



Transduodenal surgical ampullectomy: a procedure that requires a multidisciplinary approach

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Abstract

Trans-duodenal surgical ampullectomy (TSA) was first described in 1899. Nowadays its role in ampullary tumor surgery is still a matter of debate and requires a multidisciplinary approach. The aim of this study is to evaluate the results of TSA as a curative treatment for benign and selected malignant tumors arising from the ampulla in a single-institution experience. Sixteen patients with periampullary tumors that underwent TSA in our surgical units between January 2012 and January 2017 were included in the study. Patient demographic characteristics, pre or postoperative endoscopic interventions, operative procedures, postoperative morbidity and mortality, hospitalization, follow-up time, and quality of life questionnaire were analyzed. Mean operative time was 238.5 min (range 180–390), mean tumor size was 2.3 cm (range 1.5–3.9). The microscopic surgical outcome was R0 for 14 patients. The most frequent findings in terms of histological type were high-grade dysplasia/pTis (43.7%), low-grade dysplasia in 37.5% patients, invasive adenocarcinoma in 2 cases (12.5%), chronic inflammation in 1 case (6.3%). The readmission rate was 18.8% (3/16) and in 2 cases (12.5%) relaparotomy was required. The cumulative median duration of follow-up was 50 months (range 1–96). 90-days mortality was 6.2%. Mean hospital stay was 12 days (range 8–60). Our results confirm that TSA offers good results in terms of morbidity and mortality; still, it remains a challenging procedure that requires particular surgical experience and operative skills. A pre-operative planning in a multidisciplinary board should be carried out prior to the procedure.

Keywords Transduodenal surgical ampullectomy (TSA) · Pancreaticoduodenectomy (PD) · Post-pancreatectomy hemorrhage (PPH) · Delayed gastric emptying (DGE) · Endoscopic retrograde cholangio-pancreatography (ERCP)

Introduction

Vater papilla tumors are a rare disease representing 5% of all cancers of the gastrointestinal system with a prevalence of 0.04–0.12% in autopsy cases [1]. They can occur as occasional findings or in the context of genetic syndromes such as familial adenomatous polyposis (FAP). Among the wide variety of benign ampulla tumors, adenomas (also called *ampullomas*) are the most frequent lesions and have particular relevance for their potential of malignant transformation,

as described in the well known adenoma-carcinoma sequence [2].

At present, the therapeutic approaches of ampullary tumors can be both surgical and endoscopic. Surgical options include transduodenal surgical ampullectomy (TSA) first described by Halsted in 1899 [3] and the more radical pancreaticoduodenectomy (PD) introduced by Whipple in 1935 [4]. The endoscopic ampullectomy consists of resection of the ampullary region (papillectomy) and is globally recognized as a first-line procedure for benign lesions [5–9]. If endoscopic resection is not successful or feasible, a surgical approach has to be considered. Surgical treatment certainly guarantees complete removal of the lesion (especially PD), nevertheless, it is burdened with a mortality rate of about 2% and high morbidity (around 20–40%) even in high volume centers [10–12]. For this reason, the local resective approach, in selected cases, seems to be a valid alternative

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being less invasive with consequent advantages in terms of lower morbidity and mortality [13–18].

Beforehand, to establish the proper approach, periampullary lesions require an initial endoscopic ultrasound (EUS) followed by histological characterisation. Actually, there is no overall agreement regarding what kind of lesions should be treated surgically and which ones should instead undergo an endoscopic treatment. Many authors believe that endoscopy should only be reserved for cases with no evidence of invasive cancer, indeed finding of carcinoma in situ does not represent a contraindication for endoscopic treatment [19–21]. Schneider et al. in the largest series present in literature (83 pts), stated that TSA is an underestimated surgical procedure that can be performed safely with long-term efficacy [15]. It can be safely implemented in clinical algorithms for patients with benign pathologies of the ampulla of Vater, especially after unsuccessful endoscopic treatment. However, it should be clarified that surgical removal is the only definitive treatment even for adenomas with in situ carcinoma. Moreover, some authors argue that all periampullary lesions should be treated by PD due to the high recurrence rate after local excision, to the possibility that lymph nodes spread may already be present at the time of diagnosis and, finally, to the limited and fragmented bioptic specimens collection for histological examination, that can lead to a false-negative result [17, 22, 23].

Therefore TSA somehow straddles a mere endoscopic treatment and radical surgical procedures such as a PD, especially when dealing with a preoperative diagnosis of benign lesions or in situ carcinoma with no evidence of lymph nodes metastasis [24]. A critical point to ponder when planning to perform a TSA is the mandatory use of the intraoperative frozen-section histopathological procedure to further determine the characteristics of the lesion and the status of resection margins.

The aim of the study was to evaluate our experience with patients who underwent TSA for periampullary neoplasms. Indications, surgical technique, outcome, long-term results, and the multidisciplinary aspect are discussed to consider TSA as part of a curative algorithm for selected periampullary tumors.

Materials and methods

Sixteen patients with periampullary tumors that underwent TSA in our surgical units between January 2012 and January 2017 were included in this study. The patient's data were prospectively collected into a standardized electronic database and were retrospectively evaluated from clinical charts. Indications for TSA were: failure of endoscopic treatment (for instance, due to the presence of duodenal diverticulum or to a tumoral extension to pancreatic/

duodenal/biliary wall), endoscopically unresectable benign periampullary tumors (low-grade dysplasia adenomas or high-grade/carcinoma in situ (pTis), and selected cases of pT1 carcinoma with no lymph node involvement in patients with such comorbidities to preclude a highly complex surgical procedure such as PD. Also, in our experience, lesions with a diameter > 4 cm were excluded and considered more suitable for PD due to the high likelihood of an advanced tumor or an R1.

All patients were evaluated preoperatively by a multidisciplinary board (surgeons, interventional endoscopists, radiologists, and pathologists), and were counted eligible after the failure of the endoscopic procedure. Preoperative workup included computed tomography (CT-scan) and/or magnetic resonance imaging (MRI), endoscopic ultrasound (EUS) with biopsy. Endoscopic retrograde cholangiopancreatography (ERCP) was requested in case of jaundice (occurred in 9 out of 16 patients). All patients were included in a modified fast track program for pancreatic surgery [25]. During the surgical procedure, the whole tissue sample underwent a frozen-section histological evaluation of resection margins. The post-operative analgesia was performed by means of intravenous elastomer. Metoclopramide at a dosage of 30 mg/day was administered to all patients. To prevent post-operative pancreatic fistula (POPF), octreotide 0.2 mg three times a day was given until drainage removal. Considering TSA a pancreatic procedure, we evaluated as well the morbidity, including postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and postoperative hemorrhage (PPH), according to the definitions of the International Study Group for Pancreatic Surgery (ISGPS) [10, 26, 27]. Pathological findings were classified and graded according to the current WHO classification [28]. R status (R0-R1) was defined according to the current literature [29].

The follow-up was carried out by means of an outpatient check at 3 and 6 months. Afterwards, with a telephone interview, the patients were given the questionnaire for assessing the quality of life EORTC QLQ C30 extended with the addition of the specific module PAN26 [30, 31]. The QLQ-C30 pain scale items inquire about general pain while the PAN26 pancreatic pain scale items refer specifically to abdominal discomfort, back pain, pain during the night, and malaise in certain positions. Both QLQ-C30 global health status scale and PAN26 satisfaction with health care scale are functional scales and higher scores indicate better function and better health-related QOL.

A four-point scale was used to indicate how symptoms affected the patient's quality of life (e.g., "1 = not at all", "2 = a little", "3 = quite a bit", "4 = very much").

Mortality was defined as any death occurring during the hospital stay or within 90 days from surgery. Informed consent for the treatment was signed beforehand by each patient

included in the study, and the collection was recorded in accordance with the PROCESS criteria [32].

Surgical technique

At first, after a right subcostal incision, a complete exploration of the cavity was carried out. In each patient, the procedure started by classical cholecystectomy (if gallbladder was present). After identifying the duodenum, the Cattell maneuver and subsequently Kocher's maneuver was performed to allow complete exposure of the posterior duodenal wall and facilitate bimanual palpation of the tumor.

A transverse duodenotomy of about 3–4 cm of the second duodenal portion was performed, on the antimesenteric side, facing the periampullary area. To separate the wall layers, submucosal injection of adrenaline (1:1000) was performed, to confirm the presence of the "lift sign" which would exclude an infiltration by the tumor and also reduce the risk of bleeding. The tumor mass was then transfixated with a stitch to pull it away and better dissect

the ampulla of Vater. Also, this optimal lateral traction of the tumor mass during the dissection is helpful in obtaining tumor-free margins.

Both Wirsung and bile ducts were then separately cannulated with a Fogarty catheter (Fig. 1).

From a frontal view and considering the major axis of the duodenum, the papilla along with Wirsung and bile duct were usually located at around 2 o'clock. So the dissection of the duodenal wall, reaching the muscular layer, was made in a circular clockwise manner starting at 11 o'clock. The dissection was continued clockwise until the whole papilla was completely excised and a 1 cm free margin was obtained in all directions beyond the gross border of the lesion (Fig. 2). All the procedure was done avoiding the use of electrocautery to preserve the resection margin for an ideal histological evaluation.

The pancreatic and bile ducts were therefore exposed and joined together with reabsorbable stitches (5.0 PDS) so that a common ostium was created and, finally, sutured with the duodenal wall (Fig. 3). The final appearance was similar to the spoke wheel (Fig. 4).

Fig. 1 **a** Opening of the anterior duodenal wall and visualization of the ampulla tumor (blue arrow); **b** isolation of the ampulla from the underlying duodenal muscular layer (yellow arrow) (color figure online)

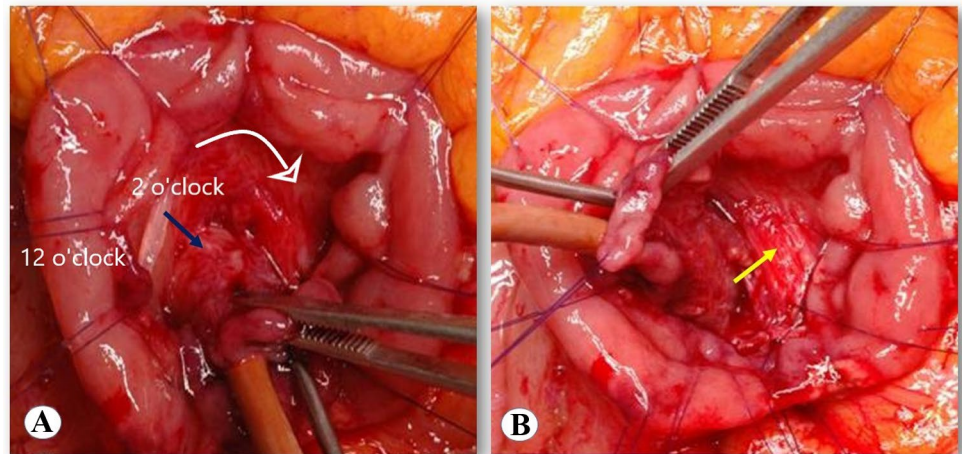


Fig. 2 **a** Visualization of the ampulla structures (1–2); **b**: The bile duct is completely opened (1) and dissected from the Wirsung duct (2) (color figure online)

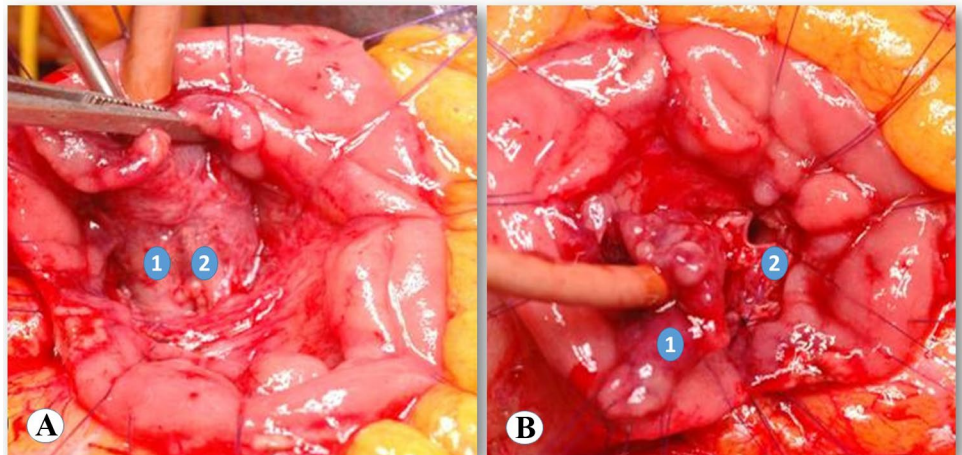


Fig. 3 **a** Full exposure of bile duct (1) and Wirsung duct (2); **b** Circular clockwise dissection (color figure online)

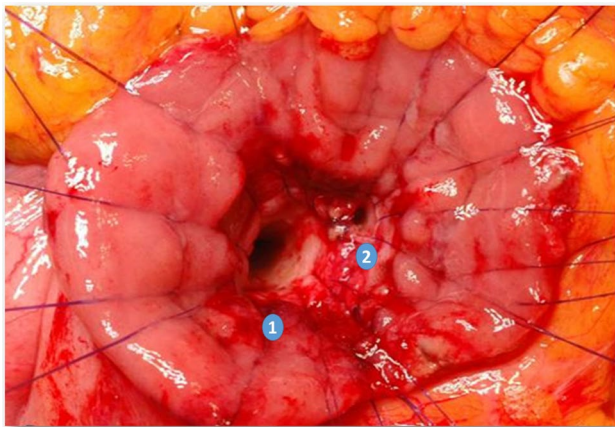
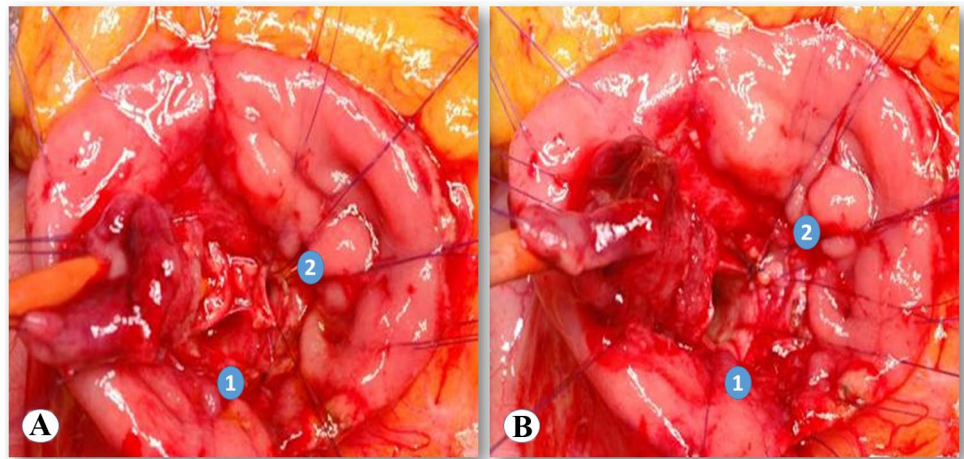


Fig. 4 Bile and Wirsung ducts (1–2) are joined together with reabsorbable stitches creating a common ostium and will be sutured with the duodenal wall in a later stage (color figure online)

Once removed, the whole papilla was sent for intraoperative frozen section analysis. If the pathological results did not meet the criteria of a potential curative local resection (for several reasons, such as infiltration of the muscular layer of the duodenal wall, extension of the lesion beyond the biliary and/or pancreatic duct and/or histology of ampullary invasive adenocarcinoma) and the patient was fit, a PD procedure was considered otherwise the TSA was carried out.

A naso-duodenal tube was placed and the duodenotomy closed transversely in a double layer with interrupted monofilament reabsorbable stitches (4.0 PDS). Double laminar drainage was then placed near the duodenotomy.

Results

Patients median age was 70 years (range 49–85). Nine patients were male (9/16), 7 females (7/16). Jaundice was the most frequent pre-operative clinical presentation (56%), followed by pancreatitis (25%) and gastrointestinal bleeding (12.5%). Three (19%) patients underwent preoperative ERCP with stent placement to solve jaundice. Mean operative time was 238.5 min (range 180–390). Mean intraoperative blood loss was 125 ml (range 50–200). Mean tumor size was 2.3 cm (range 1.5–3.9). The microscopic surgical outcome was R0 for 14 patients.

Seven (43.7%) patients had a definitive histological diagnosis of in situ adenocarcinoma (Tis). The surgical margins were free of tumor and TSA was considered curative. In six patients (37.5%), the pathological diagnosis was a tubulo-villous adenoma with low-grade dysplasia. In 1 case (6.3%) just chronic inflammation was present on the final histology. In two cases the histology revealed an invasive adenocarcinoma (12.5%): the first patient underwent to a redo surgery (completion PD), whereas the second patient, unable to withstand PD (ASA IV) was scheduled for palliative ampullectomy after two unsuccessful endoscopic attempts failed for bleeding. Two (12.5%) patients suffered from PPH grade A. The naso-gastric tube was removed between the third and sixth postoperative day. DGE was diagnosed in 4 cases (25%) (3 grade A, 1 grade B). Abdominal drainage was removed on the 6th in 14 patients, on the 10th postoperative days in those patients that presented biochemical pancreas leak, and on the 50th postoperative day in patients with a biliary leak. The first fluid intake occurred averagely on the 5th post-operative day or at least as the naso-gastric tube was removed. Stool passage occurred on median day 6th (range 4–9). The readmission rate was 18.8% (3/16). In two cases (12.5%) an operative approach was required. One patient presented with gastrectasia, vomiting, fever,

and sub-phrenic abscess collection treated with percutaneous drainage and antibiotic therapy. The second patient presented with duodenal leak underwent relaparotomy, direct suture, gastrointestinal bypass, and external biliary drainage. At follow-up, this patient presented recurrent pancreatitis. The cumulative median duration of follow-up was 50 months (range 1–96).

90-days mortality was 6.2% (1/16) and refers to a patient, unfit for PD, who underwent palliative TSA (after two endoscopic procedure failures due to bleeding) for a pT2 adenocarcinoma and died on 45th post-operative day for multiorgan failure. All patients with low-grade adenoma were alive and with no signs of local recurrence. The patient who underwent a completion PD after a definitive histological report was alive and without signs of recurrence (pT2N0). During follow-up, one patient died 5 months after surgery due to heart stroke, and one patient, who underwent palliative TSA, died for disease progression 6 months after surgery. One pTis patient died of a local recurrence and subsequent recurrent cholangitis after 22 months. The mean hospital stay was 12.5 days (range 8–60). In 4 cases (25%), a diagnosis of post-operative acute pancreatitis (defined as an elevation of serum pancreatic amylase above the upper limit of normal value on postoperative day 1, with an upper limit of normal for serum pancreatic amylase being 51 U/L) occurred. All patients recovered using medical therapy.

Demographic characteristics of the patients, pre- or postoperative endoscopic interventions, operative procedures, postoperative morbidity and mortality, hospitalization, and follow-up time were analyzed and summarized in Tables 1 and 2. In 2 cases (12.5%) due to pre-existing medical conditions, patients required continuous medical assistance. The remaining patients restarted their usual activities, without consequences on nutrition, social relationship, household chores, and self-body image perception. The discomfort did not interfere with usual daily activities. Furthermore, the surgery had limited consequences for what concerns economic, social, and psychological impact. Indeed, the quality of life of the patients surveyed with the aforementioned coded questionnaires was almost optimal. Some patients reported occasional diarrhea, mild abdominal discomfort, and meteorism. Patients with back pain reported their symptoms in relation to concomitant pathologies (osteoarthritis, myalgia). The intervention did not affect the perception of food flavors, and only a few patients reported episodes of dyspepsia. No jaundice was reported but there was one case of recurrent cholangitis and one of recurrent pancreatitis successfully treated medically. All patients, with the exception of deceased patients (3), answered the questionnaires; unfortunately, not all patients responded to all items. QoL questionnaire's results were reported in Table 3.

Table 1 Operative and postoperative data

ASA score n° (%)	
I	2(12.5)
II	5 (31.2)
III	8 (50)
IV	1 (6.3)
Operation time (mean min)	238.5 (180–390)
Intraoperative blood loss (mean ml)	125 (range 190–390)
Hospital stay (mean days)	12.5 (8–60)
Surgical morbidity	
Severe morbidity (Clavien–Dindo > IIIa), n (%)	2 (12.5)
BL	1 (6.3)
POPF	0
PPH	2 (12.5)
DGE	4 (25)
Biliary leakage	1 (6.3)
Wound infection n° (%)	3 (18.8)
Abdominal abscess n° (%)	1 (6.3)
Duodenal leak n° (%)	1 (6.3)
Pneumonia n° (%)	2 (12.5)
Post-op pancreatitis n° (%)	4 (25)
Re-intervention n° (%)	2 (12.5)
Readmission n° (%)	3 (18.8)
90-days mortality n° (%)	1 (6.3)

BL biochemical leak, POPF postoperative pancreatic fistula, PPH post pancreatectomy hemorrhage, DGE delayed gastric emptying

Discussion

The tumor of the ampulla of Vater belongs to the so-called tumors of the periampullary region. The category includes tumors arising from the pancreas, distal bile duct, and the duodenum. Benign forms are rare, and among them the most frequent is adenoma. There are still conflicting data about the appropriate management of this kind of tumor, therefore a multidisciplinary approach is mandatory. While endoscopic papillectomy remains the gold standard for benign lesions, surgical transduodenal ampullectomy (TSA) can be proposed in selected cases and when endoscopy fails. However, the PD still represents the main option for malignant periampullary tumor along with the use of neoadjuvant therapy in selected cases [12, 33].

In the present study, we report our experience in treating benign and selected malignant ampullary lesions. Analyzing our experience and the current literature, it emerges that a correct pre-operative staging within a multidisciplinary board is mandatory to offer the most tailored and a targeted therapeutic approach. Diagnosis is mostly made by endoscopy with biopsy, although endoscopic ultrasound (EUS) allows the finest assessment. However, a role is also played by ERCP, CT, and cholangio-MRI [34–36].

Table 2 Clinical history, pathological results, and long-term outcome

Pt n°	Sex	Age (y)	Tumor size (cm)	R status	Histology	Outcome	Symptoms
1	M	70	3	0	Adenoma with high-grade dysplasia/pTis	Alive	Jaundice
2	M	65	2.5	0	Adenoma with low dysplasia	Alive	Jaundice
3	M	74	3.1	0	Adenoma with high-grade dysplasia/pTis	Alive	GI bleeding
4	F	61	1.8	0	Adenoma with low-grade dysplasia	Alive	Pancreatitis
5	M	72	2.2	0	Adenoma with high-grade dysplasia/pTis	Alive	Pancreatitis
6	F	79	1.5	0	Adenoma with high-grade dysplasia/Tis	Alive	Jaundice
7	F	85	3.9	1	Invasive Adenocarcinoma	Dead	GI bleeding
8	M	55	2.4	0	Adenoma with low-grade dysplasia	Alive	Jaundice
9	F	49	2.0	0	Adenoma with high-grade dysplasia/pTis	Alive	Jaundice
10	M	56	1.9	0	Adenoma with low-grade dysplasia	Alive	Pancreatitis
11	M	73	3.4	1	Invasive Adenocarcinoma	Dead	Jaundice
12	M	70	2.0	0	Adenoma with low-grade dysplasia	Alive	Jaundice
13	M	61	2.1	0	Adenoma with low-grade dysplasia	Alive	Abdominal pain
14	F	80	2.9	0	Adenoma with high-grade dysplasia/Tis	Dead	Jaundice
15	F	49	2.6	0	Adenoma with high-grade dysplasia/Tis	Alive	Jaundice
16	F	78	1.9	0	Chronic inflammation	Alive	Recurrent Pancreatitis

Table 3 EORTC QLQ-C30 and PAN 26 quality of life questionnaires

QLQ-C30	Not at all (pt 1)	A little (pt 2)	Quite a bit (pt 3)	Very much (pt 4)	Mean value
Global health status (item 1–7)	4	6	1	0	1.6
Physical functioning (item 8–12)	5	6	0	1	1.8
Digestive disorders (item 13–17)	11	0	0	1	1.4
Cognitive functioning (item 18–28)	8	3	0	1	1.5
Quality of life (item 29–30)		From 1 to 3: 1	From 4 to 5: 2	From 6 to 7: 9	5.3
QLQ-PAN26	Not at all (pt 1)	A little (pt 2)	Quite a bit (pt 3)	Very much (pt 4)	Mean value
Pancreatic pain (item 31–35)	1	4	0	1	1.7
Appetite loss (item 36–38)	6	4	2	0	1.5
Digestive disorders (item 39–40)	6	4	1	1	1.6
Sign/symptom (item 41–45)	9	2	1	0	1.5
Altered bowel habit (item 46–47)	7	4	0	1	1.5
Mental status and wellbeing (item 48–52)	8	3	1	0	1.4
Health care satisfaction (item 53–54)	0	0	0	12	4

The latter two methods have low sensitivity for the diagnosis of the ampullary lesion, but can easily demonstrate intra/extrahepatic biliary tract distension and/or metastatic lesions (liver or lymph nodes metastases).

For what concerns the size of the tumor, it cannot be considered an absolute parameter for TSA. Results from large series demonstrate that TSA can achieve radicality in benign tumors less than 2.5 cm, and a malignant tumor less than 2.0 cm evaluated by EUS [25, 37, 38]. These data are in line with the present report where the median tumor size was 2.3 cm. Anyway, lesions greater than 2.5 can be treated by TSA but they deserve a particular surgical skill

to convert promptly the planned operation into a radical PD if needed.

We strongly believe that histology, pre-operative staging, and individual health status (read comorbidities) are the most important parameter to take into consideration. Furthermore, in patients with suspected invasive adenocarcinoma, whose general clinical conditions would not allow them to tolerate a demolitive procedure such as PD, local excision should rather be considered as an alternative procedure.

Bottger and Junginger reported that lymph node metastasis was not found in small, or T1 tumors, or in tumors with

well-differentiated histology [11]. Similar results have been also reported from other authors [39, 40]. Rattner et al. recommended ampullectomy for T1 cancer and Beger et al. for T1s or T1/N0 cancer with well or moderate differentiation [17, 21]. These findings suggest that small tumors, early-stage as T1s or selected T1 with good differentiation, appear to be ideal conditions for local resection.

Considering the deep location of the Vater's papilla, histological diagnosis of "ampulloma" remains a crucial point. The papilla is not always easily accessible endoscopically, and biopsies sometimes result in a false negative. In fact, false-negative rate at endoscopic biopsy can be up to 30% even in large series [20, 41, 42]. Also, the coexistence of three different epithelia in this region can generate difficult pathological interpretation. However, our experience showed that only one patient required radical redo-surgery because of a preoperatively misdiagnosed infiltrating adenocarcinoma.

Endoscopic papillectomy remains the procedure of choice for benign periampullary lesions but it is burdened with a certain rate of therapeutic failure [15, 42].

Endoscopic papillectomy is a technique that often requires multiple sessions to be completed and, since the tumor is sometimes removed in a piecemeal fashion, the real status of the resection margins can be missed. In addition, the use of electrocautery in endoscopy makes the pathological study of the lesions sometimes really difficult. Furthermore, endoscopic papillectomy does not remove the confluence of the Wirsung duct and the common bile duct, because it only removes the mucous membrane of this region. Regarding the recurrence, the rate we observed very excellent results with almost no recurrence at all, maybe because most patients included in the present study suffered from benign tumors or early-stage malignant tumors.

The main limitation of the present surgical experience is the limited number of patients analyzed. However, many authors, in several studies including more than 30 patients, suggested that TSA offers a recurrence rate after surgical resection of 0–9%, while for endoscopic ampullectomy is stated to be 17–20% [7, 14, 15, 43]. According to these data, TSA seems to be a more effective procedure. Underestimating the depth of invasion rarely occurs during TSA, in fact, a direct full view of the section margin allows a correct resection evaluation. In our experience, only two cases (12.5%) have reported a discrepancy between frozen section and final histological examination. Furthermore, TSA provides a clearly and impromptu involvement of the sphincter apparatus at the confluence of the Wirsung with the bile duct.

As highlighted in current literature, morbidity and mortality of this procedure are not negligible: TSA remains a difficult operation demanding particular surgical experience and technical skills. Every pancreatic surgeon should carefully evaluate every single case in a multidisciplinary board

together with radiologists, endoscopists, pathologists, and anesthetists.

As known, the number of pancreas surgeries per year and a multidisciplinary team availability are two of the most important factors that reduce postoperative complications in a highly complex procedure such as TSA [44]. The choice for TSA or a classical PD has to be made according to the histopathological characteristics of the lesion, the degree of tumor infiltration evaluated with EUS and intraoperative frozen sections, combined with preoperative results and, last but not least, the ASA score.

The observational retrospective design of this study is a limitation as it only allows a comparison of the present results with the other data in the current literature. The morbidity and mortality rates are acceptable and in line with current international literature. Based on the present results, TSA is a feasible and effective procedure with good long-term results in selected cases it represents the ideal therapeutic option, avoiding a demolitive and impactful intervention. Indeed compared to PD sequelae, almost all patients included in the study reported a better satisfactory quality of life in a long-term follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was carried out in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Since this was a retrospective study, formal consent was not required and approval of the institutional research committee was not needed.

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