Endoscopic treatment of chronic pancreatitis

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Abstract

Treatment of chronic pancreatitis has been exclusively surgical for a long time. Recently, endoscopic therapy has become widely used as a primary therapeutic option. Initially performed for drainage of pancreatic cysts and pseudocysts, endoscopic treatments were adapted to biliary and pancreatic ducts stenosis. Pancreatic sphincterotomy which allows access to pancreatic ducts was firstly reported. Secondly, endoscopic methods of stenting, dilatation, and stones extraction of the bile ducts were applied to pancreatic ducts. Nevertheless, new improvements were necessary: failures of pancreatic stone extraction justified the development of extra-corporeal shock wave lithotripsy; dilatation of pancreatic stenosis was improved by forage with a new device; moreover endosonography allowed guidance for celiac block, gastro-cystostomy, duodeno-cystostomy and pancreatoco-gastrostomy. Although endoscopic treatments are more and more frequently accepted, indications are still debated.

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Key words: Chronic pancreatitis; Endoscopic treatment

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METHODS

Endoscopic treatment needs a team (operator, anaesthesiologist) aware with Endoscopic Retrograde Cholangiopancreatography (ERCP) procedures. Specific material is necessary: good fluoroscopy with the possibility to magnify pictures, and a duodenoscope with a 4.2 channel allowing insertion of high calibre stent (10 Fr). Moreover, a wide variety of endoscopic ancillary instruments is essential: metallic and hydrophilic guide-wire, sphincterotomes, Dormia basket, balloon dilators

and bougie dilators (5-11.5 Fr), but also very thin guide wire (0.025 inches), fine-tipped sphincterotomes, Soehendra extractors (cf infra)^[1]. Impaction of stones in pancreatic ducts needs the use of extracorporeal shock wave lithotripsy before endoscopic stone extraction^[2]. Endoscopic treatment also needs naso-pancreatic drains and pancreatic stents that are either polyethylene or Teflon. The choice of length, pattern or external calibre of the stent is decided according to the anatomy of pancreatic ducts. Usually, straight stents with proximal and distal external flaps (to avoid internal or external migration), are used. Other stents like single or double pig-tail stents can be used also.

Endoscopic pancreatic sphincterotomy (PS)

Firstly described by Fujii^[3], PS is generally performed as the first step in order to improve access to the pancreatic duct. A short (5-6 mm) sphincterotomy is oriented at 13 h with a pure section cutting. Narrowness of pancreatic ducts has justified using special device (thin 0.025 guide-wire, fine-tipped sphincterotomy). Biliary sphincterotomy, which was firstly recommended before PS, seems not to be systematically performed because, contrary to the firstly experience, PS alone is not associated with a secondary biliary stenosis^[4].

Complications of PS occur in 4.2%-12.6% of cases^[4,5]. The morbidity rate also depends on other endoscopic procedures done at the same time such as pancreatic stenting or stricture dilatation. It also depends on the inclusion of patients presenting with recurrent attacks of pancreatitis secondary to sphincter of Oddi dysfunction. In this case, morbidity rate is higher, reaching 12.5%^[6]. PS is probably no more or no less harmful than a biliary sphincterotomy which is associated with a morbidity rate of 5.4%-9.8% of cases^[7-9]. Morbidity of PS seems also lower in case of post-PS drainage with a naso-pancreatic drain or a pancreatic stent^[6]. In case of complete obstruction of the main pancreatic duct in the head, it is sometimes possible to access to the body of the pancreatic duct through the accessory papilla.

Treatment of pancreatic duct strictures by dilatation and stenting

The procedure consists in setting a 3-4 m length, hydrophilic-top guide wire deep inside the main pancreatic duct to realise a stricture dilatation with balloon or dilators in order to insert a stent the calibre (5-10 Fr) and length (3-12 cm) of which depends on pancreatic duct anatomy. The length of the stent is adapted to bridge the stenosis (duct stricture and/or stone); the calibre of the stent depends on the highest calibre of dilator successfully inserted through the duct stricture.

In practice, chronic pancreatitis duct strictures are more difficult to pass than biliary stenosis. They are usually associated with an impacted stone which may prevent deep insertion of the guide-wire into the main pancreatic duct. Moreover, pancreatic duct strictures are often narrow and tight because of expanding pancreatic fibrosis. For these reasons, a high rate of failure of dilatation of pancreatic stricture has been reported. Recently, a new technique of dilatation has been reported by Brand *et al*^[11], who used a device (*Soehendra extractor*) previously designed for the extraction of migrated biliary stents. Forage is realised by screwing this instrument through pancreatic duct stenosis on the guidance of a guide-wire. The morbidity rate is low (0%-13%) because forage is realized in a fibrotic area. Finally, among patients with a stricture which could not be passed with a 7 Fr dilatator, this device (7 Fr or 10 Fr) allowed to pass over the stenosis in all cases^[1,10].

Plastic stents are clogged by lithostatine precipitates, carbonate of calcium and bio bacterial film in a mean time of four to six mo^[11,12]. Therefore, stents have to be retrieved or exchanged every four mo during a variable stenting length of time according to the main series (2-12 mo)^[13]. Some authors prefer to leave the pancreatic stent and to exchange it only in case of recurrence of symptoms or infection but this strategy is associated with a risk of complications^[14]. Metallic stent has been proposed because of a longer time of patency but those stents could also be completely obstructed by intra-luminal inflammatory granuloma with a risk of septic complication^[15]. The morbidity rate of pancreatic stenting is widely varied in series. Early complications (before d 30 after ERCP) are distinct of late complications (> 30 d). The main early complication is acute pancreatitis (5%-39%), most of cases are benign, oedematous, spontaneously resolute forms. A few cases of pancreatic abscess or cholangitis have been reported in the preliminary publications^[15,16]. Late complications are stent-related: although stent migration is rare (5%), stent occlusion is very frequently encountered. Ductal lesions after stenting (dilatation, irregularity, stenosis) have been reported in 21%-80% of cases^[17]. These lesions are associated with endosonographic parenchymal signs in 68% of cases^[18]. In fact, in more than half of the cases, stenting-ductal lesions will regress four mo after retrieval of the stent^[17].

Pancreatic stones extraction and lithotripsy

Pancreatic stones may be retrieved only after a previously PS. Since pancreatic stones are often impacted in the pancreatic duct upstream a duct stenosis, extraction of pancreatic stones is more difficult than extraction of biliary stones. Many difficulties have to be solved before: stenosis above stones have to be dilated, stones have to be fragmented with extracorporeal shock wave lithotripsy (ESWL). After good results obtained for biliary and kidney stones, ESWL has been firstly proposed for pancreatic stones in 1987^[2]. There are three kinds of lithotripter generators: electro magnetic, electro hydraulic and piezo-electric. Stones are visualised under fluoroscopic or ultrasonographic guidance or both, treatment is realized in pro-cubitus position, under general analgesia or sedation.

Results of the major series are reported on Table 1.

Table 1 Results of extracorporeal shock wave lithotripsy

Authors	Patients (n)	Sessions (n)	Symptom free (%)	Fragmentation (%)	Clearance (%)
Sauerbruch ^[19]	24	1.6	37	87	50
Ohara ^[20]	32	4.6	79	100	75
Costamagna ^[21]	35	1.9	17	100	80
Delhaye ^[22]	123	1.8	53	99	59
Schneider ^[23]	50	2.4	76	85	56
Total	264	1.6-4.6	17-79	85-100	50-75

Without ESWL, complete clearance of pancreatic stones was less than 40%. ESWL is successful in 85%-100% of cases and wash-out of stones was obtained in 50%-75%. Pain disappeared in 17%-79% of cases^[19-23]. Morbidity of ESWL is difficult to distinguish from the morbidity related to other endoscopic procedures. Nevertheless, main adverse events of ESWL are abdominal pain and attack of acute pancreatitis. Success factors are more dependant of the site than the size of the stone: juxta-papillary and main pancreatic duct stones are easier to extract than stones located in the tail or in the side branches. Large stones seem easier to break because easier to localize. Duct stenosis is often associated with a pancreatic stone and is a factor of recurrence of pain despite a complete clearance. Fragments of stones are retrieved through PS during a new ERCP, using an extractor-balloon or a Dormia basket; a naso-pancreatic drain is sometimes left to wash the pancreatic ducts during 48 h^[22].

Endoscopic drainage of pancreatic cysts and pseudo-cysts

Drainage of pancreatic cysts is realised through the stomach wall (gastro-cystostomy) or duodenum wall (duodeno-cystostomy) in case of trans-mural drainage or through the papilla in case of trans-papillary drainage. The trans-mural way is dedicated to bulging cysts into the stomach or duodenum. A diathermic puncture is realized perpendicularly on the site of maximal bulge. After insertion of the catheter deep inside the cyst cavity, a sample of cyst fluid is taken for bacteriologic, biochemical and cytological analysis. A guide-wire is inserted in the cavity in order to realise multiple loops. Then, a careful cystostomy of 5-8 mm with a papillotome or by balloon dilatation is realised. Large cystostomies appear to be associated with a higher risk of haemorrhage than balloon dilatation. Finally, one or two double-pig-tail stents are inserted. In case of infected cyst or large amount of necrotic tissues which could occlude the stent, a naso-cystic drain for washing seems more adapted than a stent.

Trans-papillary drainage is dedicated to communicating cysts. After a selective cannulation of the pancreatic duct, a guide-wire deeply inserted and a pancreatic sphincterotomy, a dilatation of the tract between the pancreatic ducts and the cyst (a down-stream duct stenosis usually being associated), is performed. A stent is inserted into the pancreatic duct in order to bridge the area of communication between the ductal system and the cyst. The mean time of drainage is usually two mo but depends on the persistence of the cyst on the morphologic explorations^[24]. In case of co-existence of pancreatic duct

Table 2 Endoscopic treatment of pancreatic duct stenosis

Authors	Patients (n)	Technical Success (%)	Early improvement of pain (%)	Follow-up (mo)	Long-term improvement of pain (%)
Grimm ^[38]	70	58	82	2-36	57
Cremer ^[14]	76	94	94	18-72	94
Ponchon ^[39]	33	85	74	12	52
Sauerbruch ^[40]	24	87	83	24	50
Delhaye ^[11]	123	95	100	14	37
Schneider ^[23]	50	86	70	20	70
Binnmoller ^[41]	93		74	58	64
Smits ^[42]	51	96	81	64	24
Dumonceau ^[43]	70		95	24	95
Adamek ^[44]	80			40	54
Heyries ^[13]	70	85	62	29	58
Rösch ^[45]	1018	70	-	59	65
Total	1758	85	81	30	61

lesions, a long-term pancreatic stenting is necessary to prevent a recurrence of the cyst.

Endo-ultrasonography

Interventional endo-ultrasonography (EUS) is particularly interesting in three issues: treatment of pain by coeliac neurolysis, drainage of pseudo cysts and trans-gastric pancreatic drainage. Coeliac block is associated with a low morbidity (diarrhoea in 3.5% of cases)^[25,26]. Treatment of pancreatic cysts under EUS guidance is dedicated for pseudo cysts which are not bulging in the gut^[27-32]. In case of complete obstruction of the pancreatic duct, a pancreatico-gastrostomy can be achieved under EUS guidance^[33,34].

RESULTS AND INDICATIONS OF ENDOSCOPIC TREATMENT

The aim of endoscopic treatment is improvement of pain. Analysis of the literature is difficult because (a) the variability of pain during the time and between patients^[35-37] (b) the pain during CP is multifactorial: ductal or interstitial pancreatic hyperpression, inflammatory infiltration of peri pancreatic nerves ("pancreatic neuritis") or pseudo-cysts. Other complications of CP could also be associated with pain: duodenal stenosis, duodenal cystic dystrophy, biliary stenosis or duodenal ulcer^[35]. Moreover, endoscopic methods are different: biliary sphincterotomy is not always associated with a pancreatic sphincterotomy, time of pancreatic stenting (two months to undetermined), or number of stents. In fact, there are several methods of treatment which aim to obtain a satisfactory drainage of a pancreatic and/or biliary duct.

Treatment of pancreatic pain

Drainage of pancreatic duct is reported in numerous articles^[11,13,14,23,38-45]. Technical success was obtained in 85% of cases (58%-96%). Stents are left during variable length of time, from two mo to endless. Short-term improvement of pain was obtained in 81% of cases (62%-100%). After a follow-up of 30 mo (14-60 mo), improvement of pain dropped to 61% of cases (24%-95%). There was no clinical predictive factor of success despite of an early

stage of CP reported in three series^[13,41,43]. Communicating cyst and juxta-ampullary stenosis were the two reported morphological predictive factor of success. Surprisingly, stop of alcohol intake did not seem to modify results of the endoscopic treatment. Nevertheless, alcohol intake has to be stopped because morbidity and mortality of CP are more attributed to toxic habits (alcohol or tobacco) than to CP itself^[46]. In cases of complete obstruction of pancreatic duct preventing access *via* the papilla, EUS-guided pancreatico-gastrostomy can be done. Results of this method are preliminary: a short series of four cases has reported good results in one case, recurrence of pain in two cases managed with another endoscopic treatment (stenosis of the pancreatico-gastrostomy in one case, disruption and spontaneous migration of the stent in the other case), and failure in one case (12 mo of follow-up)^[33]. An additional factor of pain is peri-pancreatic inflammatory infiltrate of nerves: a prospective randomized comparison of endoscopic ultrasound and computed tomography-guided celiac plexus block has reported better results under EUS whereby an immediate improvement of pain occurred in 50% of cases but this result dropped to 30% after six months of follow-up. Efficiency appeared significantly more prolonged in the EUS-group and the ratio cost-efficiency was also better in this group^[47]. More recently, a prospective study including 90 patients reported an immediate improvement of pain in 55% and in 10% after six months of follow-up^[25]. Young age or previously pancreatic surgery were factors of poor results. Indication of celiac plexus block is limited in CP because of a relative immediate efficiency and especially a frequently recurrence of pain after six mo of follow-up (Table 2).

Treatment of pancreatic cysts and pseudo cysts

Evaluation of patient and collection are the first step to decide strategic therapy. Ultrasonography, computed-tomography, MRCP and EUS make it possible for clinician to determine the two major risks of endoscopic treatment which are haemorrhage and perforation. Haemorrhage depends on the presence of pericystic or peridigestive vessels, segmental portal hypertension and the haemorrhagic content of the cyst. Perforation depends on the distance between the digestive-wall and

Table 3 Results of endoscopic cysto-enterostomy during chronic pancreatitis

Authors	Cysto-gastrost	Cysto-duodenost	Failure (n)	Recurrence (n)	Secondarysurgery	Morbidity (n)	Mortality (n)
Dohmoto ^[48]	5	1	0	-	1	0	0
Cremet ^[49]	11	22	1	3	5	3	0
Bejanin ^[50]	9	5	2	3	6	3	0
Barthet ^[51]	12	66	0	14	2	12	1
Smits ^[52]	16	10	3	3	8	5	0
Binmoeller ^[53]	24		4	6	5	5	0
Total	181		10 (5.5%)	29 (16%)	27 (15%)	28 (15.5%)	1 (0.5%)

Table 4 Results of endoscopic transpapillary drainage of pancreatic cysts

Authors	Patients (n)	Stent (Fr)	Healing (n)	Recurrence (n)	Morbidity (n)	Secondary surgery (n)
Kozarek ^[55]	8	-	7	0	3	4
Dohmoto ^[48]	6	7	6	1	2	0
¹ Barthet ^[56]	30	7-10	23	3	4	5
² Smits ^[52]	19	7-10	14	-	1	-
Binmoeller ^[53]	37	5-7	35	5	1	-
Catalano ^[57]	21	5-10	17	1	1	2
Total (n)	121	7 Fr	102 (85%)	10 (9.8%)	12 (10%)	11 (11%)

¹transpapillary drainage + cysto-gastrostomy (n = 5); + cysto-duodenostomy (n = 5); ²transpapillary drainage + cysto-gastrostomy (n = 4); + cysto-duodenostomy (n = 2); + cysto-gastrostomy and cysto-duodenostomy (n = 1).

the cyst which should not exceed 10 mm. Results of transmural drainage were reported in six series between 1989 and 1992 including 191 cysts (Table 3)^[48-53]. Mean rate of healing, failure and recurrence were respectively 78% (51%-82%), 5.5% (0%-16%) and 6.5% (3%-13%). Secondary surgical procedure was necessary in 14.9% of patients (12%-30%). Morbidity was 15.5% including, according to increasing rates of frequency, haemorrhage, perforation, and infection. Haemorrhage seems more frequent in case of gastro-cystostomy than for duodenocystostomy^[51]. The only death reported concerned a patient who presented cirrhosis complicated by portal hypertension and associated with haemorrhagic pancreatic ascitis^[51]. Long-term results of transmural drainage are not well-known, follow-up not exceeding 31 mo. A recent study including 34 patients followed 46 mo, reported good results in 62% of cases (in intent to treat) with only 71% of initially technical success^[54]. Three cases of recurrence were reported, of whom two cases were successfully managed endoscopically.

Results of trans-papillary drainage have been also reported in six series from 1991 to 1995 including 121 cysts (Table 4)^[48,53,55-57]. Symptom-free rates were 87% (76%-87%) and healing rates of cysts were 84% (76%-94%). Recurrence of cyst was 9.2%, morbidity was 10% with essentially septic complications and post-ERCP acute pancreatitis. A secondary surgical procedure was necessary in 10.8% of cases (9%-50%). Endoscopic drainage is intended for symptomatic cysts. In the other cases, drainage is necessary if the size of the cyst is more than 4 cm, particularly if the cyst is localized out of pancreatic area because, in this case, it uncommonly collapses spontaneously^[58]. Trans-papillary drainage appears a first choice treatment in case of CP because pancreatic stent treats also pancreatic ductal lesions

down stream the cyst and because it is less invasive than transmural way. Transmural drainage is especially reserved to large cysts but must be avoided in presence of segmental portal hypertension. Results of EUS-guided pseudo-cysts drainage have been recently reported in six series including 69 cases^[27-32]. The most important monocentric study included 35 patients of whom 20 pancreatic abscess: after 27 mo of follow-up, drainage was successful in 94% of cases, a pneuoperitoneum occurred in a case and has been managed conservatively, recurrence of cyst occurred in three cases of whom two abscess, surgical drainage was necessary in four cases of whom were four abscess. This method seems satisfying but has to be more evaluated in larger series^[31].

Endoscopic treatment of biliary stenosis

Long-term results of biliary stenting have been reported in three series including 102 patients^[59-61]. Although initial improvement was reported in 100% of cases, the rate of symptom free patients decreased to 17.5% (10%-28%) after 10 mo (14-49 mo) of follow-up; moreover, 68% of patients underwent a surgical bili-digestive diversion or were still stenting. Plastic stents temporarily improve cholestasis but are not able to dilate adequately common bile duct. In contrast with the previous series, a recent study including 25 patients using balloon dilatation before biliary stenting has reported excellent results in 80% of cases after 13 mo of follow-up^[62]. These recent optimistic results attributed to the balloon dilatation, have to be confirmed. Morbidity is low (8%-9%) except migration or obstruction of the stent observed in respectively 14/25 and 18/25 patients of series of Deviere *et al* and Vitale *et al*^[59,62]. Draganov *et al* tried to improve results by using several stents: nine patients underwent a biliary stenting with 2-(n = 3) or 3-(n = 6) 10 French-stent; 48 mo after

Table 5 Results of endoscopic biliary stenting of biliary stenosis associated with chronic pancreatitis

Authors	Patients (n)	Clinical improvement (%)	Stent obstruction (%)	Stent migration (%)	Healing (%)	Length of time of stenting (mo)
Devrière ^[59]	25	100	32	40	12	-
Barthet ^[60]	19	100	0	5	10.5	10
Smits ^[61]	58	100	62	7	27	10
Vitale ^[62]	25	100		56	80	13

retrieval of stents, biliary stenosis recurred in only 55% of cases, absence of cephalic pancreatic stones was a factor of success^[63]. Because plastic stent are not adapted for a long-term drainage, Deviere *et al* tested metallic expansive stent with an excellent result in 18/20 patients, after 33 mo of follow-up^[64]. Nevertheless, the two remaining patients presented an obstruction of the stent secondary to epithelial hyperplasia in contact with the stent. More recently, a study including 13 patients presenting a biliary stenosis and unfit for surgical procedure, reported good results in 9/13 (69%) patients after 50 mo of follow-up, mean time of stent patency was 60 mo^[65]. A single stent was enough in five cases, obstruction of the stent was managed by insertion of a plastic stent inside the metallic stent ($n = 3$) or by an extractor balloon ($n = 1$). In four (21%) cases, biliary drainage was not effective because of occluded stent ($n = 3$) or duodenal migration of the stent ($n = 1$). Three patients died for a cause not related to the biliary stenosis. Nevertheless, those metallic stents being not extractable, after a long-term follow-up, there is a possibility of stent occlusion by granulation reaction against a foreign body (Table 5).

Management of pancreatic exocrine and endocrine functions

Although improvement of pancreatic exocrine and endocrine functions is frequently discussed in surgical series, this notion is seldom reported in endoscopic series^[13,22]. This is probably due to the difficulties to correctly explore the pancreatic exocrine function and also to the relatively short-term follow-up of endoscopic series in compared with surgical series. A temporary improvement of diabetes mellitus has been reported in 10% of cases after endoscopic treatment, while aggravation was noted in 12%^[22]. Although another series reported an improvement in 26% of cases^[13], most of the series did not noted any improvement^[42,44]. Therefore, diabetes mellitus alone should not be an indication of endoscopic treatment of CP.

Evaluation of the effects of endoscopic treatment on pancreatic exocrine function is also seldom precise. A few studies report a gain of weight but this gain probably reflects more improvement of pain than improvement of exocrine function^[13]. Evaluation of pancreatic exocrine function with a C¹⁴ breath test reports a 50%-60% improvement after endoscopic treatment^[22].

Endoscopic treatment of pancreatic fistulas

Three major series included 39 patients presenting with a pancreatic fistula after acute pancreatitis ($n = 19$) and associated with CP ($n = 12$)^[55,66,67]. Treatment consisted

in a trans-papillary drainage of pancreatic duct in 34 cases, associated with a transmural drainage of a cyst in four cases. Rate of success was 92 %, with complications occurring in seven cases (17%). Complications included mainly acute pancreatitis and sepsis. Seven (17%) patients underwent surgical procedures 11 to 16 mo after endoscopic treatment. Few isolated cases of pancreaticopleural fistula successful treated by endoscopic drainage, have been reported^[68]. Trans-papillary drainage is also reported as a successful treatment for pancreatico-peritoneal fistulas.

ENDOSCOPIC TREATMENT AND SURGICAL PROCEDURES

Up to now, few randomised series have covered this topic. A recent study concludes in favour of surgery^[69]. This study randomized 72 patients and after a follow-up of five years, although incomplete improvement of pain was equivalent in the two groups (46% *versus* 52%), a significant difference appeared for the complete resolution of pain (37% in the surgical group *versus* 14% in the endoscopic group). Nevertheless this series presents a bias because 80% of patients in the surgical group underwent a resection procedure and only 20% underwent a derivation procedure. Therefore, results of endoscopic treatment have to be compared with surgical procedure of derivation. Moreover, half of patients accepted randomization between surgery and endoscopy, this high rate of refusal emphasizes the difficulties in comparing the two methods and to set-up this kind of study. Nevertheless, more recently, another prospective series reported that surgical drainage of the pancreatic duct was more effective than endoscopic treatment^[70]. Thirty-nine symptomatic patients having CP with distal obstruction of the main pancreatic duct and without inflammatory mass were randomized: 19 underwent endoscopic trans-papillary drainage (16 of whom also underwent ESWL) and 20 had operative pancreaticojejunostomy. After 24 mo of follow-up, patients who underwent surgery had a significant ($P < 0.001$) lower pain score compared to endoscopic drainage. Moreover, complete or partial pain relief was achieved in 75% of patients of "surgical group" and only 36% of patients of "endoscopic group" ($P = 0.007$). Morbidity rate and length of hospital stay were similar in the two groups but there were more procedures in the "endoscopic group" than in "surgical group" (a median of 8 *vs* 3). To conclude, strategy depends on the expertise of the local teams, endoscopic treatment could be proposed as a first line treatment, before surgical procedure.

CONCLUSION

Endoscopic treatment of CP has certainly improved during the last two decades. Although results are clearly accepted as excellent for pancreatic cysts and pancreatic fistulas, long-term improvement of biliary and pancreatic ducts stenosis remains controversial.

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