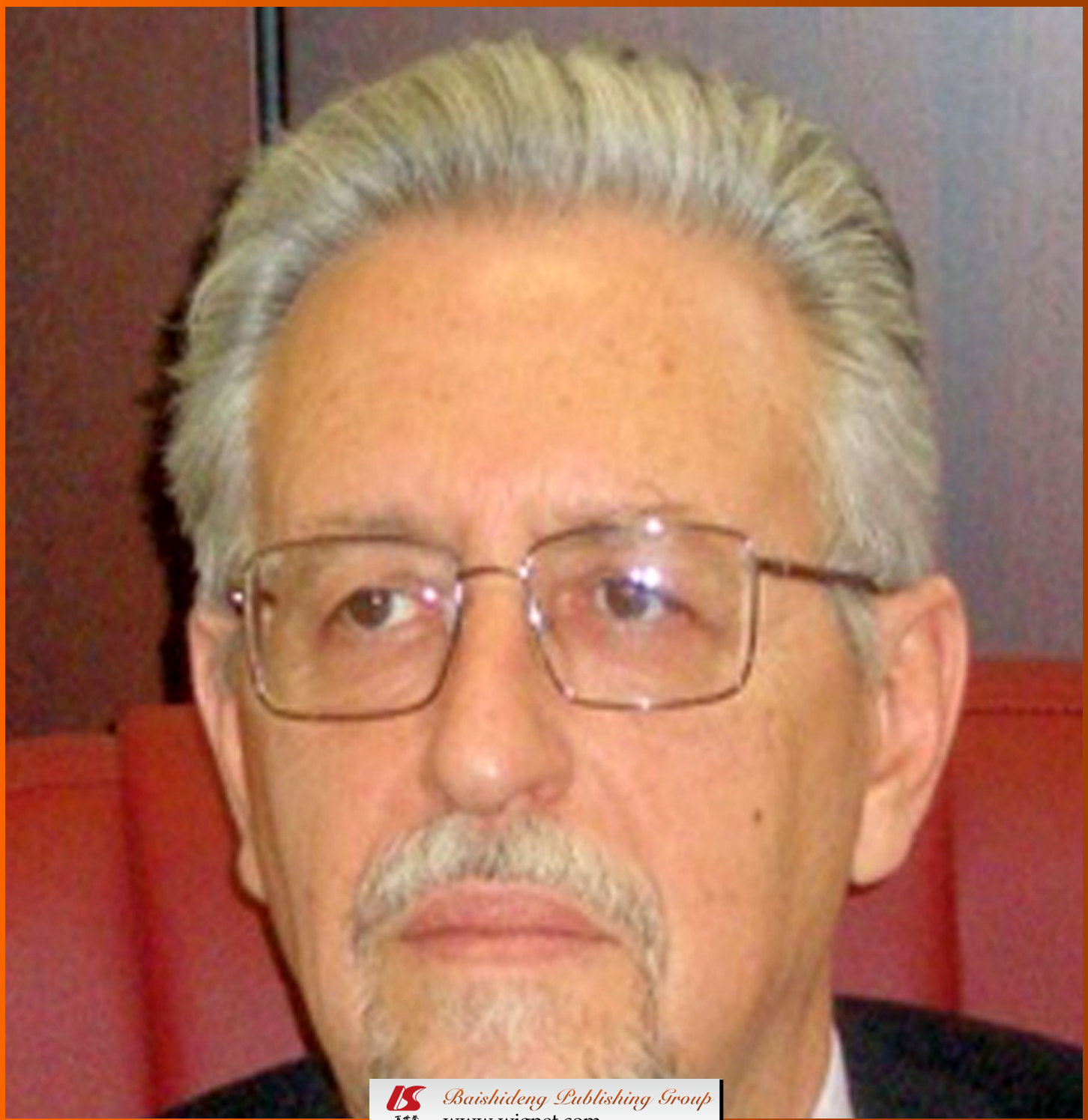

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EDITORIAL

Diagnosis and management of ampullary adenoma: The expanding role of endoscopy

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Abstract

Ampullary adenoma is a pre-cancerous lesion arising from the duodenal papilla that is often asymptomatic. It is important to distinguish whether the adenoma is sporadic or arises in the setting of familial adenomatous polyposis as this has important implications with respect to management and surveillance. Multiple modalities are available for staging of these lesions to help guide the most appropriate therapy. Those that are used most commonly include computed tomography, endoscopic ultrasound, and endoscopic retrograde cholangiopancreatography. In recent years, endoscopy has become the primary modality for therapeutic management of the majority of ampullary adenomas. Surgery remains the standard curative procedure for confirmed or suspected adenocarcinoma. This review will provide the framework for the diagnosis and management of ampullary adenomas from the perspective of the practicing gastroenterologist.

Key words: Ampullary adenoma; Ampullectomy; Duodenal papilla; Familial adenomatous polyposis; Papillectomy

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INTRODUCTION

Ampullary adenomas are glandular dysplastic lesions that arise in and around the duodenal papilla. Adenomatous tissue has been found in up to 90% of resection specimens of ampullary adenocarcinoma, suggesting that these lesions have pre-malignant potential[1-6]. Autopsy series have estimated the prevalence of ampullary adenoma to be 0.04% to 0.12%[7,8]. They may occur sporadically or in the setting of familial adenomatous polyposis (FAP). Patients with FAP almost invariably develop duodenal adenomas and have a risk for ampullary carcinoma that is 124-fold greater than the general population[3,9,10]. In fact, ampullary carcinoma is the most common malignancy and leading cause of death in FAP patients who have previously undergone colectomy[11-16]. Consequently, surveillance upper endoscopy is an important aspect of management for these patients. Ampullary adenomas are more frequently being recognized because of the increased availability of endoscopy for evaluation of gastrointestinal-related symptoms as well as surveillance programs for patients with FAP. Multiple modalities are now available for diagnosing and staging these lesions. Therefore, a good understanding of the diagnostic and therapeutic options available is essential for making an informed management decision.

Historically, ampullary adenomas were removed by radical surgery. Endoscopic advances in recent years have

shifted the paradigm of treatment toward attempted endoscopic resection prior to consideration of surgery because endoscopy is less invasive and has lower morbidity. Nevertheless, the complications associated with endoscopic removal of ampullary adenomas are high compared to other endoscopic therapies, making it imperative that it be performed in experienced hands. In patients with ampullary adenocarcinoma, surgery remains the standard curative therapy, but endoscopy can provide adequate palliation in cases where the patient is deemed not to be a surgical candidate. This review will discuss the clinical manifestations, diagnosis, and management of ampullary adenomas, with particular focus on the endoscopic management of these lesions.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical presentation

Ampullary adenomas are often asymptomatic and incidentally discovered on endoscopy. Patients may present with symptoms related to obstruction of the biliary or pancreatic duct. These symptoms may include jaundice from biliary obstruction, which in rare instances progresses to cholangitis[17,18]. Acute recurrent pancreatitis may result from pancreatic duct obstruction[19]. Other non-specific symptoms may include nausea, vomiting, abdominal pain, and weight loss. Significant weight loss in a patient with an ampullary lesion should alert the clinician to the possibility of a more invasive process.

Diagnosis

The diagnosis of ampullary adenoma is based on endoscopic appearance and histology. In order for endoscopic evaluation of the lesion to be complete, a side-viewing endoscope is necessary. Endoscopic features suggesting that these lesions are benign include regular margins, no ulceration, soft consistency, and no spontaneous bleeding[20,21]. Confirmation of adenoma is necessary with biopsy of the suspect lesion. The accuracy of forceps biopsy has been questioned due to several factors. Intraobserver variability exists between pathologists in interpreting the histologic specimen, making it particularly important to have the specimen reviewed by an experienced pathologist prior to deciding to undergo therapeutic intervention. In addition, forceps biopsy may not take a representative sample of the lesion and may miss foci of adenocarcinoma within adenomatous tissue. Bellizzi *et al*[22] recently reported a diagnostic agreement of only 64% when comparing biopsy samples to the eventual resected specimen. Forceps biopsy has been associated with accuracy rates of 62% to 85% in other series[23-27]. Therefore, final histologic assessment should be based on the resected specimen.

Staging

Once adenoma is confirmed by biopsy, further evaluation is necessary to help dictate management decisions. Modalities that may be used include trans-abdominal ultrasound (US), computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic US (EUS), and intraductal US (IDUS).

Both trans-abdominal US and CT do not adequately visualize the ampullary area for staging of adenomatous lesions. Their primary role is to identify biliary and pancreatic ductal dilation. In cases of ampullary adenocarcinoma, CT can also provide valuable information by identifying locoregional lymphadenopathy and distant metastatic lesions.

EUS can provide information regarding the depth of the ampullary lesion as well as locoregional lymph node status. Multiple studies have shown that EUS is superior to CT, MRI, and transabdominal US in local periampullary tumor staging[28-30]. IDUS is a newer imaging modality that was originally developed to visualize arterial structures in various pancreaticobiliary diseases. IDUS has higher resolution than EUS because of the use of high frequency waves (20-30 MHz) compared with EUS (7.5-10 MHz). Several studies have reported increased accuracy in staging of ampullary neoplasms with IDUS as compared to EUS[31-34]. Nevertheless, IDUS is not routinely performed as part of the ampullary adenoma staging, mainly due its lack of availability at many centers.

MRCP is typically reserved for patients with bile duct abnormalities previously identified on CT or US that need further clarification prior to more invasive investigative studies. ERCP is performed to visualize the extent of the ampullary lesion into the biliary or pancreatic duct as well as to perform decompression if there is evidence of obstruction. Given the sensitivity of other modalities now available for initial staging, ERCP with both biliary and pancreatic duct evaluation is usually performed immediately preceding possible endoscopic therapeutic intervention in the same session[35]. The use of cholangiopancreatoscopy at the time of ERCP to evaluate for intraductal spread of the adenoma has also been described[36].

ENDOSCOPIC THERAPY

An important distinction when considering the appropriate management for newly diagnosed ampullary adenoma is whether the adenoma is sporadic or arises in the setting of FAP. Patients with FAP often have multiple duodenal polyps. Spigelman *et al*[11] devised a classification system for duodenal polyps in the upper gastrointestinal tract in the setting of FAP (Table 1). Severity of polyposis is assessed by assigning a score (1-3) in each of four categories. Spigelman stage is then determined by the sum of the four categories (Stage 0: Score 0, Stage Ⅰ: Score 1-4, Stage Ⅱ: Score 5-6, Stage Ⅲ: Score 7-8, Stage Ⅳ: Score 9-12). Traditionally, patients with Spigelman stage 0-Ⅲ are followed with close endoscopic surveillance programs, while those with stage Ⅳ undergo more ag-

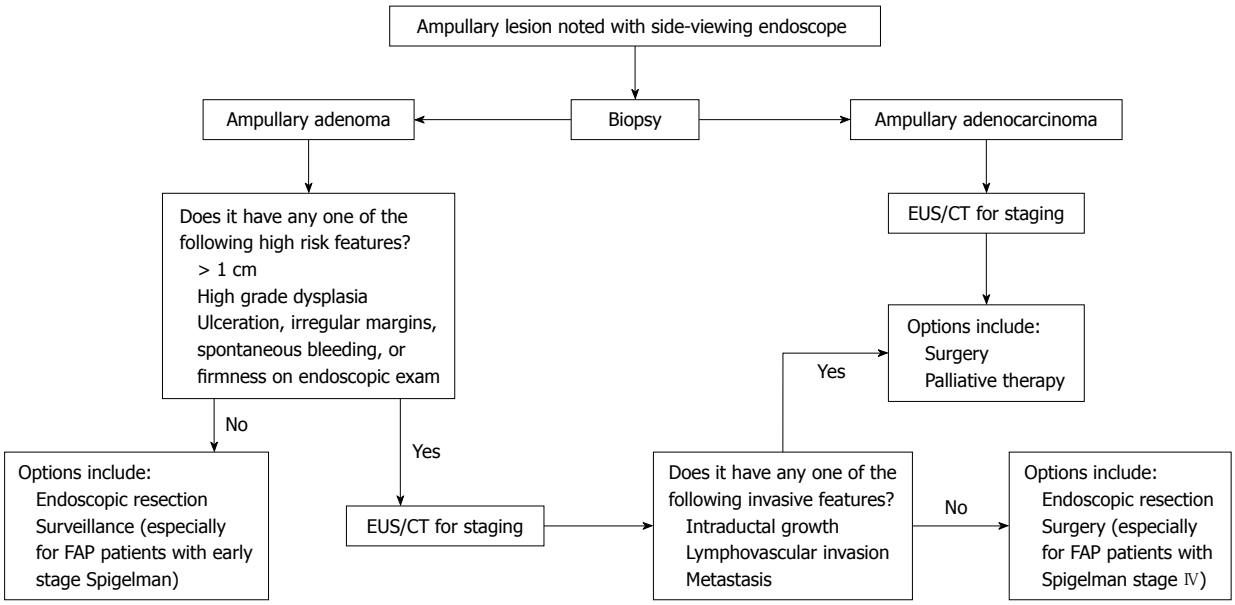

Figure 1 Suggested algorithm for management of ampullary lesion noted with side-viewing endoscope. FAP: Familial adenomatous polyposis; EUS: Endoscopic ultrasound; CT: Computed tomography.

Table 1 Spigelman classification of duodenal polyps in familial adenomatous polyposis

	Score		
	1	2	3
No. of polyps	1-4	5-20	> 20
Size (mm)	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

gressive therapy. In FAP, endoscopic resection has not been shown to decrease the need for eventual pancreaticoduodenectomy, as the malignancy risk is related to the extent of polyposis within the duodenum and not just the ampullary lesion[20,37]. Interestingly, studies have found that the progression in Spigelman classification categories over time has more to do with the increase in size and number of polyps as opposed to changes in histology[38].

A suggested algorithm for the management of newly diagnosed ampullary adenoma is shown in Figure 1. Given the heterogeneity of the lesions and patient population, it is difficult to set out guidelines that would encompass all possible scenarios, so each case must be taken on an individual basis. Advances in endoscopic therapy have allowed clinicians to be more aggressive in endoscopic resection of adenomas and there have even been case reports of focal ampullary adenocarcinomas removed endoscopically[21,39-43]. Most clinicians would agree that patients with known ampullary adenocarcinoma should be offered surgery if they are deemed appropriate surgical candidates. On the other hand, management of high grade dysplasia (HGD) is a controversial topic. A retrospective review of 23 patients who had endoscopic resection for what turned out to be HGD or focal T1 ampullary adenocarcinoma found that none of these patients had residual tumor on follow-up endoscopy or surgically resected specimen[44]. Therefore, the authors concluded that endoscopic resection is appropriate management for ampullary adenomas with HGD. Other investigators have advocated endoscopic resection for HGD if the tumor is only extraductal, and in situations where intraductal growth is less than 1 cm[45]. Proponents of radical surgery for HGD point to several studies that underlie the fact that diagnostic yield for picking up foci of adenocarcinoma and lymphovascular invasion pre-operatively is suboptimal[46,47].

Endoscopic resection technique

Endoscopic removal of ampullary adenomas remains non-standardized and highly variable, which reflects the relatively small number of formal investigations into this topic. Furthermore, there is no uniform agreement on the terminology used to describe various resection modalities. The terms papillectomy and ampullectomy are frequently used interchangeably but some authors restrict the use of "papillectomy" for endoscopic resection and "ampullectomy" for surgical resection[48]. The following is a discussion of the most commonly used endoscopic resection techniques based on a review of the literature and our experience.

Submucosal injection prior to papillectomy may be performed similar to the technique used when performing endoscopic mucosal resection for colorectal polyps. The failure of a lesion to manifest a "lift sign" is associated with malignancy and is considered a contraindication to attempts at complete endoscopic removal[49,50]. It is speculated that injection of epinephrine may also decrease the risk of bleeding during resection. Most commonly injected fluids include saline and epinephrine,

although methylene blue and viscous material such as hydroxypropyl methylcellulose and sodium hyaluronate have also been used[3,43,49-54]. Successful endoscopic resection of adenomas has also been described without the use of submucosal injection[40,55,56]. In fact, we generally avoid submucosal injection at our institution for two main reasons. One is the concern that injection may distort the ampullary anatomy due to the "anchoring" effect from the bile and pancreatic duct running through the lesion, creating a central depression at the site of the ampullary opening. Second, injection may create a "dome" effect and make effective snare placement for *en bloc* resection more difficult.

Endoscopic papillectomy is performed by the use of endoscopic snares and electrocautery. Standard or "braided" polypectomy snares are typically used, although fine wire snares specifically designed for ampullary resection are available[3,50,57]. If the lesion can be completely ensnared, *en bloc* resection with electrocautery may be performed. This has the advantage of shortened procedure time, reduced use of electrocautery, and providing complete tissue specimen for pathologic examination. Some authors have described the use of an electrosurgical needle knife to make an incision circumferentially around the lesion to facilitate snare capture[3]. Piecemeal resection is sometimes necessary for lesions larger than 2 cm or in cases where visible tissue is left in place with *en bloc* technique. The type of current and power settings used for ampullary resection are variable. Many authors describe the use of blended current, whereas others utilize pure-cutting current[58-60]. Few have also described the use of pure coagulation current[50].

The role of ablative therapies [argon plasma coagulation (APC), laser, bipolar electrocautery] is mainly to destroy any remaining tissue that may be left following snare resection of a specimen. APC is most frequently used for this purpose. The main disadvantage in using this technique is tissue that is ablated cannot be retrieved for pathology review. In fact, some clinicians avoid the use of APC altogether primarily for this reason[35]. Catalano *et al*[58] reported their results from 103 papillary resections and found no difference in overall rate of success or recurrence in patients who did and did not have APC.

Pancreatic or biliary sphincterotomy is often performed following papillectomy, with the goal of improving pancreaticobiliary drainage. One of the known complications of papillectomy is pancreatitis. Placement of a pancreatic duct stent following ampullary adenoma resection has been found to reduce the incidence of post-ERCP pancreatitis based on a meta-analysis of five prospective series[61]. Recently, a randomized control trial also showed a decrease in the rate of pancreatitis in patients who received a pancreatic duct stent[62]. Some authors perform sphincterotomy and placement of pancreatic duct stent prior to resection[21,50], although we favor post-resection stent placement in an attempt to maximize the opportunity for *en bloc* resection. Placement of a biliary stent to reduce the risk of post-procedural cholangitis is infrequently performed, and mainly done if there is concern for incomplete biliary drainage despite biliary sphincterotomy[3,50,63]. In our institution, we place a pancreatic duct stent in every patient undergoing endoscopic papillectomy as the data available strongly support its use. We reserve the use of a biliary stent only for patients that are believed to have slow drainage after biliary sphincterotomy.

Outcome

A systematic review by Han *et al*[48] reported the success rates for endoscopic removal of ampullary adenomas to range from 46% to 92%, and recurrence rates to range from 0% to 33%. Most recently, a large retrospective series which included 102 patients diagnosed with ampullary adenoma that underwent endoscopic resection showed a success rate of 84%[64]. Factors affecting success in this study were smaller lesion size (< 2 cm) and the absence of dilated ducts.

Complications

Even in experienced hands, complications arising after endoscopic papillectomy are high compared to other endoscopic procedures. They include pancreatitis, perforation, bleeding, cholangitis, and papillary stenosis. In their review, Han *et al*[48] found a morbidity rate of 23% (range 10%-58%) and a mortality rate of 0.4% (range 0%-7%). Bleeding and pancreatitis were the most common complications. Each occurred in up to 25% of cases in one small study, although the remainder of the studies showed bleeding rates of 0% to 21% and pancreatitis rates of 0% to 15%[48].

Surveillance

There is no consensus regarding the most appropriate surveillance interval following endoscopic resection of ampullary adenomas. Initial surveillance endoscopy is generally performed at 1 mo to 6 mo following resection. Following the initial surveillance endoscopy, the clinician may decide to follow with endoscopy every 3 mo to 12 mo for the next 2 years, and then less frequent intervals thereafter[3,50,52,58,63,65-67]. A side-viewing endoscope should be used for surveillance purposes. One recent study suggests improved rates of detection of duodenal polyps with the use of chromoendoscopy in FAP patients[68]. Patients with sporadic ampullary adenomas are at increased risk for colon polyps and should be offered screening colonoscopy.

NON-ENDOSCOPIC THERAPY

Surgery

Surgery had been the traditional approach for removal of ampullary adenoma before the advances related to endoscopic therapy in the last 10 to 20 years. Surgery remains the standard curative therapy for confirmed or suspected ampullary adenocarcinoma, although endoscopy can provide adequate palliation in patients deemed not to be surgical candidates.

Surgical approaches may include pancreaticoduodenectomy, surgical ampullectomy, and pancreas-preserving duodenectomy. The reason for the shift towards endoscopic removal of adenoma is related to the significant morbidity and mortality associated with radical surgery. Data from multiple series for pancreaticoduodenectomy demonstrated an operative mortality of 1% to 9% and operative morbidity as high as 41%[69,70]. Less invasive surgical options such as surgical ampullectomy are available, but recurrence is a possibility when these less invasive surgical interventions are employed. Similar to endoscopy, these patients will also require follow-up endoscopy, whereas those who receive pancreaticoduodenectomy do not require further surveillance. FAP patients are unique in that they will require surveillance regardless of intervention given their propensity to develop adenomas throughout the duodenum.

Medical therapy

Non-invasive therapy is also an option in certain cases of diagnosed ampullary adenoma. While there is no data studying the effect of non-steroidal anti-inflammatory drugs (NSAIDs) specifically on ampullary adenomas, there is literature that studies the effect of NSAIDs on duodenal and colorectal polyps in the FAP population. The most commonly studied NSAIDs have been celecoxib and sulindac. In a randomized control trial involving 49 post-colectomy FAP patients, celecoxib was found to significantly reduce duodenal polyposis when compared to placebo[71]. Another study involving 24 post-colectomy FAP patients found that sulindac reduced rectal polyp progression, but had no significant effect on duodenal polyp regression[72]. Increased erosions at the anastomotic site in the NSAID group have also been reported in at least one study[73].

CONCLUSION

Endoscopic advances in recent years have expanded the role of endoscopy in the therapeutic management of ampullary adenomas. Prior to considering therapy, clinicians should utilize the staging modalities available in order to make the most appropriate management decision for these patients. Radical surgery remains the treatment of choice for ampullary adenocarcinoma, adenomas with extensive intraductal growth, and should be strongly considered in a certain subset of FAP patients. Future studies and case experience will allow us to make more definitive guidelines with respect to appropriate treatment and surveillance for ampullary adenoma.

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EDITORIAL

Intraoperative ERCP: What role does it have in the era of laparoscopic cholecystectomy?

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Abstract

In the treatment of patients with symptomatic cholelithiasis and choledocholithiasis (CBDS) detected during intraoperative cholangiography (IOC), or when the preoperative study of a patient at intermediate risk for CBDS cannot be completed due to the lack of imaging techniques required for confirmation, or if they are available and yield contradictory radiological and clinical results, patients can be treated using intraoperative endoscopic retrograde cholangiopancreatography (ERCP) during the laparoscopic treatment or postoperative ERCP if the IOC finds CBDS. The choice of treatment depends on the level of experience and availability of each option at each hospital. Intraoperative ERCP has the advantage of being a single-stage treatment and has a significant success rate, an easy learning curve, low morbidity involving a shorter hospital stay and lower costs than the two-stage treatments (postoperative and preoperative ERCP). Intraoperative ERCP is also a good salvage treatment when preoperative ERCP fails or when total laparoscopic management also fails.

Key words: Intraoperative endoscopic retrograde cholangiopancreatography; Laparoendoscopic treatment; Postoperative endoscopic retrograde cholangiopancreatography; Rendezvous technique

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INTRODUCTION

The rate of choledocholithiasis (CBDS) in patients with symptomatic cholelithiasis is estimated to be approximately 10%-33%, depending on the patient's age[1]. For many years, open cholecystectomy (OC) with choledochotomy or sphincteroplasty and cleaning of the bile duct were the gold standard to treat both pathologies. Over the past decade, laparoscopic cholecystectomy (LC) has replaced OC in the treatment of biliary lithiasis. The technical difficulties in the laparoscopic treatment of CBDS and the development of endoscopic retrograde cholangiopancreatography (ERCP)[2] have led to considerably broader endoscopic/surgical treatment possibilities for patients with cholelithiasis and suspected CBDS. No consensus currently exists regarding universally accepted therapeutic management.

One of the most important consequences of the

universal use of LC is the promotion and development of various pre-operative screening methods for CBDS, which had already been used during the open surgery era.

Intraoperative cholangiography (IOC) was used selectively in patients with suspected CBDS, since it required longer surgery time. It also had a false positive rate of up to 26%[3] which affected the performance of unnecessary therapeutic surgical procedures, such as choledochotomy or sphincteroplasty, with a higher risk of secondary postoperative complications and morbidity of 17%-21%[4-6].

The universal use of LC rekindled an old debate concerning the need for the routine use of IOC, which ultimately led it to being used selectively on patients with suspected CBDS during preoperative studies[7]. The low rate of CBDS during negative screening tests, from 2%-4%[8], and the low rate of anatomical alterations of the bile duct that could involve a real surgical risk do not justify its systematic use. Consequently, the selective use of IOC helps to reduce surgical morbidity and minimises the use of unnecessary resources[7,9].

Clinical criteria (jaundice, recent history of pancreatitis, cholecystitis), analytical criteria (elevation of total bilirubin, elevation of cytolytic and cholestatic enzymes) and ultrasonographic (EUS) criteria (dilated bile duct or visualisation of repletion defects in the bile duct) have been used and combined as preoperative screening methods for CBDS. A multitude of scores have been published using these criteria, attempting to assess the risk of CBDS, none of which have been implemented in a general manner. In fact, only 27%-54% of patients selected with suspected CBDS ultimately have calculi[7,10].

In 2001, and more recently in 2010[11], the American Society for Gastrointestinal Endoscopy (ASGE) published a review of the pros and cons of each preoperative screening method used to detect CBDS. It proposed a scoring system to categorise CBDS risk into high, intermediate and low and also devised a diagnostic and therapeutic algorithm for its management.

The high risk group would include patients with symptomatic cholelithiasis, total bilirubin > 4 mg/dL, ascending cholangitis, the presence of intracholedochal calculi, or those with a dilated bile duct and total bilirubin of 1.8 mg/dL. For patients > 55 years, alterations in liver biochemistry other than bilirubin or with a recent history of biliary pancreatitis would have intermediate risk. If they do not present with any of these criteria, the patients have low CBDS risk.

The use of magnetic resonance cholangiography (MRC) has facilitated the non-invasive study of the bile duct, with 85%-92% sensitivity and 93%-97% specificity for CBDS[12]. This technique is less sensitive when common bile duct stones measure less than 6 mm and during episodes of acute biliary pancreatitis[13,14].

EUS has also proved very useful in diagnosing CBDS and its morbidity did not at all compare to that of ERCP, with 89%-94% sensitivity and 95% specificity[15,16], although it is probably more operator dependent than MRC and is sensitive in detecting common bile duct stones measuring less than 6 mm[17].

The Spanish National Health Institute[18] and the ASGE[11] recommend patients with intermediate CBDS risk to use non-invasive radiological techniques prior to undergoing preoperative ERCP due to their high diagnostic performance. This would enable candidates undergoing preoperative ERCP before LC to be more appropriately selected. However, the limited availability of resources and the cost of these diagnostic techniques mean that they cannot be used universally as a replacement for the screening methods used to date. They should be used selectively in order to improve the diagnostic yield of patients with intermediate risk.

However, although at least 10% of cases with symptomatic cholelithiasis who undergo surgery could be included in the intermediate risk group for CBDS, the repercussions from implementing the aforementioned diagnostic strategy in clinical practice and its cost have not yet been established. Also, it might be difficult to use under certain circumstances due to its scarcity or lack of availability, intolerance or contraindication[19].

Furthermore, the sensitivity and specificity of these diagnostic techniques vary in relation to the quality of the technology available and the experience of the teams that interpret them at different hospitals. Lastly, there is a small group of intermediate risk patients in which, despite the fact that MRC or EUS fail to confirm the existence of CBDS, diagnostic doubts remain due to conflict between clinical, analytical and ultrasound findings[14].

Therefore, MRC or EUS are not the definitive solution for diagnosing CBDS, and at the moment, its diagnosis during the intraoperative stage still has an important role. We must also remember that there is a group of patients with negative screening tests, in which the surgical findings during surgery recommend that IOC be performed in order to rule out CBDS, with an estimated rate of 2%-4%[3].

There is a general consensus regarding the therapeutic algorithm of high and low CBDS risk patients. The first group would require preoperative ERCP followed by LC, and the second only LC. However, intermediate-risk patients have a great variety of endoscopic/surgical therapeutic options (LC with total laparoscopic cleaning of the bile duct in a single stage, or with the assistance of intraoperative ERCP, or two-stage management with preoperative ERCP followed by LC, or LC and postoperative ERCP). Currently, there is still a lack of consensus and the most appropriate therapeutic management is the subject of debate between the various surgical and endoscopic groups.

AVAILABLE TREATMENTS FOR CHOLELITHIASIS AND CBDS

ERCP was introduced in the 1970s as a treatment for residual or recurrent CBDS, with a success rate of over 85%-90%, immediate severe morbidity of 2.5%-11%, and mortality of 0.5%-3.7%[20].

It has become increasingly indicated including the treatment of possible CBDS before laparoscopic surgery[4,21], because during the OC era, when it was used before surgery it failed to show any advantages over the total surgical management of CBDS[22].

Preoperative ERCP followed by LC has been the most widely used endoscopic/surgical treatment method over the past decade and it is still currently used at many endoscopic units, despite the fact that its routine use to ultimately detect CBDS is unacceptable, due to the high rate of normal explorations and the cost and morbidity inherent to the technique[10,11].

In fact, one of the best preventive measures to reduce ERCP complications is not to perform it if it is unnecessary. This is one of the main reasons why the ASGE[11] has published its guidelines to quantify the risk of CBDS, proposing a therapeutic management algorithm.

When the possibility of CBDS cannot be ruled out for certain using the appropriate preoperative radiological studies - MRC or EUS -, or if they are unavailable, there are long waiting lists causing an unacceptable delay in diagnosis, or if there is an unexplained clinical and radiological discordance, the surgeon must decide between using LC with or without IOC, depending on the reliability of the different radiological studies in his or her environment. IOC has very high specificity (93%-100%), with lower sensitivity (53%-100%)[23].

If IOC shows the presence of CBDS, there are three possible therapeutic options: total laparoscopic management, intraoperative ERCP (single-stage treatment), or immediate postoperative ERCP. However, there are very few surgical groups with sufficient experience and resources to resolve CBDS laparoscopically or many surgeons that agree on leaving stones in the bile duct in order to extract them endoscopically at the postoperative stage, although some studies estimate that approximately 50% of CBDS detected by IOC can resolve spontaneously[3,24].

LAPAROSCOPIC MANAGEMENT OF CBDS (SINGLE-STAGE TREATMENT)

Laparoscopic surgery of CBDS was introduced over 15 years ago[25] and various surgical groups have shown that it has a high success rate[26-30], and is just as efficient and safe as pre- or postoperative ERCP associated with LC, thereby avoiding the need to perform additional procedures[1,27,31]. Nevertheless, its technical difficulties, its long and difficult learning curve and the need for the allocation of technical resources (high-quality fluoroscopy and choledochoscopes), which are not available at many operating theatres[32], has curtailed its expansion.

During the laparoscopic treatment of CBDS, the first surgical step involves the transcystic exploration and extraction of the common bile duct stones[33-35]. Most of the stones (66%-93%) are eliminated in this manner[36,37] using wash-outs, balloons or Dormia baskets in order to extract the small stones through the cystic duct or the papilla. All of these manoeuvres have difficulty in accessing the bile duct through fine or bead-like cystic ducts, sometimes requiring dilations to be performed before the cystic duct. When transcystic extraction is not possible, a choledochotomy must be performed and the bile duct explored[33,36] using balloons or Dormia baskets or through choledochoscopes. All of these techniques are more difficult and dangerous if the bile duct is narrow or if it is affected by inflammatory changes. When exploration of the bile duct is complete, if a primary suture is not performed - which always poses a risk - drains (a Kher tube) are placed which will prolong the patient' s hospital stay. On the whole, the laparoscopic extraction of CBDS has a success rate of 83%-89%, with greater efficiency and lower morbidity for transcystic exploration and extraction of common bile duct stones (68% and 10%, respectively, compared to 31% efficiency with morbidity of 5%-18% for laparoscopic common bile duct exploration)[31,35]. When its efficiency and costs were compared to the two-stage treatment with preoperative ERCP during a multicentric clinical trial, bile duct cleaning and morbidity had similar success rates, but involved a shorter hospital stay[31].

The difficulties regarding the laparoscopic management of CBDS have been shown in certain algorithms proposed, which show intraoperative or postoperative ERCP as a salvage treatment in the event of failure of the transcystic duct or laparoscopic choledochotomy[37-39], encouraging joint endoscopic-laparoscopic treatment of CBDS, with which clinical trials have also been performed comparing their results.

The current use of these therapeutic options depends, to a great extent, on the technical skills and experience of the endoscopic and surgical teams, which must reach a clearly established and accepted consensus[29,38].

The timing of the two-stage treatment with preoperative ERCP and subsequent LC was determined by the ASGE[11] for patients at high risk of CBDS only.

POSTOPERATIVE ERCP AS A TWO-STAGE TREATMENT FOR CBDS

Postoperative ERCP is an important cost-efficient therapeutic alternative[19], which would be indicated to treat CBDS diagnosed intraoperatively, irrespective of the reason for performing IOC[11] and provided that laparoscopic treatment is unavailable or has failed[27,35-38]. One of the pros of postoperative ERCP is that it is available at all equipped hospital centres using the findings from IOC (with high specificity) to establish its indication. However, it also has disadvantages. It requires highly experienced endoscopic support groups with a low ERCP failure rate and the hospital stays are longer than for single-stage treatments[1,27,40]. The possibility that postoperative endoscopic failure could require further surgery should always be taken into account. Accordingly, the specific circumstances of each hospital centre determine whether or not there is a reluctance to implement the aforementioned

technique in clinical practice, although certain studies are available that propose a hopeful wait and see attitude, especially with common bile duct stones measuring less than 5-6 mm[3,10,24].

It was also indicated that the possible failure of postoperative ERCP could be avoided by leaving a transcystic catheter in place or by placing removable biliary prostheses, however, removing them could lead to an increase in the rate of biliary fistula or biliperitoneum[6].

INTRAOPERATIVE ERCP AS A SINGLE-STAGE TREATMENT FOR CBDS

A short and successful series of intraoperative ERCP during LC was published in 1993, describing the insertion of a Fogarty balloon catheter into the transcystic duct in order to direct and correctly perform endoscopic papillotomy[41] and a further series of intraoperative ERCP during OC[42]. In 1994 a new series of intraoperative ERCP was published in which a sphincterotomy was performed using a laparoscopic procedure by inserting the sphincterotome into the transcystic duct using the duodenoscope to ensure its correct position in the papilla[43]. A series of reports was subsequently published, which could be included under the Perioperative ERCP heading, attempting to resolve CBDS in a single stage during LC. They include intraoperative ERCP using the rendezvous technique. Using this technique, a transcystic guide wire is inserted laparoscopically and recovered in the duodenum using the endoscope, facilitating selective access to the bile duct and the subsequent sphincterotomy[44-48]. Initially, perioperative ERCP also included ERCPs performed in theatres using the standard ERCP technique, prior to, during or immediately after surgery[49-52]. The main difference we are aware of regarding postoperative ERCP, is that it is performed in the theatre immediately after surgery while the patient is still under anaesthesia in order to try to shorten hospital stay, thereby allowing the endoscopic/surgical treatment to be performed in a single stage. However, they do not have the benefits offered by the rendezvous technique. Three different types of catheters or Fogarty balloons[41] or even Dormia basket catheters were initially used which were inserted into the transcystic duct to facilitate insertion of the papillotome in the papilla[53]. However, most endoscopic groups have used and still use a transcystic guidewire.

The use of intraoperative ERCP has slowly increased among various endoscopic groups, combining its ease of use with a short learning curve, without the high technical requirements needed by laparoscopic management of the bile duct[54-58].

Very few comparative studies have been made between laparoscopic management[31] with or without intraoperative ERCP[55,59,60] single-stage treatments, and the two-stage treatment with preoperative ERCP that has similar or higher success rates, but has lower morbidity, shorter hospital stay[60] and lower cost. Randomised studies have also been performed comparing the two most important options of the single-stage treatment, such as total laparoscopic CBDS management compared to intraoperative ERCP[32], where no differences in success rate, complications, hospital stay or cost were found.

La Greca *et al*[58] reviewed all the published studies on intraoperative ERCP and found 27 original papers that included between 8 and 96 patients each, thus analysing a total of 795 patients. The success rate ranged between 69.2%[61] and 100%[45,48,57], with an average of 92.3%. The average duration of intraoperative endoscopy was 35 min and the average duration of surgery was 104 min. The average conversion rate to open surgery was 4.7% and morbidity was 5.1% (0%-19%). Mortality is extremely rare, and of the 27 publications reviewed, only three patient deaths were reported, giving rise to a total mortality of 0.37%.

INTRAOPERATIVE ERCP TECHNIQUE

In the rendezvous technique, firstly, a transcystic guidewire (0.025-inch Jagwire; Boston Scientific Inc., Watertown, Massachusetts, United States) is inserted through the cholangiography catheter. Once it emerges from the papilla, it should be grasped with a standard snare. It is then withdrawn through the endoscope placed opposite the papilla. A double-lumen sphincterotome is then advanced over the guidewire to facilitate bile duct cannulation and to perform the sphincterotomy, followed by bile duct clearance using a Fogarty balloon or a Dormia basket catheter. Finally, the cystic duct is closed and the surgeon proceeds with LC. If the guidewire does not come out through the papilla, the surgeon should try to advance a stiffer Fogarty catheter through the papilla and then a pre-cut sphincterotomy can be performed. If all of these steps fail, intraoperative ERCP must be considered to have failed and postoperative ERCP could be performed using the best technical support available in the Radiology Department or a decision might be made to proceed with OC.

PROS AND CONS OF INTRAOPERATIVE ERCP

Pros

The main advantage of intraoperative ERCP using the rendezvous technique is the selective cannulation of the bile duct, preventing Wirsung opacification using contrast agents, damage and manipulation of the papilla and the use of risky techniques to access the papilla, such as precut sphincterotomies[57]. This technique results in a lower rate of pancreatitis compared to preoperative ERCP[55,59], and of post ERCP acute cholecystitis if the cholecystectomy is delayed[55]. The hospital stay and costs of the process were lower compared to the most used two-stage sequential treatment (preoperative ERCP and laparoscopic surgery)[55,59,60].

Intraoperative ERCP can be an alternative to the laparoscopic management of CBDS[38,46,53] as a salvage treat-

ment during surgery when the bile duct is not adequately cleaned or as an alternative to endoscopic-laparoscopic management in two stages, both with preoperative or postoperative ERCP[37,52,54]. Its main advantage is that it is a single-stage treatment and there is no risk of reintervention in the event of intraoperative ERCP failure. It also offers the possibility of salvage for failed preoperative ERCP[62], attempting to avoid open surgery.

Intraoperative ERCP is not a particularly difficult challenge for an endoscopist with expertise in biliary endoscopic treatment. Performing intraoperative ERCP in theatre with the patient under anaesthesia and in the supine position is infrequent in normal practice, but there is always a patient on whom it is necessary to perform intubated ERCP in order to maintain adequate ventilation, irrespective of the cause. The supine position facilitates and guarantees management of the airways, thereby avoiding the greater risk of adverse cardiorespiratory events that arise when ERCP is performed in the supine patient. No differences were identified in the success, complication and morbidity rates between both forms of ERCP if the endoscopist has sufficient experience[63].

From a technical viewpoint, rotating the patient 180 degrees requires a 90-degree rotation of the endoscope and endoscopist to the right, in order to be positioned opposite the papilla. In practice, this gesture is performed intuitively by the endoscopist and in most reports, there was not much emphasis placed on technical difficulties, and when this was specifically assessed, only 3.7% of the procedures were considered to be technically difficult[57].

Cons

The main problem is the need to coordinate and synchronise the surgical and endoscopic teams, which must work together. This has caused the most difficulty in generalising its use and this opinion is shared by various authors[58].

The endoscopic team must be familiar beforehand with the patient's surgery programme and be ready to go into theatre once CBDS has been confirmed by IOC. While the endoscopic team is getting ready for theatre, the surgeon passes the guidewire into the duodenum through the IOC catheter. Afterwards, the duodenoscope is introduced in order to grasp the wire. It is important to reduce waiting time as much as possible.

The endoscopist will have to work in an environment he/she is not used to. He/she should be positioned between the patient's left arm, usually extended during the surgery, and the patient's head, which causes a certain degree of discomfort. The ERCP should be performed with the patient in the supine position and the radiological quality offered by traditional X–ray rooms that he/she might require will not be available. However, once IOC has been performed, the X-ray arch can be removed, since the rendezvous technique permits selective cannulation of the bile duct without the need for radiological support. After performing the papillotomy, the guidewire is usually removed and reinserted into the bile duct to prevent the Fogarty catheter from ending up in the cystic duct, or the guidewire is removed completely through the duodenoscope to insert the Fogarty catheter or Dormia basket without the guidewire and the bile duct is cleaned. The insistence of, or the need for, the use of radiology in surgery will depend mainly on the number and size of the common bile duct stones. However, the endoscopist should be aware of the risk of producing Glisson's capsule hematomas if the guidewire is introduced deep into the bile duct without radiological control.

Once the papillotomy has been performed and if the bile duct has not been cleaned completely, a second postoperative ERCP, in the usual radiological environment, is technically easy without the risks associated with the first ERCP.

It is important for the surgical and endoscopic team to agree on the therapeutic options to follow if the rendezvous technique fails. If the guidewire does not emerge through the papilla, an attempt should be made to insert a Fogarty balloon into the transcystic duct, which must always be stiffer than the guidewire, which can prevent it from moving in a retrograde fashion towards the intrahepatic biliary tree. Once the Fogarty balloon emerges from the papilla, a pre-cut papillotomy can be performed using a needle-knife sphincterotome, controlled with the help of the Fogarty balloon catheter. If both manoeuvres fail, the therapeutic options available would be as follows: perform ERCP using a standard technique in surgery immediately after the cholecystectomy has been completed[29,49,50,52], postpone the ERCP to the postoperative stage depending on the patient's evolution or convert the LC to open surgery. The option to take will vary depending on the anatomical characteristics (intradiverticular papilla) and the difficulties envisaged in the standard ERCP of that patient, the quality of the surgical equipment available in theatre and the size of the CBDS.

Special mention should be made of intraoperative ERCP treatment for patients with common bile duct stones measuring more than 15-20 mm detected intraoperatively, or when multiple stones are found. In these cases, although intraoperative ERCP may not be as definitive and conclusive as when it is performed in our usual radiological environment, at the same time, it can prolong the length of surgery unnecessarily. However, it allows and guarantees that intraoperative papillotomy can be performed with lower morbidity than conventional ERCP, helping in particular if the bile duct has not been fully cleaned, during a second stage with postoperative ERCP, with or without dilation of the papilla or with the use of mechanical lithotripsy systems.

Lastly, we would like to refer to the subsequent difficulties of LC in relation to the air insufflated during ERCP on which certain groups have manifested their concern. However, this should not be the case. The surgical teams normally perform LC from the fundus of the gallbladder to the neck with dissection of Calot's triangle, suture of the cystic artery and dissection and section of the cystic duct in order to perform the IOC, so that when

the endoscopist is getting ready to perform ERCP, the LC is virtually finished. When endoscopy is over, usually within an average of 35 min[58], the air introduced is aspirated efficiently in order to restore the visibility of the surgical field and the surgeons have no difficulty in completing the final surgical manoeuvres.

CURRENT ROLE OF INTEROPERATIVE ERCP

During the preoperative study of cholelithiasis pending surgery, it is clear that the risk of associated CBDS must be assessed. Using its algorithm, the ASGE suggests that the preoperative study should be completed using MRC or EUS in patients with intermediate risk or in an intraoperative manner using intraoperative ultrasound or IOC[11]. However, we will still find patients in whom clinical-analytical-radiological discordance makes it advisable to perform a new radiological study, such as IOC, to establish the most appropriate surgical treatment, or patients in which CBDS appears as a casual finding in IOC. The three possible therapeutic options for these intermediate risk patients are the single-stage treatment, total laparoscopic treatment with intraoperative ERCP or the two-stage treatment with postoperative ERCP. At present, there is no scientific evidence to justify the choice of one option or another. The three types of treatment are correct and their choice will depend on the particular circumstances and on the experience of the different endoscopic and surgical teams at each centre.

Intraoperative ERCP could also be a perfect salvage treatment for failed preoperative ERCP[62] in order to avoid open surgery, maintaining a foreseeably high success rate with very low morbidity and mortality.

Therefore, in coming years, we may witness an increase in the use of intraoperative ERCP, not to compete with the indications of preoperative ERCP in general, but rather to prevent the improper use of preoperative ERCP in patients at intermediate risk for CBDS, and to provide a diagnostic and therapeutic alternative to sophisticated techniques that are not always available in all societies and countries throughout the world.

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REVIEW

Endoscopic tattooing of colorectal lesions: Is it a risk-free procedure?

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Abstract

Endoscopic tattooing is one of the most useful tools for the localization of small colorectal lesions especially in the laparoscopic setting. This is a minimally invasive endoscopic procedure without risk of major complications. However, many studies have revealed complications resulting from this procedure. In this article, several topics are reviewed including the accuracy, substance preparation, injected techniques and complications related to this procedure.

Key words: Colorectal cancer; Complication; Endoscopic tattooing; Preoperative localization

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in the US population[1]. In 2007, the incidence was 52.7 per 100 000 population and 53 219 people died from this disease, making it the second leading cause of cancer-related death in the United States[2]. CRC screening is recommended in people older than 50 years because 90% of CRC cases are diagnosed in this age range[3] with an increasing incidence of CRC over time[4]. Family history of CRC is one of the most important risk factors. A meta-analysis showed that the relative risk of a first-degree relative of a CRC patient was 2.24. Moreover, the risk increased to 3.97 if two or more first-degree relatives were affected[1,5]. There are several other risk factors for CRC, such as personal history of adenoma, sessile serrated polyps or chronic inflammatory bowel disease, which are not covered in detail in this review.

Endoscopy, including flexible sigmoidoscopy and colonoscopy, is one of the CRC screening tools in addition to fecal occult blood test, stool DNA test, double contrast enema, and computed tomography colonography. Thirty to 50% of individuals older than 50 years were discovered to have one or more polyps with all screening methods[6]. From these findings, the prevalence of malignant polyps ranges from 0.2% to 11%[7]. Currently, most of the lesions can be removed endoscopically as a result of improving skills with more advanced endoscopic techniques. Unfortunately, some patients still need subsequent surgical resection, due to a high risk of lymph node metastases or positive resected margins.

The intraoperative localization of small lesions or a

previous polypectomy site is often challenging, especially during the laparoscopic approach. Therefore, without precise preoperative localization, it is possible to remove an incorrect segment of intestine. Currently, various methods are widely used for preoperative localization. Double-contrast barium enema is an effective method for identifying large tumors, whereas small lesions are frequently missed[8]. Approximately 10%-20% of tumor locations identified from colonoscopy are inconsistent with the intraoperative tumor site[9-11]. Adding a secondary intervention to colonoscopy, such as endoscopic tattooing, seems to be less invasive and a more common approach for preoperative localization. Indications, techniques, and complications of endoscopic tattooing are reviewed in this article.

ENDOSCOPIC TATTOOING

In 1958, Sauntry *et al*[12] first reported the technique of tattooing using blue dye at the base of the polyps. Subsequently, Knoernschild[13] reported on a series of 190 patients who underwent endoscopic tattooing. In 1975, Ponsky *et al*[14] initially proposed the endoscopic tattooing of colonic lesions for intraoperative localization. After that, tattooing under endoscopic procedures became more common due to high accuracy with minimal risk of complications. The accuracy, failure rate and complications of this technique are summarized in Table 1.

From our investigations, the accuracy of endoscopic tattooing for localization varies from 70% to 100%. False positive and invisible lesions at the time of surgery ranged from 1.6% to 7% and 1.6% to 15%, respectively. Most of the invisible cases required intraoperative colonoscopy to identify the lesions. The reasons for invisibility may be the result of superficial injection or an injection into the mesenteric side. The rate of dye spillage into the intraperitoneal cavity varies from 2.4%-13%. No clinical infections were detected in these patients. The details of these complications will be discussed later.

The indirect benefit of endoscopic tattooing is an improvement in the adequacy of lymph node dissection from pathological analysis in terms of the number of lymph nodes harvested from the surgical specimens as a result of likely staining in the lymphatic system. One retrospective study demonstrated a significantly higher mean number of lymph nodes examined in tattooed specimens than in non-tattooed specimens (23 *vs* 19, $P = 0.03$). In addition, the proportion of adequate lymph nodes examined ($\geqslant$ 12 nodes) in the tattooed group was significant greater than that in the non-tattooed group (87.1% *vs* 72.3%, $P = 0.02$)[22].

Endoscopic tattooing also allows identification of the site of locally advanced rectal cancer after neoadjuvant chemoradiation[23]. With regard to the disadvantages of tattooing a rectal lesion, the plane of dissection may be obscured if transmural injection and spillage of dye occurs. Moreover, transmural injection can cause inflammatory-related changes in the pathological segment. Therefore, the role of tattooing in rectal lesions is stills a controversial issue.

SUBSTANCES

In 1989, Hammond *et al*[24] reported on the use of eight different dyes, including methylene blue, indigo carmine, toludine blue, lymphazurine, hemotoxylin, eosin, indocyanine green (ICG), and India ink injected into dog colon. Only India ink and hematoxylin produced adverse tissue reaction. Mucosal ulceration was found in hematoxylin-injected specimens, whereas India ink produced marked inflammation. This inflammation can be the result of the composition of substances within India ink, including ethylene glycol, phenol, shellac, and animal products (i.e., gelatin)[25].

Spot (GI Supply, Camp Hill, PA, United States) is a sterile suspension of highly purified and very fine carbon particles. This is a non-India ink permanent marker for endoscopic tattooing. Spot is the only substance that has been approved by the US Food and Drug Administration for endoscopic tattooing. Askin *et al*[26] reported on the safety and efficacy of Spot in 113 patients who underwent endoscopic tattooing. None of the patients developed symptoms or signs of inflammation after the procedure. The stain remained for up to 1 year in this study.

Historically, ICG was used for the evaluation of cardiac output and hepatic function with a high level of safety. In 1993, Hammond *et al*[27] reported on the injection of ICG as a dye for colonic tattooing in 12 patients (15 colonic lesions), 1 d prior to surgery. ICG remained at the site for at least 36 h. Only one patient developed subclinical local inflammation at the site of injection. Miyoshi *et al*[21] reported on the injection of a solution of ICG in 40 cases, who subsequently underwent surgical resection. ICG solution contains 25 mg of powdered ICG in 2 mL sterilized water, and this solution was prepared by the manufacturer. The accuracy of ICG staining was 100% in the group who underwent surgery within 8 d and 92.7% in the later group.

PREPARATION AND STERILIZATION

During the early period of using India ink for endoscopic tattooing, non-sterile India ink was used in approximately 42% of all procedures[28]. This may have been the possible cause of adverse effects following the tattooing technique, causing an inflammatory reaction due to too-high concentrations of the substance. Subsequently, several studies proposed preparation and sterilization techniques. Salomon *et al*[29] recommended the preparation of India ink with 0.9% normal saline of 1:100 dilution. The ink was then sterilized by autoclaving for 20 min at 110°C to 121°C before storage. The American Society for Gastrointestinal Endoscopy[25] later approved this technique as the standard recommended preparation. Another proposed technique was the passage through a bacteriostatic

Table 1 Summary of the accuracy, false positive and spillage rates of endoscopic tattooing for localization before surgery from previously published reports

Authors	*n*	Substances	Techniques	Mean interval	Accuracy (%)	False positive (%)	Invisible (%)	Spillage (%)
Cho *et al*[9]	96	India ink	NA	6 d	97.9	0	2.1	6.3
Fu *et al*[15]	36	India ink	0.2 mL injected directly	30.8 d	86	0	14	8.3
	55	India ink	0.2 mL injected after 3 mL injection of saline solution	17.6 d	98	0	2	1.8
Arteaga-González *et al*[16]	21	India ink	Total 0.2-0.5 mL of 90% India ink injected after 3 mL injection of saline solution	NA	100	0	0	14.3
Park *et al*[17]	63	Spot	1-1.5 mL injected after 1 mL injection of saline solution	1 d (all)	96.8	1.6	1.6	9.5
Feingold *et al*[18]	50	Spot	1-4 mL tangentially injected into multiple sites distal to the lesions	1 d (60%)	88	0	12	NA
Conaghan *et al*[19]	54	Spot	NA	NA	70	7	15	NA
Hwang *et al*[20]	20	Spot	0.5 mL injected after 0.5 mL injection of saline solution, 3 sites at 1 cm distal to the lesions	3 d	90	0	10	5
Miyoshi *et al*[21]	41	Indocyanine green	1 mL injected after 2 mL injection of saline solution	4 d	92.7 (100, ≤ 8 d)	0	7.3 (> 9 d)	2.4

NA: Not available.

Millipore filter (0.22 μm)[28,29].

TECHNIQUES

Depth of injection is one of the crucial points in endoscopic tattooing. An optimal technique is needed to prevent possible complications due to transmural or too deep injections and invisible lesions from superficial injections. In addition, superficial injections, another possible explanation for invisible lesions, results from injection into the mesenteric or retroperitoneal side of the intestine. To prevent this adverse event, Hyman *et al*[30] recommended a "four quadrant" circumferential tattooing technique to improve intraoperative visualization. The technique which involves the injection of 0.2-0.5 mL of India ink, raising a bleb, into the colonic wall 1 cm distal of the tumor was suggested. The needle should be inserted tangentially to prevent transmural injection[31].

Sawaki *et al*[32] proposed a two-step marking method with a first injection of 0.5 mL of saline solution into the submucosal space to create the bleb. India ink was subsequently injected into the saline-blebs. One study compared the two tattooing techniques in 91 patients, 55 patients underwent the two-step approach and 36 patients underwent the conventional method. The results showed that the saline injection technique provided better tumor visualization ($P = 0.034$). The rate of complications was slightly lower in patients who underwent the two-step approach (1.8% *vs* 8.3%, $P = 0.297$)[15]. However, the spillage rate due to transmural injection was up to 14.3% in the saline injection group. Therefore, only one method is not the answer to eliminate overall complications. The important issue is awareness of possible complications at every step.

In our unit, we prefer to use the "four quadrant" technique by the one step approach with a 1:100 solution of India ink and normal saline because of the cost and availability. The solution is injected tangentially into the colonic wall at 0.5-1 cm distal to the lesion. The volume per injection is 0.2-0.5 mL. The total volume of the injected solution is about 10-20 mL. After endoscopic tattooing, the patient will undergo surgery within the next couple of days.

COMPLICATIONS

Several studies have proved that endoscopic tattooing is a safe technique. According to a large review of 447 cases by Nizam *et al*[28], the risk of clinical complications was only 0.22%. McArthur *et al*[33] reported a small number of complications in a study of 195 patients who underwent endoscopic tattooing. None of the patients in this study had any overt complications. In addition, a prospective study of endoscopic tattooing using India ink in 55 patients by Shatz *et al*[34] showed no clinical short-term complications. Moreover, we reviewed the long-term safety of India ink tattoos in the colon. None of 280 patients had endoscopic abnormalities over a mean follow-up period of 36 mo. Of these, biopsies from the tattoo sites revealed mild chronic inflammation in 8 patients (2.9%) and only one patient had hyperplastic changes at the biopsy site.

The number of complications following endoscopic tattooing is relatively small but not limited, and most are related to transmural injection. From our investigations, the spillage rate of transmural injections varies from 2.4% to 13% (Table 1). Most of these cases did not have any symptoms resulting from those complications. Case reports and case series of the adverse effects of endoscopic tattooing, including focal peritonitis[35,36], infected hematoma and/or abscess formation[36-38], inflammatory pseudotumor[39], idiopathic inflammatory bowel dis-

Table 2 Summary of complications of endoscopic tattooing for colorectal lesion localization from previously published reports

Authors	Location	Interval time	Material	Amount	Instrument	Complications
Yano *et al*[41]	NA	NA	India ink	0.7 mL undiluted	NA	Post-op adhesion
Bahadursingh *et al*[43]	Sigmoid	NA	India ink	NA	NA	Transmural injection to small bowel
Singh *et al*[35]	Rectosigmoid	NA	India ink	NA	NA	Transmural injection, focal peritonitis
Park *et al*[36]	Descending	18 h	India ink	0.5 mL diluted 1:10	Sclerotherapy needle	Colonic abscess with focal peritonitis
Gopal *et al*[40]	70, 85 cm from Anal verge	No surgery	India ink	4 mL undiluted	NA	Idiopathic inflammatory bowel disease
Tutticci *et al*[42]	Rectum	75 d	Spot	2 mL (0.5 mL each)	25G endoscopic needle	Pigmentation peritoneal adenocarcinoma (tumor inoculation)
Marques *et al*[37]	Sigmoid	3 d	Spot	4 mL (0.5 mL each)	NA	Infected intramural hematoma
Alba *et al*[38]	Sigmoid	10 d	India ink	1 mL diluted 1:10	Sclerotherapy needle	Rectus muscle hematoma and abscess
Coman *et al*[39]	Sigmoid	5 d	India ink	2 mL (0.5 mL each) diluted 1:1	NA	Inflammatory pseudotumor
	Sigmoid	14 d	India ink	2 mL (0.5 mL each) diluted 1:1	NA	Inflammatory pseudotumor
Cappell *et al*[44]	Cecum	7 d	India ink	4 mL total	Sclerotherapy needle	Transmural injection Spillage of dye into peritoneal cavity
	Cecum	13 d	India ink	4 mL total	Sclerotherapy needle	Transmural injection Spillage of dye into peritoneal cavity

NA: Not available.

ease[40], post-operative adhesions[41], and tumor inoculation[42] have been published. A summary of the complications of endoscopic tattooing from previously published reports is shown in Table 2.

One of most the common preparations from the standard recommendation is the concentration of India ink for injection, which consists of undiluted, 1:1, or 1:10 dilution solutions. These solutions might be one of the possible reasons for the adverse results seen when using this technique. Another technical concern is the intraperitoneal scatter of dye from transmural injection. Consequently, this can lead to a number of complications including infection and inflammatory reaction. Moreover, a major concern, although there is only one case report of needle tract inoculation that might be contaminated with cancer cells from the intraluminal area to the intraperitoneal cavity, was reported by Tutticci *et al*[42]. This interesting case report is a concern and questions whether all the scattered dye in the peritoneal cavity should be examined or removed at the time of surgery. Unfortunately, there are no recent data to answer this question. Further study is needed.

CONCLUSION

CRC screening is recommended in the US population for individuals older than 50 years. As a result, 30%-50% of all subjects were found to have polyps and 0.2%-11% had a malignancy. Some polyps can be removed endoscopically, but some require further surgical intervention. Therefore, localization of the lesion is crucial to prevent false segment resection, especially for the laparoscopic approach.

Endoscopic tattooing is one of the most common preoperative localization techniques. From this review, the accuracy of endoscopic tattooing is high and varies from 70% to 100%. The false positive rate is 1.6%-7% and the incidence of intra-operative invisible lesions is 1.6%-15%. The number of complications is small but not limited, and most are related to transmural injection. The spillage rate varied from 2.4% to 13%, but most patients with dye spillage were asymptomatic. Following the standard recommendation, including the preparation of substances and injection techniques can prevent unanticipated events.

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Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011
Miami, FL 33101, United States

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011
San Francisco, CA 94143, United States

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 04-05, 2011
13th Duesseldorf International Endoscopy Symposium
Duesseldorf, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week
Westin Bayshore, Vancouver
British Columbia, Canada

March 03-05, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL 32614, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011
Birmingham, England, United Kingdom

March 17-19, 2011
41. Kongress der Deutschen Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.
Munich, Germany

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology 2011
Jacksonville, FL 34234, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey

April 07-09, 2011
International and Interdisciplinary Conference Excellence in Female Surgery
Florence, Italy

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Stauffenbergstr. 26
Berlin 10785, Germany

April 18-22, 2011
Pediatric Emergency Medicine: Detection, Diagnosis and Developing Treatment Plans
Sarasota, FL 34234, United States

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong
Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

April 28-30, 2011
4th Central European Congress of Surgery
Budapest, Hungary

May 07-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis
London, England, United Kingdom

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV Spigc II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

September 10-11, 2011
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street
Los Angeles, CA 90015, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel
Brussels 1210, Belgium

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 02, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku
Tokyo 107-0052, Japan

December 01-04, 2011
2011 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical & Research Conference
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INSTRUCTIONS TO AUTHORS

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The columns in the issues of *WJGE* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in gastrointestinal endoscopy; (9) Brief Article: To briefly report the novel and innovative findings in gastrointestinal endoscopy; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGE*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal endoscopy; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in gastrointestinal endoscopy.

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Acknowledgments

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In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/wjg/help/15.doc.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and

Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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