A multimodal, one-session endoscopic approach for management of patients with advanced pancreatic cancer

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Abstract

Background A number of patients with inoperable pancreatic cancer may concurrently complain of pain, biliary obstruction, and duodenal stenosis. Endoscopic palliative treatments and opioid therapy are generally performed in these patients. The study aimed to assess the efficacy and safety of a multimodal 'one-Session Three Endoscopic Procedures' (one-STEP) to simultaneously treat cholestasis, restore duodenal transit, and achieve pain relief in selected patients with advanced pancreatic cancer.

Methods Selected patients diagnosed with an advanced pancreatic cancer presenting with biliary obstruction, duodenal stenosis, and severe pain treated with the one-STEP were considered. The one-STEP endoscopic approach included biliary and duodenal stenting, and EUS-guided celiac plexus neurolysis. The technical success rate, complications, pain relief, and opioid use at follow-up were assessed.

Results A total of 15 patients were treated. The one-STEP was successful in 13 (87 %) cases, while it failed in two patients due to the impossibility of dilating the neoplastic mass for creating a fistula. No endoscopy-related complications occurred. The median of pain intensity was 8 (range 7–10) at entry and significantly decreased to 2 (range 2–4) 72 h following celiac plexus neurolysis. At follow-up (median survival 4 months; range 3–8), only 3 (20 %) needed of narcotic treatment in the last period.

Conclusions The multimodal one-STEP is an effective and safe endoscopic approach for palliative treatment of biliary and duodenal stenosis, and for relieving chronic pain in patients with advanced pancreatic cancer.

Keywords Pancreatic cancer · Endoscopic therapy · Endoscopic ultrasound · Celiac plexus neurolysis

The incidence of pancreatic cancer has increased over the last decade [1]. Unfortunately, such a neoplasia is diagnosed at a resectable stage in only 12–20 % of patients, so that the overall survival at 5 years is 6 % for men and 10 % for women [2, 3]. Undeniably, chronic, intolerable pain is one of the most important symptoms in patients with an advanced pancreatic cancer, mainly due to the peri-pancreatic invasion of neural structures or muscles [4]. Therapeutic treatment of pain starts with non-opioid drugs stepping up to opioids, such as tramadol, fentanyl, and morphine. Regrettably, this therapy not infrequently causes relevant side effects, including nausea, constipation, somnolence, addiction, confusion, or respiratory depression [5]. Therefore, an endoscopic ultrasound-guided celiac plexus neurolysis has been introduced as an alternative palliative treatment of pain in these patients [6]. On the other hand, obstruction of either biliary tree or duodenum due to an advanced pancreatic cancer is associated with a relevant

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morbidity, and the mean survival is only 12 weeks when a duodenal stenosis develops [7]. Therefore, a minimally invasive treatment is generally advised in these end-stage patients, mainly based on biliary and/or duodenal stent positioning at endoscopy. In clinical practice, a number of patients with an advanced pancreatic cancer may concurrently complain of pain, biliary obstruction, and duodenal stenosis. In these cases, a comprehensive therapeutic approach could be advantageous for both reducing patients discomfort and utilization of resources. We describe a 'one-Session Three Endoscopic Procedures' (one-STEP) aimed to simultaneously treat cholestasis, restore duodenal transit, and achieve pain relief in a selected series of end-stage pancreatic cancer patients.

Methods

Biliary drainage

The procedure for biliary drainage varied according to type and extent of duodenal obstruction [8, 9]. In detail, one of two following approaches was performed according to the endoscopist preference/skill: (a) endoscopic ultrasound-guided biliary drainage (EUS-BD) with insertion of a 19 G needle from the duodenal bulb to the dilated biliary duct. After puncture, bile was aspirated and iodine contrast was injected to obtain a cholangiogram. A 0.035-inch guide wire (Jagwire, Microvasive Endoscopy, Boston Scientific Corp., Natick, Massachusetts, USA) was positioned in the common bile duct [CBD], followed by a pneumatic dilatation of the fistula by using a 6 mm × 4 cm biliary balloon dilatation catheter. A fully covered SEMS was placed between the CBD and duodenal bulb. Thereafter, the duodenal stenosis was approached with a stent, or (b) a self-expandable metallic stent (SEMS) was firstly positioned to pass through the duodenal stenosis, so that an endoscopic retrograde cholangiopancreatography-guided biliary drainage (ERCP-BD) was carried out by positioning a SEMS into the CBD through the mesh of the duodenal SEMS, as previously described [9].

Duodenal stenting

To treat duodenal stenosis, standard gastroscope or duodenoscope was used to reach the duodenal obstruction. A guide wire equipped with an imaging catheter (0.035-inch JagwireTM, Boston Scientific, USA, or a 0.025-inch VisiGlideTM, Olympus Medical System) was passed through the site of obstruction, until to reach an area distant as far as possible from the stenosis. The proximal lumen of the site of obstruction was captured, and after having confirmed the length of obstruction, the appropriate uncovered SEMS was positioned under endoscopic and fluoroscopic guidance.
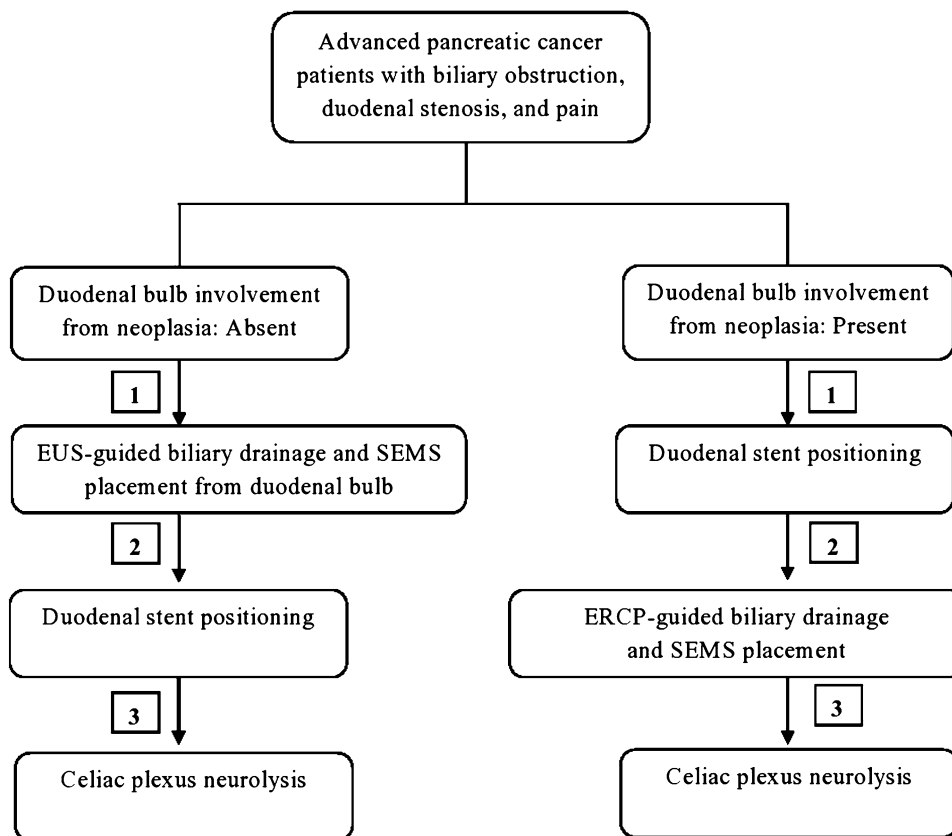
Celiac plexus neurolysis

In patients without allergy to bupivacaine, a puncture site was chosen in the gastric fundus, by avoiding proximity to the diaphragm and after exclusion of vessel-gut interposition at color Doppler assessment. In detail, either central or bilateral injection was planned by using a 22 G or 19 G needles (Cook Medical, Winston-Salem, NC, US). For the central injection, the needle was advanced above the celiac trunk, in the space between the aorta and the origin of the celiac axis. When bilateral injection was chosen, the echo-endoscope was situated above the celiac axis, and it was rotated to one side until the origin of the celiac axis was no longer seen, and then, a half solution was injected. The procedure was repeated on the opposite side. Before injecting, an aspiration was performed in order to rule out the placement of the needle inside a vessel. The injection started with 6 mL of a local analgesic (bupivacaine 0.25 %) to prevent transient pain exacerbation induced by the neurolytic agent. Subsequently, 10 mL of a neurolytic agent (98 % dehydrated alcohol) was injected, and a hyperechoic cloud was immediately seen in the area of the needle tip as the substance spreads. When ganglia were targeted, the echo-endoscope was rotated clockwise and celiac ganglia were found above the celiac trunk, alongside the trunk, and below the trunk, just above the superior mesenteric artery takeoff. The ganglia are small hypoechoic nodules with hyperechoic foci in the center. Sometimes their interconnection can be seen. The celiac plexus neurolysis was performed with a preprocedural hydration with 500 mL saline. All patients were kept under close observation for 2 h after the procedure, to monitor blood pressure, heart rate, and temperature and to identify any immediate complications. All patients received prophylactic antibiotics prior to the endoscopic procedures, which were performed under sedation with propofol. A specific informed consent was obtained from each patient before performing the one-STEP. A flowchart with the endoscopic procedures is provided in Fig. 1.

Pain evaluation

Assessment of pain intensity at entry of and pain relief following celiac plexus neurolysis was performed by using a Likert visual scale, validated for pain assessment in pancreatic cancer patients [10]. In detail, before the procedure, patients were asked to grade their level of pain from 0 to 10, with a 0–3, 4–7, and 7–10 values corresponding to mild, moderate, and severe pain, respectively. Assessment of pain severity was repeated 72 h following

Fig. 1 Two varieties of one-STEP approaches performed in the study. *EUS* Endoscopic ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *SEMS* self-expandable metallic stent

Results

A total of 15 patients diagnosed with a pancreatic cancer in an advanced stage and meeting the inclusion criteria (jaundice, duodenal stenosis, and chronic pain) were considered for the 'one-STEP' therapeutic approach. There were 12 males and 3 females, the mean age was 65.6 years (range 38–80), the median diameter of neoplasia was 5 cm (range 4–6), and the histology was adenocarcinoma in all, but one patient (male, 38-year old) with a neuroendocrine tumor. Before procedure, seven patients were receiving tramadol (100 mg/6–8 h), while the remaining eight patients were on morphine (20–200 mg/12 h) for pain treatment. There were 11 patients in ASA II score, three patients in ASA III, and one patient in ASA IV. All patients were receiving a parenteral nutrition. At entry, the median of bilirubin levels was 7 mg/dl (range 5.8–9.3 mg/dl). All endoscopic procedures were performed in deep sedation with propofol by using a pump, preceded by an induction with midazolam i.v. In only one patient (ASA IV), intubation was performed without complication. The anesthetist was present during the entire procedure.

the procedure. Moreover, change at follow-up was assessed by phone interviews every month. The consumption of analgesic and/or morphine equivalent was registered.

To treat biliary stenosis, the EUS-BD approach was attempted in 12 patients, and it was successful in 10 (83.3 %) cases. In two cases, the procedure failed following the bulb puncture due to impossibility of dilating the neoplastic mass for creating a fistula, even by using a Cremer's cystoenterostomy. These patients underwent elective surgical biliary derivation. The ERCP-BD procedure following the duodenal stenting was performed in the remaining three patients, and it was successful in all cases. Therefore, the biliary stenting was cumulatively successful in 13 (87 %) cases. Overall, a full-covered SEMS, 4 cm length, was positioned in 12 cases and a partial-covered SEMS, 6 cm length, in the remaining patients. Jaundice recovered in all patients. In two patients, a biliary obstruction due to food impaction was retreated at endoscopy by using a Dormia basket or Fogarty's balloon.

The median length of duodenal stenosis was 2 cm (range 2–3), and a 6-cm-long, uncovered SEMS was successfully placed in all cases (Fig. 2). No patient complained of symptoms requiring duodenal re-stenting, and no stent migration was observed. Oral feeding with semi-liquid diet was reintroduced in all patients, so that parenteral nutrition was interrupted within 1 week in all, but one patient who continued parental nutrition for 3 weeks.

For celiac plexus neurolysis, the central approach was performed in all, but two patients (Fig. 3). The median of
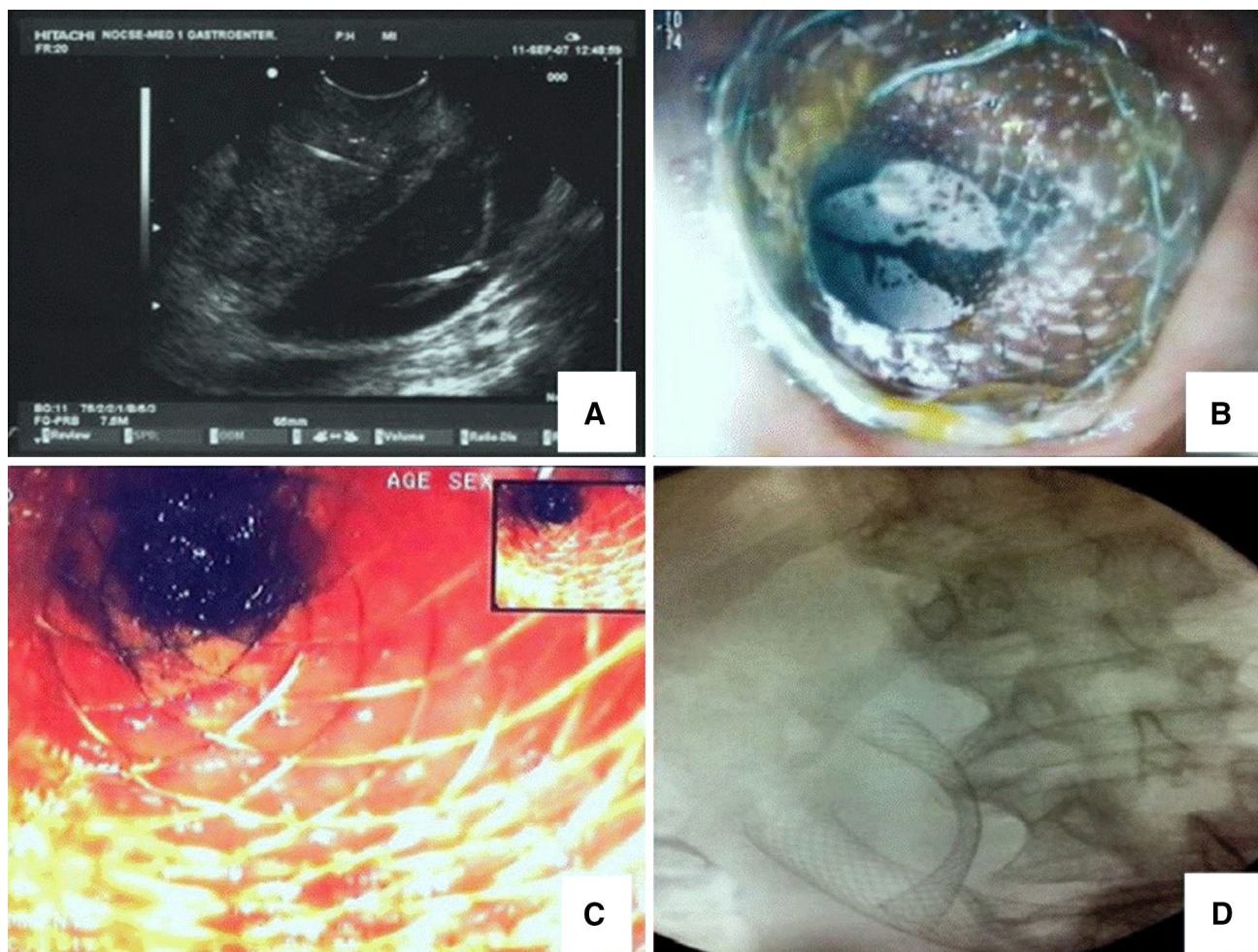
Fig. 2 Endoscopic stenting of biliary and duodenal stenosis. Transduodenal EUS-guided biliary fistula. EUS-guided puncture of dilated common bile duct from the duodenal bulb (**A**); fistula creation with a SEMS (**B**); duodenal SEMS positioned before transpapillary drainage of CBD by ERCP (**C**); and radiological image at the end of procedure showing the well-positioned duodenal and biliary SEMS

pain intensity was 8 [range 7–10] at entry and decreased to 2 (range 2–4) at 72 h ($P = 0.00064$; Wilcoxon signed-rank test), with improvement in all patients (Fig. 4). The median survival was 4 months (range 3–8). During such a period, only three (23 %) needed of morphine treatment, in the last 2 months in two patients (survival 8 and 5 months) or 1 month in one patient (survival 6 month).

Overall, the median time for the endoscopic procedures was 70 min (range 60–110 min). No early or late complications (bleeding, perforation) related to the endoscopic procedures were observed. During the one-STEP, only one patient (ASA III) developed atrial fibrillation which was promptly corrected with drugs. In this case, the endoscopic procedure was temporarily suspended for 10 min and thereafter successfully completed. All patients were hospitalized. In detail, the 13 inpatients of our hospital were discharged 3 days following a successful procedure. Two patients were referred directly to our endoscopic unit from other hospitals, where they returned in the same day of procedure.

Discussion

Some patients with an advanced pancreatic cancer may simultaneously complain of jaundice, duodenal stenosis, and persistent pain, due invasion/compression of biliary tree, duodenum, and visceral pain stimulation by the neoplastic mass. In addition, up to 38 % with unresectable pancreatic cancer and biliary stents who received chemotherapy and/or radiation therapy developed a duodenal obstruction [11], which is associated with a very short survival rate [7]. Therefore, it is not uncommon to encounter these patients in clinical practice. A palliative approach is the only possible therapy in these patients, mainly based on endoscopic or radiological drainage of biliary tree, stenting of duodenum,
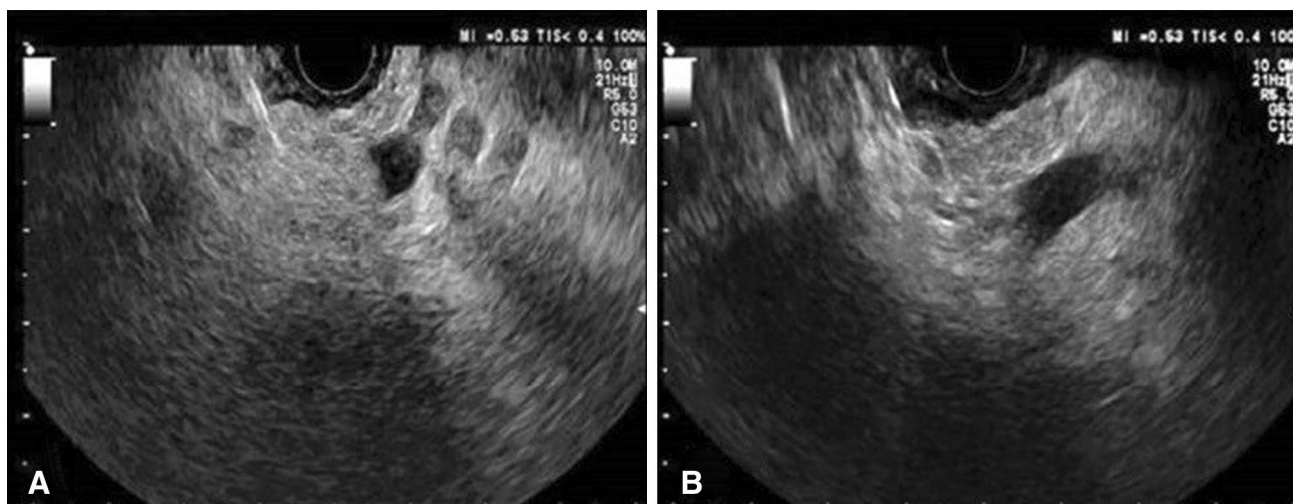
Fig. 3 Celiac plexus neurolysis. Needle positioned above the celiac plexus (**A**), and hyperechoic image after ethanol injection (**B**)
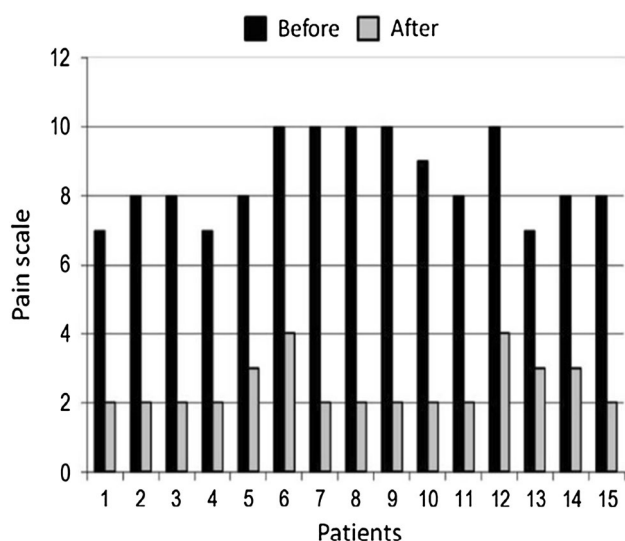

Fig. 4 Pain intensity before and 72 h following celiac plexus neurolysis

and opioid drugs [12]. In order to limit patients discomfort and reduce utilization of resources, a combined approach in applying endoscopic biliary and duodenal stents has been introduced. A recent case series showed a 100 % clinical success rate on 17 patients without any significant complications, demonstrating that the dual endoscopic procedure is effective and safe [13]. In addition, a long-term patency, comparatively to patient survival, of both stents has been proven in the majority of cases [14, 15], so that the re-stenting was needed only in some patients [16]. Of note, a combined biliary and duodenal stenting has be found possible even when the duodenal stenosis involved the papilla—i.e., type II stenosis CBD—through the mesh of the duodenal SEMS, as reported elsewhere [9].

Besides biliary and duodenal obstruction, a number of pancreatic cancer patients complained of an intense, not infrequently refractory, pain. Therefore, we attempted a novel one-STEP approach to contemporarily treat the three conditions. Data of our case series showed that such an approach is safe and feasible in the majority of patients. In detail, the biliary and duodenal stenosis stenting was successfully achieved in more than 80 % of the cases, and no relevant complications related to the endoscopic procedures occurred. However, a careful attention should be paid during the needle puncture of biliary tree at EUS to avoid injury which may cause leakage of bile into the retroperitoneal space during the following ERCP [17]. In our series, the patency of stents was comparable with patients' survival. In addition, the celiac plexus neurolysis yielded a prompt relief of pain in all treated patients. Of note, such an improvement persisted at follow-up, so that only a minority of patients needed of opioid therapy in the last period of survival. This is a definite advantage in terms of patient comfort and lacking of potential side effects associated with narcotics use. Our data are in agreement with that of a systematic review (8 studies; 283 pancreatic cancer patients) showing that EUS-guided celiac plexus neurolysis achieved a sustained pain relief in 80 % (95 % CI 74–85) [18]. In addition, the clinical success rate was ranging from 48 to 94 % in a more recent systematic review (13 studies; 503 pancreatic cancer patients), without significant difference in central or bilateral neurolysis procedure or neurolytic agent used [19, 20]. Although our data and other studies found that the majority of patients did not require narcotics at follow-up, a larger randomized trial found a nonsignificant different morphine use between patients who underwent celiac plexus neurolysis and controls [9]. Therefore, further data are warranted in such a field.

In conclusion, this study showed that the one-STEP approach we proposed is an effective and safe palliative endoscopic treatment for biliary and duodenal stenosis and for relieving chronic pain in patients with inoperable pancreatic cancer. Implementation of such a procedure in clinical practice is expected to reduce utilization of resources and to limit patient's discomfort.

Compliance with ethical standards

Disclosure Raffaele Manta, Rita Conigliaro, Santi Mangiafico, Helga Bertani, Edoardo Forti, Massimilano Mutignani, Marzio Frazzoni, Giuseppe Galloro, and Angelo Zullo have no conflicts of interest or financial ties to disclose.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ (2008) Cancer statistics, 2008. CA Cancer J Clin 58:71–96
2. Bilimoria KY, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP, Talamonti MS (2007) Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer 110:738–744
3. Jooste V, Grosclaude P, Remontet L, Launoy G, Baldi I, Molinié F, Arveux P, Bossard N, Bouvier AM, Colonna M (2013) Unbiased estimates of long-term net survival of solid cancers in France. Int J Cancer 132:2370–2377
4. Seicean A (2014) Celiac plexus neurolysis in pancreatic cancer: the endoscopic ultrasound approach. World J Gastroenterol 20:110–117
5. Cherny Nathan I (2005) Opioids in the management of cancer pain. Eur J Cancer 3:61–75
6. Teshima CW, Sandha GS (2014) Endoscopic ultrasound in the diagnosis and treatment of pancreatic disease. World J Gastroenterol 20:9976–9989
7. Ghaneh P, Costello E, Neoptolemos JP (2007) Biology and management of pancreatic cancer. Gut 56:1134–1152
8. Giovannini M, Bories E, Téllez-Ávila FI (2012) Endoscopic ultrasound-guided bilio-pancreatic drainage. Endosc. Ultrasound 1:119–129
9. Mutignani M, Trincali A, Shah SG, Perri V, Familiari P, Iacopini F, Spada C, Costamagna G (2007) Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. Endoscopy 39:440–447
10. Wyse JM, Carone M, Paquin SC, Usatii M, Sahai AV (2011) Randomized, double-blind, controlled trial of early endoscopic ultrasound–guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol 29:3541–3546
11. Shah A, Fehmi A, Savides TJ (2014) Increased rates of duodenal obstruction in pancreatic cancer patients receiving modern medical management. Dig Dis Sci 59:2294–2298
12. Boulay BR, Parepally M (2014) Managing malignant biliary obstruction in pancreas cancer: choosing the appropriate strategy. World J Gastroenterol 20:9345–9353
13. Yu J, Hao J, Wu D, Lang H (2014) Retrospective evaluation of endoscopic stenting of combined malignant common bile duct and gastric outlet-duodenum obstructions. Exp Ther Med 8:1173–1177
14. Canena J, Coimbra J, Carvalho D, Rodrigues C, Silva M, Costa M, Horta D, Mateus Dias A, Seves I, Ramos G, Ricardo L, Coutinho AP, Romão C, Veiga PM (2014) Endoscopic bilio-duodenal bypass: outcomes of primary and revision efficacy of combined metallic stents in malignant duodenal and biliary obstructions. Dig Dis Sci 59:2779–2789
15. Hamada T, Isayama H, Nakai Y, Kogure H, Yamamoto N, Kawakubo K, Takahara N, Uchino R, Mizuno S, Sasaki T, Togawa O, Matsubara S, Ito Y, Hirano K, Tsujino T, Tada M, Koike K (2014) Transmural biliary drainage can be an alternative to transpapillary drainage in patients with an indwelling duodenal stent. Dig Dis Sci 59:1931–1938
16. Sasaki T, Isayama H, Nakai Y, akahara N, Hamada T, Mizuno S, Mohri D, Yagioka H, Kogure H, Arizumi T, Togawa O, Matsubara S, Ito Y, Yamamoto N, Sasahira N, Hirano K, Toda N, Tada M, Koike K (2014) Clinical outcomes of secondary gastroduodenal self-expandable metallic stent placement by stent-in-stent technique for malignant gastric outlet obstruction. Dig Endosc 4 [Epub ahead of print]
17. Di Matteo F, Shimpi L, Gabbrielli A, Martino M, Caricato M, Esposito A, De Cicco ML, Coppola R, Costamagna G (2006) Same-day endoscopic retrograde cholangiopancreatography after transduodenal endoscopic ultrasound-guided needle aspiration: do we need to be cautious? Endoscopy 38:1149–1151
18. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR (2009) EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci 54:2330–2337
19. Fabbri C, Luigiano C, Risotti A, Cennamo V, Virgilio C, Caletti G, Fusaroli P (2014) Endoscopic ultrasound-guided treatments: are we getting evidence based-a systematic review. World J Gastroenterol 20:8424–8448
20. Ishiwatari H, Hayashi T, Yoshida M, Ono M, Masuko H, Sato T, Miyanishi K, Sato Y, Takimoto R, Kobune M, Miyamoto A, Sonoda T, Kato J (2014) Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for East Asian alcohol-intolerant upper gastrointestinal cancer patients: a pilot study. World J Gastroenterol 20:10512–10517