From endoscopic resection to pancreatoduodenectomy: a narrative review of treatment modalities for the tumors of the ampulla of Vater

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Background and Objective: Tumors of the ampulla of Vater are a rare set of lesions that arise at the confluence of the common bile duct (CBD) and the pancreatic duct. They can be benign or malignant, often not easy to discriminate before treatment. Malignant tumors have low chances of survival (overall 5-year survival between 0% and 60%) and surgery is still the only curative option. Prognostic factors are being investigated to tailor therapeutic approach and improve outcomes. Due to their location in a complex anatomical region, all treatment options are challenging and associated with relevant morbidity. In this review we discuss different excisional techniques for the treatment of ampullary tumors (AT).

Methods: A review of medical databases (PubMed and Google Scholar) was conducted selecting most relevant articles in English language without a specific timeframe. After first selection, most relevant citations were identified through snowballing.

Key Content and Findings: Pancreatoduodenectomy (PD) is the gold standard in malignant tumors, achieving the most radical treatment, at the price of worse perioperative morbidity/mortality and quality of life. Trans-duodenal ampullectomy (TDA) was developed before endoscopic resection (ER) and maintains a role only in selected patients. ER is now the first choice for benign lesions and expanding towards early stages malignant AT.

Conclusions: Pancreatodudenectomy remains the best option for the radical excision of malignant AT, recently being offered also via minimally invasive approach. However, in early-stage malignant tumors, ER is gaining importance with foreseeable further expansion. Transduodenal ampullectomy still has a role in selected patients, such as unfit for PD when ER is not possible mainly due to anatomical abnormalities.

Keywords: Intestinal adenocarcinoma; jaundice; biliary obstruction; endoscopic retrograde cholangiopancreatography (ERCP); surgical treatment

Submitted Oct 23, 2021. Accepted for publication Jun 09, 2022.

doi: 10.21037/cco-21-141

View this article at: https://dx.doi.org/10.21037/cco-21-141

Introduction

Periampullary tumors are lesions that originate in a complex anatomical region. The periampullary region consists of the ampulla of Vater, distal common bile duct (CBD), second portion of the duodenum, and head of the pancreas.

Pure ampullary tumors (AT) (or tumors of the ampulla of Vater) are those that grow within the ampullary complex, distal to the confluence of the CBD and the pancreatic duct (*Figure 1*). AT are considered distinct from cancers of the duodenum, distal bile duct, and pancreas (1). Pure ampullary cancers are rare, and account for merely around 0.5% of gastrointestinal malignancies (2) and represent only about 6% of periampullary lesions (3). It is nevertheless, a deadly disease, with reported 5-year survival rates ranging from 17% to 80% (4).

The mainstay for the treatment of AT, at present, is surgical excision (5). There have been advances in technology and technique but still today a negative resection margin is considered the treatment goal. The role of chemotherapy and radiotherapy (adjuvant or neoadjuvant) in AT is still not clear as demonstrated by inconclusive results in clinical trials (6). Consensus has not been produced by either the European Society for Medical Oncology (ESMO) (7) or National Comprehensive Cancer Network (NCCN) (8). The main treatment modalities for the excision of AT are pancreatoduodenectomy (PD), transduodenal ampullectomy (TDA) and endoscopic resection (ER) (9). PD has long been considered the standard (10), whilst both TDA and ER seem to be acquiring a growing role as the knowledge around this disease advances.

Factors that influence outcomes are extremely important for treatment planning. Categorizing AT based on anatomical location can be challenging because data on outcomes have not been consistent over the years and due to the difficulty in discerning the precise location of the tumor even during the pathology examination. Histological classification was created subdividing adenocarcinomas into intestinal type and pancreaticobiliary (PB) type (11). This classification continues to be revised, while the PB type has consistently shown poorer outcomes (12).

One of the main difficulties about guiding treatment according to histology is that, not always the microscopic pathology is known before surgery (13). Achieving an accurate diagnosis, and ruling out malignancy based on preoperative studies can be tricky. The risk of inaccurate sampling and missing small foci of invasive carcinoma within large adenomas translates into low negative predictive values of endoscopic biopsies. The rate of false negative biopsies ranges between 16–60% (14).

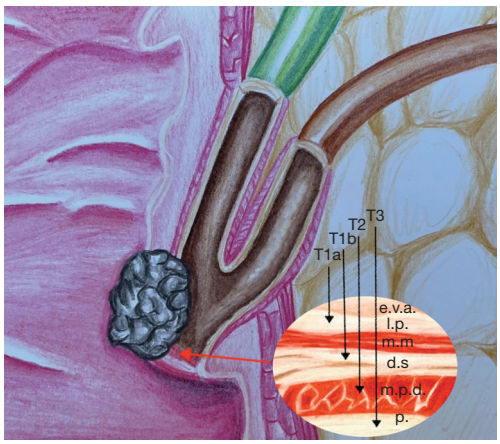

Figure 1 The periampullary region, tumors within the ampulla of Vater. e.v.a., epithelium of Vater's ampulla (mucosa); l.p., lamina propria of Vater's ampulla (mucosa); m.m, muscularis mucosa of Vater's ampulla (mucosa) (mucosa: a. + l.p. + m.m); d.s, duodenal submucosa; m.p.d., muscolaris propria of duodenum; p., pancreas; T1a, tumor limited to ampulla of Vater; T1b, tumor invades beyond the sphincter of Oddi and/or duodenal submucosa; T2, tumor invades into the muscularis propria of duodenum; T3a, tumor directly invades pancreas (up to 0.5 cm); T3b, tumor extends more than 0.5 cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the celiac axis or superior mesenteric artery; T4 (not shown in figure), tumor involves the celiac axis, superior mesenteric artery, and/or common hepaticartery, irrespective of size (not shown in figure).

Other preoperative prognostic factors for the outcome of AT include TNM staging, which plays an important role in stratifying prognosis both for overall survival and disease-free survival (15). If available, precise molecular diagnosis and staging are advisable to obtain when planning for treatment.

In this review we present the main treatments to excise AT in relation to patient and disease characteristics. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-141/rc).

Methods

A literature review was performed using PubMed and Google Scholar databases including all English scientific articles published up to January 2022. The relevance

Table 1 The search strategy summary

Items	Specifications
Date of search	01/04/2021–31/12/2021
Databases and other sources searched	PubMed & Google Scholar
Selection process	All authors contributed in including cited articles according to their role. Further included articles were found by snowballing technique. The final decision regarding selection was approved by all authors
Timeframe	All articles published up to January 2022
Inclusion and exclusion criteria	Inclusion criteria: review and research articles in English on the management of Ampullary neoplasia's
	Exclusion: authors excluded poor quality papers and publications with low reliability
Search terms used	Ampulla of Vater [MeSH]; Ampullary cancer; Ampullary adenocarcinoma; ampulla of Vater cancer; Ampullary adenoma; ampulla of Vater adenoma; Pancreatoduodenectomy [MeSH]; Trans-duodenal ampullectomy, Endoscopic surgical procedures [MeSH]; Gastrointestinal endoscopy [MeSH]

of articles was discussed in meetings during the review planning. Additional relevant publications were identified by snowballing technique and always discussed before inclusion during authors consultations. Search terms are specified in *Table 1*.

PD

PD is one of the most challenging abdominal surgeries for both patient and surgeon. PD preferably is to be conducted in high volume centers (>35 cases per year) (16). Despite the progress in the last twenty years, the perioperative mortality after this procedure remains around 3% even in very experienced settings (17). Postoperative complications occur in 20–40% of patients including pancreatic fistula, pneumonia, intra-abdominal infections, anastomotic leak, bleeding and delayed gastric emptying (18).

PD is aimed at removing the head of the pancreas *en bloc* with duodenum, gallbladder, CBD and depending on technique part of the stomach. This procedure comprises lymphadenectomy that can be extended as far as the inferior mesenteric station. The recommendation regarding the minimum number of lymph nodes in the surgical specimen is 12–15 (19), but this number was set after a consensus statement on pancreatic ductal adenocarcinoma. It is not clear yet whether the same principles stand for AT too. PD may be conducted via open or minimally invasive surgery (MIS) approaches. Laparoscopic (20) and robotic (21) techniques have gained momentum in the last 20 years achieving good results in terms of oncological proficiency, postoperative morbidity and mortality. The difficulties in reproducing such techniques still limits their widespread to a handful of high volume centers.

Pancreaticoduodenectomy is the upfront treatment in malignant AT. However, malignant disease may be difficult to detect preoperatively and PD may serve as a back-up option when malignancy is encountered within specimen obtained from ER for suspected benign AT (22). Curative removal can be obtained in up to 80% of the cases when resection margins are clear from tumor (23). It is evident that from an oncological point of view this approach has an advantage over any other possible treatment at the price of higher morbidity and mortality compared to ER (9). Other than removing the primary location of the tumor, PD provides extensive lymphadenectomy. Compared to pancreatic tumors, AT have specific lymphatic drainage that involves a definite number of lymph nodes close to the ampulla, which allow to obtain a precise and effective lymphadenectomy (24). This is particularly important because nodal status is one of the most influential predictors of survival. In a study from Taiwan, the 5-year disease-specific survival rate was 63.7% for node-negative versus 19.1% for node-positive patients (4). In ampullary carcinoma, the evidence of increasing the total harvested lymph nodes resulting in better prognostic determination was observed by Chen *et al*. (25). This theory was also discussed in an earlier study that evaluated the number of involved nodes divided by the total number of examined

nodes, which is referred to as the lymph node ratio (LNR), suggesting that this ratio is a powerful prognostic factor (26). For this reason the latest TNM staging for AT takes in account also the number of lymph nodes involved (15). It is still discussed whether lymphadenectomy might confer a survival benefit. As an example a recent prospective, randomized study of 62 patients subjected to PD for ampullary carcinoma found no variation in the 5-year survival in the group undergoing standard versus extended lymphadenectomy (27).

A study by Aranha *et al.* (28) focusing on technical aspects, registered a higher incidence of pancreatic fistula after PD in patients with AT compared to pancreatic cancer (28% versus 6%), possibly due to a softer pancreas which makes pancreatic anastomosis more prone to leakage. The oncologic proficiency of MIS has been reported in the last 5 years through publications that demonstrated non-inferiority of oncologic outcomes of laparoscopic versus open PD for AT. On the side, perioperative outcomes such as postoperative length of stay and quality of life after surgery seem to be superior for patients treated laparoscopically (29,30). Valle *et al.* (31) described their 10-year experience with robotic PD for AT, showing comparable outcomes to those described in the literature for open surgery. It is plausible that robotic will soon reach the same results of laparoscopic surgery.

In summary, PD is the gold standard in malignant tumors, achieving the most radical treatment, at the price of worse perioperative morbidity/mortality and quality of life.

TDA

First described by Halsted *et al.* (32) in 1899, TDA consists in the removal of the ampulla of Vater through a duodenotomy. A Kocher maneuver is performed to mobilize the duodenum, and after a duodenotomy the ampulla is excised. Reconstruction is usually started with the creation of a communication between the pancreatic and bile ducts that are then sawn to the duodenum. Lymphadenectomy may be performed but it does not include lymph node stations along the superior mesenteric artery. Usually frozen sections are sent to the pathologist during surgery to determine the local invasion and histology of the tumor, the more aggressive cases are the transformed to PD, when this is feasible. The procedure can be performed with traditional open technique or using MIS (33,34).

In general TDA is considered for the resection of small (up to 4 cm) (35) benign tumors after previous unsuccessful ER (36). It is still discussed whether expanding its use to early ampullary cancers, due to the high risk of recurrence after TDA (37).

It is considered a safe procedure with a mortality around 1% (13). Perioperative morbidity ranges in the largest single center studies between 22% and 44% (38,39). When directly compared to ER in treating benign lesions, TDA produced higher morbidity and mortality rates (38). An interesting study by Ceppa *et al.* (40) showed that in patients with benign ampullary lesions, ER had lower morbidity and identical mortality. These findings suggested that patients with benign lesions would likely benefit from an endoscopic approach before considering surgery. In fact, ER is nowadays considered the gold standard (41). Nevertheless, ER might turn unsuccessful and TDA can be implemented in clinical algorithms for patients with benign lesions (42).

For malignant lesions to be treated by TDA, two conditions should be fulfilled: no suspected lymph node involvement and the feasibility to achieve a free resection margin (43). For these reasons, the best way to treat malignancy still remains PD (44). Nevertheless, there is generalized agreement to consider TDA only for malignant tumors that do not invade the muscularis propria of the duodenum (T2, AJCC8) (45). Concerns regarding radicality are justified as demonstrated by Nappo *et al.* (39) who reported a 13.0% rate of R1 resections with TDA. Similarly, di Mola *et al.* (46) in a recent paper reported a 28.5% rate of R1 resections up to T2 AT with TDA.

The other key question is whether TDA allows an adequate lymphadenectomy. Most authors agree there is lymph node involvement in patients with T1 tumors (47,48). Another important aspect to consider is recurrence rate. An interesting study by Song *et al.* (35) highlighted the differences between TDA and PD in T1 AT. Recurrence was observed in 10 out of 26 patients in the TDA group and no recurrence in the PD group. This means that even if perioperative mortality is superior in the PD group, overall survival is counterbalanced by the higher cancer-related mortality due to recurrence after TDA.

Summing up, TDA has been a long-standing surgical approach that maintains a role only in selected patients.

ER

ER is a minimally invasive and most recently introduced technique to resect AT. First described in 1983 with 2 patients treated for malignant disease (49), it has gained popularity in recent years, and indications are widening.

The objective of this intervention is the *en bloc* resection of the lesion with R0 free lateral and deep margins (50). This is not always possible, as in lateral spreading tumors. In these cases, piecemeal excision is the preferred choice even if recurrence rates seem to be higher (51). The excision is accomplished through the introduction of an endoscopic snare. Another option is to use electrosurgical current or pure cutting current. Sometimes endoscopic excision can be testing for surgeons and endoscopists, for this reason ablative techniques have been devised. These options are used as adjunctive therapy to treat residual tumor tissue after R1 resections and include argon plasma coagulation, photodynamic therapy, monopolar and bipolar coagulation, intraductal radiofrequency ablation and neodymium-yttrium aluminum garnet laser. However, the benefits of this adjunctive treatments are still controversial. Success rate appear to be similar between adjuvant thermal ablative treatments compared to those who did not undergo adjunctive therapy (52). The use of submucosal injection (saline, methylene blue or epinephrine) has not been clarified. Injecting a substance to lift the tumor is used in other parts of the gastrointestinal tract. However, due to the complex anatomy of the ampulla, establishing a standard technique remains difficult. A prospective multicenter study on the role of submucosal injection in AT by Hyun *et al.* (53) showed no clear superiority of submucosal injection against simple snare resection regarding complete resection.

Other procedural tactics can be applied to diminish perioperative complications, such as pancreatic and/or biliary sphincterotomy and stent placement. Sphincterotomy eases the access to the pancreatic duct after resection and the assessment of intraductal extension of the tumor prior to excision. However, it may tamper with the possibility of performing a complete resection, jeopardize complete histologic evaluation due to thermal injury, and increase the risk of complications (54). Prophylactic pancreatic duct stenting in the course of ER is endorsed by the American Society for Gastrointestinal Endoscopy to reduce the risk of post-procedural pancreatitis (55), although consistent consensus has not been reached (56).

In terms of post-operative complications and invasiveness, ER is a consistently safe procedure especially when compared to TDA & PD. This was partially confirmed by Heise *et al.* (9) in a recent meta-analysis on ER versus PD and TDA in ampullary lesions, highlighting a higher risk of complications in the most radical surgical interventions (PD/TDA). Adverse events in ER do exist and include bleeding (0–20%), pancreatitis (0–20%), papillary stenosis (0–9%), cholangitis (0–5%), perforation (0–4%) (50) and mortality (0–3%) (57).

Endoscopic excision to treat ampullary adenomas has developed remarkably in recent years, and is now considered superior to surgical excision (40,55). The indications to ER are rapidly evolving as expertise is gained and new endoscopic devices are developed. In a nutshell, indications are dictated by the clinical aspects of the patient and the surgical endoscopist expertise. Contraindications are: presence of malignancy, certain (biopsy-proven) or suspected (macroscopic appearance at duodenoscopy or suggestive pre-operative imaging). Five cm diameter AT size remains the most commonly adopted limit for ER. Lastly, there must not be evidence of intraductal growth. However, as time passes indications progress, and exceptions to these rules are emerging. For example, piecemeal resection has shown interesting results in the excision of large (>5 cm) and laterally spreading adenomas with comparable results in terms of single treatment procedure and total resection (58). Bohnacker *et al.* (59) pioneered the ER of benign AT with intraductal growth already in 2005, and later Kim *et al.* (60) reported the technical feasibility for totally unexposed types of intraductal growing ampullary masses.

Regarding malignancy, some authors have recently proposed the possibility of treating T1a AT with ER in their retrospective analysis of a single center of 177 patients who underwent ER. There was no lympho-vascular invasion or lymph node metastasis in any T1a AT (27 patients). As for incomplete resection, there was no significant difference between adenoma and carcinoma, while bigger size was associated with worse results (61). Other than resectability, which may depend on the technical ability to excise small tumors, the question regarding the indication based on the TNM staging has been debated. Some authors showed no lympho-vascular invasion, lymph-node metastasis, or ductal involvement in T1a AT (62). Similarly, Hwang *et al.* (63) retrospectively analyzed patients undergoing ER alone or ER followed by PD for Tis and T1a. Even though they found 5.7% lympho-vascular invasion for all T1a and Tis, there was no statistically significant difference in tumor recurrence rates between the two groups (ER and ER/PD). The authors concluded endoscopic management provided not only better quality of life but also lower procedure-related morbidity and mortality.

In conclusion, ER is now the first choice for benign lesions and expanding towards early stages malignant AT.

Discussion

Histology and molecular sub-types

AT are a rare set of tumors that arise in the same anatomical region, with increasing incidence in the last 30 years (2). The histology of primary AT more often resembles that of adenomas/adenocarcinomas. In one study of 170 ampullary lesions, the most common histologic subtype was intestinal (47%), followed by pancreatobiliary (24%), poorly differentiated adenocarcinomas (13%), intestinal-mucinous (8%), and invasive papillary (5%) (64). Such variety is suggestive of different types of disease that from the surgical perspective are still grouped together, only for treatment purposes. There is growing evidence that different molecular subtypes are associated with different survival patterns, with the intestinal subtype showing more favorable prognosis (65). If this were confirmed, treatment paths might be tailored based on histologic subtype. Additionally, molecular prognostic factors such as kirsten rat sarcoma (KRAS), Tumor protein P53, have been proven to be negative predictors of survival unrelatedly of histological subtype. Other mutations seem to be involved; 4 membrane erythroblastosis oncogene B (ERBB), wingless/integrated (WNT) pathways, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K). These could be used to define possible responsive tumors to target therapy, such as everolimus in PI3K-mutated cases (66).

Pre-operative management

Ampullary adenomas and adenocarcinomas usually present with jaundice in around 80% of cases (10). The diagnostic evaluation of patients with obstructive jaundice has the objective of discriminating between benign from malignant disease. The role of preoperative biliary drainage is still controversial. Because obstructive jaundice can lead to cholangitis and multiorgan dysfunction, it was hypothesized that drainage would diminish postoperative morbidity and mortality. However, the results from randomized trials and meta-analysis of preoperative drainage versus no drainage are conflicting (67,68). One study addressed biliary drainage in a retrospective series of 82 patients with AT, showing a decreased incidence of wound infection but no correlation with other postoperative complications or survival (69). No widespread agreement regarding preoperative biliary drainage has been reached yet. Clinical practice may vary widely across centers and patients may be sent for stenting before they are referred to specialized centers. A common management scenario is to stent only patients with high-grade jaundice (bilirubin >15 mg/dL) who will not undergo surgery within the next seven days (70).

Staging

To evaluate the extent of AT, all patients should receive at least one high-quality imaging examination (computed tomography and/or magnetic resonance imaging) before treatment. A side-view duodenoscopy is usually performed because it permits identification of the tumor, biopsy, and biliary decompression via endoscopic retrograde cholangiopancreatography (ERCP) if needed. Endoscopic ultrasound (EUS) is the most accurate modality to assess the T stage of AT, which is critical for planning surgical intervention. The efficacy decreases when evaluating the N stage even if fine needle aspiration of suspicious lymph nodes may further increase the accuracy.

Treatment of AT

Definitive treatment for AT remains complete excision. The outcome of resected malignant AT is determined by the extent of local invasion (T stage), status of the surgical margins, and the presence/absence and number of lymphnode metastases (N stage). Other than lymph nodes, AT usually metastasizes to liver, adjacent organs (peritoneum) and lungs, even if more unusual locations cannot be excluded (71). For patients with unresectable or distant metastatic disease, endoscopic stenting for biliary decompression is an appropriate palliative procedure. The main goal of surgical intervention is complete resection with negative margins. ER is slowly gaining consensus when considering presumably benign adenomas. The endoscopic treatment appears to be as radical as surgical excision but has definitely improved perioperative morbidity and mortality. Some limitations are still valid, such as size of the adenoma and depth, although high volume centers are challenging the boundaries of dimension. Even so, adenomas may hide malignant adenocarcinoma foci between 11.7% and 60% (72) of times. In these cases, ER turns into a diagnostic tool and can be followed by the definitive treatment with PD. ER may have a role in early T1a carcinomas, where results in terms of R0 and recurrence rate have been similar to those of PD in small series. *Table 2* resumes the main studies regarding ER including more than 5 cases of

Table 2 Studies on the treatment of AT with ER with more than five cases with malignant histology

Author, year	No. patients	No patients with malignancy	Additional surgery (PD) performed	Procedure related early complications	Procedure related mortality	Type of resection achieved	Recurrence (mon)	Histology	Stage	Survival
Hwang *et al.* (63), 2021	70	70	28	NDA	0%	CR: 57%	18% 57.9 (42–99) FUP	Adenocarcinoma	Tis (n=1), T1a (n=41)	DFS (5 years)→ ER 79.1%, DFS (5 years)→ ER + PD 87.4%
Lee *et al.* (73), 2021	53	30	1	Total: 18.9%	0%	NDA	NDA	HGD (n=23), intramural carcinoma (n=2), invasive carcinoma (n=5)	NDA	NDA
Yamamoto *et al.* (61), 2019	177	35	NDA	Total: 25.8%, bleeding: 19%, pancreatitis: 9.7%, cholangitis: 3.2%, perforation: 3.2%	0%	CR: 83.9%, TR: 100%	0% 26.5 (5–60) FUP	Adenocarcinoma	Tis, T1a (n=27), T1b (n=4), T2 (n=4)	NDA
Alvarez-Sanchez *et al.* (74), 2017	173	28	14	NDA	NDA	CR: 43%, (100% in Tis)	7% 66 (5–108) FUP	Adenocarcinoma	T2/n+	NDA
Kang *et al.* (75), 2017	104	32	NDA	Total: 31.7%, pancreatitis: 15.4%, bleeding: 17.3%, perforation: 7.7%	2.3%	NDA	NDA	HGD (n=17), adenocarcinoma (n=17)	NDA	NDA
Dubois *et al.* (38), 2017	11	11	4	Total: 9%	0%	NDA	NDA	NDA	NDA	NDA
Hyun *et al.* (53), 2017	50	16	NDA	NDA	0%	NDA	NDA	HGD (n=12), adenocarcinoma (n=4)	NDA	NDA
De Palma *et al.* (76), 2015	27	7	2	Total: 18.3%, bleeding: 7.4%, pancreatitis: 11.1%	0%	NDA	NDA	HGD (n=4), adenocarcinoma (n=3)	NDA	NDA
Ismail *et al.* (77), 2014	61	10	3	Total: 24.6%, pancreatitis: 9.8%, bleeding: 18%	0%	NDA	42% 14 (5–28) FUP	Adenocarcinoma	N0, N1	NDA
Laleman *et al.* (78), 2013	91	35	18	Total: 25.2%, pancreatitis: 15.6%, bleeding: 12.1%, cholangitis: 4.4%	0%	CR: 43%	18% 32 FUP	HGD (n=19), adenocarcinoma (n=16)	–	90% < OS (5 years) < 100% if R0
Petrone *et al.* (79), 2013	15	15	NDA	NDA	NDA	NDA	42.9% 29.6 (8–81) FUP	Adenocarcinoma	T1	DFS 8.2 mon (1–16 mon)

Table 2 (*continued*)

Table 2 (*continued*)

Author, year	No. patients	No patients with malignancy	Additional surgery (PD) performed	Procedure related early complications	Procedure related mortality	Type of resection achieved	Recurrence (mon)	Histology	Stage	Survival
Will *et al.* (80), 2013	58	18	2	Total: 18.5%, pancreatitis: 12.9%, bleeding: 5.5%, perforation: 1.9%	0%	CR: 75%	20% 18.5 (1–84) FUP	Adenocarcinoma	NDA	DFS 88.9% (1–84 mon)
Ito *et al.* (81), 2012	28	12	NDA	Total: 36%, bleeding: 25%, pancreatitis: 9.3%, perforation: 7.1%, cholecystitis: 7.1%	0%	NDA	NDA	Adenocarcinoma	NDA	NDA
Salmi *et al.* (82), 2012	61	21	4	Total: 18%, pancreatitis: 10%, bleeding: 5%, perforation: 3%	0%	CR: 76.2%, TR: 81%	10% 36 (14–46) FUP	HGD (n=11), adenocarcinoma (n=10)	T1	NDA
Harano *et al.* (83), 2011	28	11	2	Bleeding: 18%, pancreatitis: 7%, cholangitis: 7%	0%	CR: 82%, TR: 93%	NDA	Adenocarcinoma	NDA	NDA
Jeanniard-Malet *et al.* (84), 2011	42	10	NDA	Total: 21%, pancreatitis: 14.3%, bleeding: 7%	0%	NDA	NDA	Adenocarcinoma	NDA	NDA
Kim *et al.* (72), 2009	20	6	2	NDA	5%	NDA	NDA	HGD (n=5), adenocarcinoma (n=1)	NDA	DFS 16 mon in HGD
Irani *et al.* (57), 2009	127	8	8	Total: 21%	0%	NDA	NDA	Adenocarcinoma	NDA	NDA
Boix *et al.* (85), 2009	21	14	12	Pancreatitis: 23.8%	0%	NDA	NDA	HGD (n=4), adenocarcinoma (n=10)	NDA	NDA
Yoon *et al.* (62), 2007	83	23	7	NDA	4.3%	CR: 100%	0% 27.1 (10–60) FUP	HGD, adenocarcinoma	Tis (n=13), T1 (n=10)	NDA
Bohnacker *et al.* (59), 2005	106	10	10	NDA	0%	NDA	NDA	HGD (n=4), invasive carcinoma (n=6)	NDA	NDA
Catalano *et al.* (86), 2004	103	20	6	Total: 9.3%	0%	NDA	NDA	HGD (n=14), adenocarcinoma (n=6)	NDA	NDA

Type of resection achieved: complete resection is when R0 is achieved at first attempt, total resection is when R0 is achieved in more than one attempt. AT, ampullary tumors; ER, endoscopic resection; PD, pancreatoduodenectomy; NDA, no data available; DFS, disease-free survival; FUP, follow-up; HGD, high grade dysplasia; OS, overall survival; CR, complete resection; TR, total resection; mon, months.

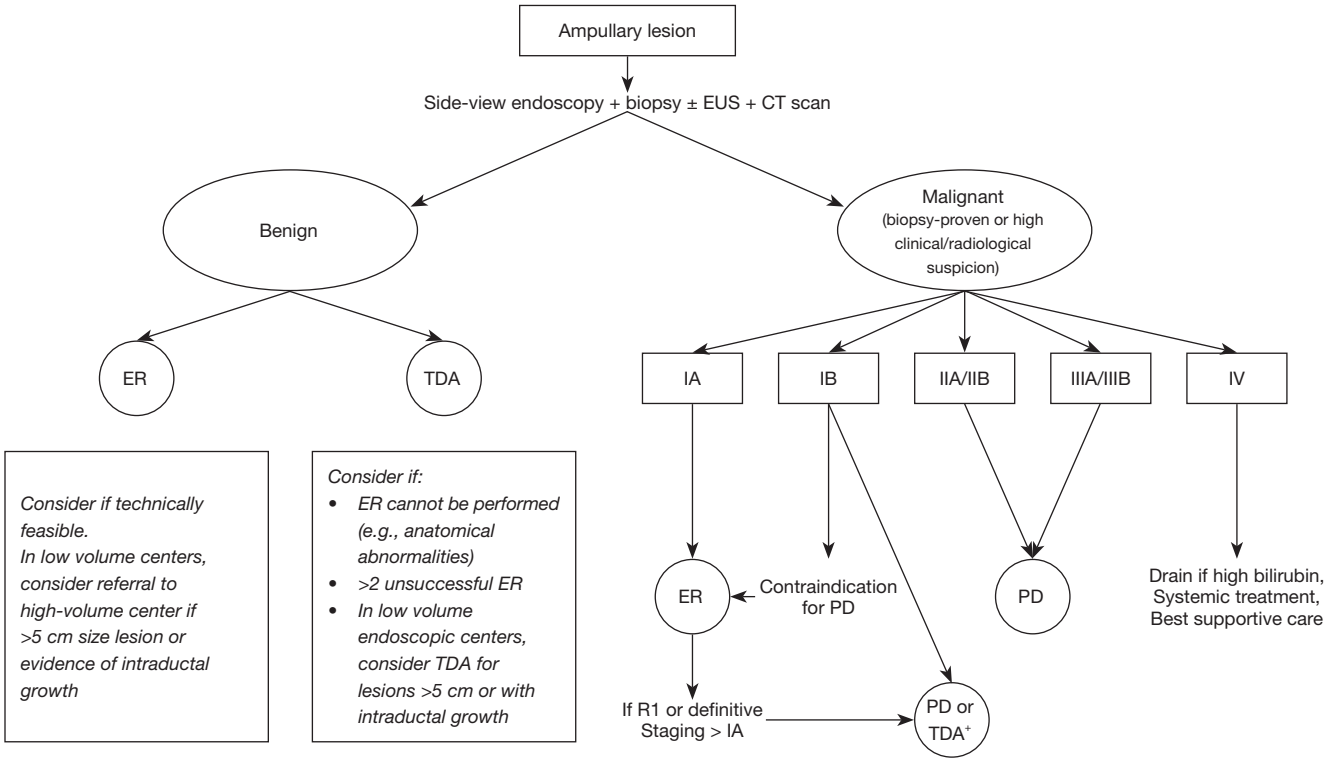

Figure 2 Treatment algorithm for ampullary lesions. EUS, endoscopic ultrasound; CT, computerized tomography; ER, endoscopic resection; TDA, trans-duodenal ampullectomy; PD, pancreatoduodenectomy.

malignant AT (61,63,73-86). Significant data are expected in the near future and technological advances are likely to expand the role of ER in early malignant AT, especially in patients not fit for surgery. PD is still the gold standard for malignant ampullary lesions, providing the highest rates of complete resection and extended lymphadenectomy. On the other side, PD is a demanding procedure, and not all patients are fit for it. AT tend to be technically resectable lesions, uncommonly requiring vascular resection. This makes them ideal for MIS, compared to other tumors such as pancreatic cancers. There is growing evidence of non-inferior oncological outcomes when comparing traditional PD versus MIS-PD, whilst MIS appears to improve peri-operative outcomes and quality of life. The least practiced surgical procedure for AT is TDA. In the past, it had a role in filling the gap between ER and PD, but as ER gathers drive, TDA is losing ground. In the era of precise medicine and tailored treatment, TDA is still indicated in benign lesions that cannot benefit from ER (e.g., anatomical anomalies) and in malignant lesions when patients are unfit for PD.

Diagnostic and treatment algorithm

In general, we have synthetized these concepts in a diagnostic and treatment algorithm (*Figure 2*). Depending on the clinical presentation, the diagnostic workup is started with a side-view endoscopy to assess the macroscopic morphology of the tumor and biopsy. EUS can define the boundaries of the lesion and local lymph nodes. ERCP offers the possibility of stenting patients with cholangitis. Benign disease can be treated with ER, whilst TDA has a role when anatomical abnormalities are present or if ER is unsuccessful in more than two occasions. In cases of suspected or confirmed malignancy, a staging CT can rule out metastatic disease and address patients to potentially curative tumor excision. In patients with high suspicion of malignancy despite benign biopsy histology [e.g., double duct sign on computerized tomography (CT scan) or lymphadenopathy], EUS can aid in the diagnosis, especially if there are malignant looking lymph nodes that can be biopsied. Treatment for malignancy in our opinion should be guided by TNM staging. In malignant disease ER can

be used in stage IA and in selected cases stage IB. TDA is only suitable up to stage IB, since stage IIA consists of T3a tumors (pancreas is involved and radicality would not be assured). PD is always possible, however patient comorbidities and postoperative morbidity should always be taken into account when planning a PD. As for the role of systemic therapy, associating surgery with chemotherapy seems to be effective in more advanced stages of disease, either as adjuvant or neoadjuvant treatment (87-89).

Future perspectives

Having considered the current limitations around the understanding and management of AT, it would be advisable to concentrate future studies on expanding AT characterization. Differentiating histological subtypes and mutation genotyping would help develop and select more effective treatments. Surgery will likely maintain its primary role for long time, while the refined understanding of tumor biology will provide further insight on how to adapt surgical technique to tumor behavior.

Conclusions

In conclusion, the low incidence of AT compared to other solid tumors slows the construction of solid evidence around diagnostic and treatment modalities. Extensive research is expected before establishing clear guidelines for the treatment of AT. Finally, AT is a complex group of tumors with many facets, highlighting the importance of a multidisciplinary approach.

Acknowledgments

We thank Dr. Francesca Moschetta for the drawing of the original illustration of this manuscript (*Figure 1*).
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Giovanni Levi Sandri) for the series "Hepatobiliary and Pancreatic Cancers: an Update of Surgical Treatments" published in *Chinese Clinical Oncology*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-21-141/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-21-141/coif). The series "Hepatobiliary and Pancreatic Cancers: an Update of Surgical Treatments" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Taliente F, Bianco G, Moschetta G, Franco A, Giovinazzo F, Agnes S, Spoletini G. From endoscopic resection to pancreatoduodenectomy: a narrative review of treatment modalities for the tumors of the ampulla of Vater. Chin Clin Oncol 2022;11(3):23. doi: 10.21037/cco-21-141