Introducció de l'ecoendoscòpia intervencionista i terapèutica en un hospital universitari. Combinació amb la colangiografia retrògada endoscòpica en patologia biliopancreàtica: aspectes clínics i econòmics

Joan B. Gornals Soler

TESI DOCTORAL

FACULTAT DE MEDICINA

INTRODUCCIÓ DE L'ECOENDOSCÒPIA INTERVENCIONISTA I TERAPÈUTICA EN UN HOSPITAL UNIVERSITARI. COMBINACIÓ AMB LA COLANGIOGRAFIA RETRÒGRADA ENDOSCÒPICA EN PATOLOGIA BILIOPANCREÀTICA: ASPECTES CLÍNICS I ECONÒMICS.

Tesi doctoral presentada per Joan B. GORNALS SOLER per optar al grau de DOCTOR en MEDICINA

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Grup de recerca: Patologia Hepato-bilio-pancreàtica

Barcelona, març 2013

AUTORITZACIÓ DELS DIRECTORS DE TESI

José CASTELLOTE ALONSO, doctor en Medicina i Cirurgia, membre de la unitat de Hepatologia i Trasplantament Hepàtic del servei de Aparell Digestiu de l'Hospital Universitari de Bellvitge; i **Xavier CORBELLA I VIRÓS**, doctor en Medicina i Cirurgia, professor associat de la Facultat de Medicina de la Universitat Internacional de Catalunya, i Director Gerent de l'Hospital de la Santa Creu i Sant Pau.

CERTIFIQUEN

Que la memòria titulada **'Introducció de l'ecoendoscòpia intervencionista i terapèutica en un Hospital Universitari. Combinació amb la colangiografia retrògrada endoscòpica en patologia biliopancreàtica: aspectes clínics i econòmics'** presentada per **Joan B. GORNALS SOLER** per optar al grau de Doctor en Medicina, s'ha realitzat sota la nostra direcció. Una vegada finalitzada, s'autoritza la seva presentació per ser jutjada pel tribunal corresponent.

Per que quedi constància als efectes oportuns, es signa la present a Barcelona, 15 de març de 2013.

Dr. José Castellote Alonso

Dr. Xavier Corbella i Virós

Universitat de Barcelona

Dedicada a:

Als meus pares, Bernat i Linita, pels valors que m'han transmès de ben petit.

Al meu fill, Bernat, per donar-me la força necessària per començar i acabar aquest projecte.

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“ I would urge you to write not because it is a good thing, not because it is nice to see your name in print, but rather because you will really get to know a field only if you contribute to it”

Mahoney MJ, Psychology of the Scientist 1979.

INDEX:

AGRAÏMENTS

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PRESENTACIÓ:

La meva introducció al món de l'endoscòpia digestiva fou durant la residència en Aparell Digestiu a l'Hospital Universitari de Bellvitge, perïode 2000-2004, amb els Drs. Lluis Vilar, Josep M. Badosa, Carles Badosa, Antoni Surós, José Nogueira i Josep M. Miquel. Posteriorment, davant el meu interès en la tècnica, vaig voler ampliar la formació en tècniques intervencionistes més avançades, com la colangiopancreatografia retrógrada endoscòpica o la col·locació de pròtesis, amb el Dr. Miquel a la mateixa unitat d'endoscòpia.

Des del mateix centre, se'm va oferir l'oportunitat de voler-me formar en ecoendoscòpia digestiva amb una estada a l'estranger (University of Texas Medical Branch, Galveston, Texas, EUA; de juny a desembre, 2006) i a un centre estatal (Hospital Clínic, Barcelona; de gener a març, 2007). Amb aquesta aposta per part del centre i a la formació específica del doctorand, el 20 de novembre del 2007 es va dur a terme el primer procediment d'ecoendoscòpia digestiva a la unitat d'Endoscòpia, i per tant, es donava com introduïda la tècnica a l'Hospital Universitari de Bellvitge.

Gràcies a la sensibilitat i comprensió de la complexitat de la tècnica per part de Direcció Mèdica, encapçalada aleshores pel Dr. Eduard Jaurrieta, progressivament es va anar dotant del personal (anestessiòleg, equip de citopatologia, personal d'infermeria), i material específic (agulles, pròtesis i altres utensilis) necessaris per dur a terme procediments intervencionistes.

Paral·lelament a la introducció de la tècnica, es van oferir vàries sessions sobre les indicacions generals de l'ecoendoscòpia digestiva adreçades a diferents serveis del centre (Aparell Digestiu, Cirurgia General i Digestiva, Pneumologia, Radiologia, Anatomia Patològica, Oncologia Mèdica) i personal

del centre (Infermeria de la unitat d'Endoscòpia), amb l'objectiu de facilitar la seva introducció i difusió a la pràctica clínica del centre.

Per una millor integració de la tècnica als circuits assistencials, es van redactar fulls informatius específics de la tècnica (USE alta, USE baixa, USE i PAAF) i circuits d'ingrés amb observació clínica de 24 hores en el cas de les ecoendoscòpies intervencionistes o terapèutiques, així com els fulls de recomenacions clíniques posteriors a una ecoendoscòpia amb punció.

La introducció de l'ecoendoscòpia ha sigut paral·lela al treball multidisciplinar i al desenvolupament de les unitats funcionals de tumors fruit de la col·laboració dels 2 centres, Hospital Universitari de Bellvitge i Institut Català d'Oncologia. Aquesta coincidència no ha sigut a l'atzar, donat que la petició inicial d'introduir la tècnica a HUB, va néixer dels orígens de l'actual Unitat Funcional de Tumors Esofagogàstrics o UTEG (Dr. Manel Sans, Dra. Maica Galán). Per aquest motiu, el doctorand ha sigut membre de la UTEG des de la seva arribada de la formació de la tècnica i ha participat en les diferents edicions que s'han fet dels protocols d'actuació en el càncer d'esòfag toràcic i càncer gàstric del nostre centre. D'altra banda, el doctorand també ha participat en la redacció del protocol del maneig del tumors neuroendocrins.

Respecte al punt de vista d'investigació, des de la introducció de la tècnica, s'ha tingut una especial cura en la recopilació de les imatges (fototeca) i de vídeos (videoteca) dels procediments realitzats, i la creació d'una base de dades. L'estudi, gestió i revisió d'aquest material i dades ha permès iniciar una activitat científica i produir una sèrie de treballs que s'han remés com comunicacions a varis congressos locals, nacionals i internacionals, i posteriorment s'han treballat per publicació.

Aquesta Tesi és el fruit de la conjunció de tots els fets exposats en aquesta presentació, i de l'esforç de vàries persones, que m'han ajudat contínuament, dia a dia.

La present Tesi Doctoral està estructurada seguint les directrius de la normativa per a la presentació de tesis doctorals com un compendi de publicacions, aprovat pel Consell del Departament de Medicina de la Universitat de Barcelona.

Els estudis que conformen aquesta Tesi Doctoral pertànyen a una mateixa línea d' investigació, dirigida a analitzar el paper de la introducció de la ultrasonografia endoscòpica en un hospital universitari i terciari, i la seva combinació amb la colangiopancreatografia retrògrada endoscòpica. Els resultats d' aquests estudis han aportat informació nova i rellevant en aquest camp i han estat recollits en 4 articles originals, tres d'ells en revistes d'àmplia difusió internacional, i un altre d'àmbit estatal, amb un factor d'impacte global de 14,711 punts.

PRODUCCIÓ CIENTÍFICA RELACIONADA AMB EL TEMA DE LA TESI:

Articles que formen part de la Tesi:

1. **Gornals J**, Varas M, Catalá I, Maisterra S, Pons C, Bargalló D, Serrano T, Fabregat J. *Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography.* **Rev Esp Enferm Dig 2011; 103: 123-128** (Factor d'impacte: 1,548)

2. **Gornals JB**, De la Serna-Higuera C, Sanchez-Yague A, Loras C, Sanchez-Cantos A, Perez-Miranda M. *Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent*. **Surgical Endoscopy 2012, dec 12 (Epub ahead of print).** (Factor d'impacte: 4,013)

3. **Gornals J**, Loras C, Mast R, Botargues J, Busquets J, Castellote J**.** *EUS-guided transesophageal drainage of a mediastinal pancreatic pseudocyst using a novel lumen apposing metal stent*. **Endoscopy 2012; 44: E1-E2.** (Factor d'impacte: 6,096)

4. **Gornals JB**, Moreno R, Castellote J, Loras C, Barranco R, Catala I, Xiol X, Fabregat J, Corbella X. *Single-session endosonography and endoscopic retrograde cholangiopancreatography for biliopancreatic diseases is feasible, effective and cost beneficial*. **Digestive and Liver Disease (2013)**, http://dx.doi.org/10.1016/j.dld.2013.01.023 (Factor d'impacte: 3,054)

Altres articles publicats relacionats amb aquesta Tesi:

1. **Gornals JB**, Varas M. J, Bhutani M.S. Novel aspects of diagnostical and interventional Endosonography. **Rev Esp Enferm Dig 2007; 99 (supl.II): 36-56.** (Factor d'impacte: 1,548)

2. **Gornals JB**, Baixeras N, Paules MJ, Mast R, Pujol R. *Diagnosis of Whipple's disease by EUS-guided-FNA and endoscopic biopsy at the same procedure.* **Gastrointest Endosc 2012; 75: 895-896** (Factor d'impacte: 5,608)

3. Salord S, **Gornals JB**, Maisterra S, Pons C, Busquets J, Fabregat J. Endoscopic closure of duodenal perforation with an over-the-scope clip during endoscopic ultrasound-guided cholangiopancreatography. **Rev Esp Enferm Dig 2012; 104: 489-490** (Factor d'impacte: 1,548)

4. **Gornals JB**, Parra C, Pelaez N, Secanella Ll, Ornaque I. Double endosonography-guided transgastric and transduodenal drainage of infected pancreatic-fluid collections using metallic stents. **Rev Esp Enferm Dig 2013**. (acceptat, pendent de publicació) (Factor d'impacte:1,548)

Comunicacions a congressos:

Els resultats dels treballs que constitueixen la base d'aquesta Tesi doctoral han sigut presentats en els congressos que es relacionen a continuació:

1. **JB Gornals**, R Moreno, C Loras, C Masuet, D Buisac, B Ortiga, JL Nin, C Capdevila, J Nogueira, X Corbella. *Cost-minimization analysis of single-stage endoscopic ultrasound and endoscopic retrograde cholangiopancreatography, instead of two-stage sessions, in pancreaticobiliary diseases.* UEGW 18th United European Gastroenterology Week, Barcelona October 23-27, 2010. **Endoscopy 2010**; **42: A157.**

2. C Loras, **JB Gornals** , C Pons , E Garcia-Recio , E Vargas, M. de la Hera , S Maisterra , I Catala , J Nogueira , J Fabregat. *Clinical impact of single-session endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in biliopancreatic diseases.* UEGW 18th United European Gastroenterology Week, Barcelona October 23-27, 2010. **Endoscopy 2010**; **42: A160.**

3. Maisterra S, **Gornals JB**, Pons C, Varas M, De la Hera M, Catalá I, Serrano T, Bargalló D, Peláez N, Fabregat J. Utilidad de la PAAF guiada por ultrasonografia endoscópica en el diagnóstico de tumores neuroendocrinos. XXXII Jornada Nacional de la Sociedad Española de Endoscopia Digestiva, León 26-27 Noviembre 2010. **Endoscopy 2010; 42: A55.**

4. **Gornals J**, Moreno R, Loras C, Masuet C, Buisac D, Ortiga B, Nin JL, Capdevila C, Xiol X, Corbella X. Estudio de minimizacion de costes de la combinacion de la USE y la CPRE en un mismo procedimiento. XXXII Jornada Nacional de la Sociedad Española de Endoscopia Digestiva, León 26-27 Noviembre 2010. **Endoscopy 2010; 42**: **A43.**

5. Loras C, **Gornals J**, Pons C, de la Hera M, Maisterra S, Catala I, Pelaez N, Busquets J, Nogueira J, Fabregat J. Impacto clínico de la combinación de la USE y CPRE en un mismo procedimiento en la patologia biliopancreática. XXXII Jornada Nacional de la Sociedad Española de Endoscopia Digestiva, León 26-27 Noviembre 2010. **Endoscopy 2010; 42: A:53.**

6. Loras C, **JB Gornals-Soler**, C Pons, S Maisterra, I Catala, N Pelaez, J Busquets, J Castellote, J Fabregat, X Xiol. *Single-session Endoscopic Ultrasonography and Endoscopic Retrograde Cholangiopancreatography for Patients with Biliopancreatic diseases.* DDW; ASGE Meeting, Chicago, May 7-10, 2011. **Gastrointest Endosc 2011; 73: AB258.**

7. **Gornals JB**, de la Serna-Higuera C, Sánchez-Yagüe A, Loras C, Sánchez-Cantos AM, Espinós JC, González-Canoniga A, Varas M, Pérez-Miranda M. Drenaje de colecciones pancreáticas guiado por USE mediante nueva prótesis metálica de aproximación luminal-AXIOS. XXXIII Jornada Nacional de la Sociedad Española de Endoscopia Digestiva, Madrid, 11-12 Noviembre 2011. **Endoscopy 2011; 43: A70.**

8. **Gornals JB**, de la Serna-Higuera C, Sánchez-Yagüe A, Loras C, Sánchez-Cantos AM, Espinós JC, Pons C, Varas M, Pérez-Miranda M. Drenatge de col·leccions pancreàtiques guiat per ecoendoscòpia amb nova pròtesi metàl·lica d'aproximació luminal-AXIOS. XXI Congrés de la Societat Catalana de Digestologia, Girona, 26-28 de gener 2012. **Annals de Medicina 2012; 95: s1-41.**

Ponències:

Ponències relacionades amb el tema de la Tesi als diferents escenaris científics i docents:

1. **'Punció guiada per ecoendoscòpia digestiva a la patologia pancreàtica. Quan està indicat?'**. A la sessió de pàncrees organitzat per la Societat Catalana d'Endoscòpia Digestiva i Médico-quirúrgica de l'Acadèmia de Ciències Mèdiques, dia 31 de març de 2009. Barcelona.

2. **'Indicacions i utilitat de la ecoendoscòpia en els tumors malignes de pàncrees'** dins la sessió de 'Tumors malignes de pàncrees' organitzat per la Societat Catalana d'Endoscòpia Digestiva i Médico-quirúrgica de l'Acadèmia de Ciències Mèdiques, dia 1 de desembre de 2009. Barcelona.

3. **'La ultrasonografia endoscòpica terapèutica: Un pas imprescindible per a la terapèutica transmural'.** XVI Curs de Formació en Digestologia: Endoscòpia en la pràctica clínica i les seves perspectives de futur. XX Congrés de la Societat Catalana de Digestologia. Lleida, del 28 al 30 de gener, 2011.

4. **'Drenaje de colecciones mediante sistema semiautomático X-Lumena guiado por USE: Experiencia inicial'**. XIII Jornada Nacional en Ultrasonografia Endoscópica. Hospital Universitario Quirón. 4-5 Noviembre, 2011. Madrid.

5. Conferència magistral. '**Avances en Ecoendoscopia terapéutica. Ecoendoscopia versus CPRE ¿Cuál es de primera elección?'.** XXV Congreso de la Sociedad Valenciana de Patología Digestiva. Castellón, 18-19 noviembre, 2011.

6. Conferència internacional. '**New indications and technologies in pancreatic disease: Endoscopic treatment of pancreatic pseudocyst'**. 5 curso internacional NOTES-WIDER Barcelona, 21-22 noviembre, 2011.

7. **'Opcions terapèutiques en el drenatge de col·leccions pancreàtiques: Drenatge transmural guiat per Ecoendoscòpia'**. Societat Catalana de Pàncrees i Centre Mèdic Teknon. Barcelona, 15 de març, 2012.

8. ‘**Accesos biliares guiados por Ecoendoscopia: errores evitable y nuevas oportunidades’**. XIV Jornada Nacional de Ultrasonografia Endoscópica. Hospital Universitario Cruces, Barakaldo, Bilbao, 28-29 septiembre, 2012.

9. Conferència internacional. **‘New indications and technologies in pancreatic disease: Endoscopic treatment of pancreatic pseudocyst’**. 6 curso internacional NOTES-WIDER Barcelona, 3 y 4 de diciembre, 2012.

AJUDES PERSONALS REBUDES:

El període de formació del doctorand en la tècnica d'endoscòpia avençada, Ultrasonografia Endoscòpica, va rebre el suport de:

- La **Beca per l'estada a l'estranger** (6 mesos), convocatòria 2006/2007, per part de la Fundació Privada: Acadèmia de Ciències Mèdiques de Catalunya i Balears- Societat Catalana de Digestologia.

- Ajuda econòmica de **l'Hospital Universitari de Bellvitge - IDIBELL** per a una estada a l'estranger de 7 mesos específica per l'aprenentatge en ecoendoscòpia digestiva al *Center for Endoscopic Ultrasound Medicine* de la *University of Texas Medical Medical Branch*, Galveston (Texas, Estats Units d'Amèrica).

ABREVIATURES:

ASGE: *American Society for Gastrointestinal Endoscopy*

CEA: antígen carcino- embrionari

E: especificitat

Estadi T: infiltració intraparietal local del tumor

Estadi N: metàstasis ganglionars regionals

Estadi M: metàstasis a distància

CPES: colangiopancreatografia guiada per ecoendoscòpia

CPRE: colangiopancreatografia retrògrada endoscòpica

CPRM: colangiopancreato ressonància magnètica

CTPH: colangiografia transparietohepàtica

MHz: megaHerz

PAAF: punció aspirativa amb agulla fina

S: sensibilitat

SEMS: self-expanding metallic stents

TNE: tumor neuroendocrí

TCMD: tomografia computeritzada multidetector

USE: ultrasonografia endoscòpica o ecoendoscòpia digestiva.

USE-PAAF: punció aspirativa amb agulla fina guiada per ecoendoscòpia

VBP: via biliar principal

I. INTRODUCCIÓ

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1. Ultrasonografia Endoscòpica o Ecoendoscòpia

1.1 Generalitats

L'ecoendoscòpia digestiva o ultrasonografía endoscópica (USE) integra en un mateix tub imatges d'endoscòpia iguals a les d'un videoendoscopi convencional, i imatges ecogràfiques que s'obtenen per l'existència d'un transductor localitzat a la punta del tub.

L'ecoendoscopi sol presentar un diàmetre major (10-13 mm) que la majoria de videoendoscopis i la visió endoscòpica pot ser oblíqua o frontal depenent de la casa comercial i model. Existeixen fonamentalment 3 sistemes: minisondes, sistema radial i sistema lineal o sectorial.

El sistema radial, es tracta d'un videoecoendoscopi que consta d'un transductor radial de 360º, el qual emet ultrasons perpendiculars a l'eix del tub. Les imatges obtingudes seran més anatòmiques, oferint una millor orientació espaial, semblants a les d'una tomografia computeritzada multidetector (TCMD). La seva funció és purament diagnòstica, i no permet realitzar cap tipus d'intervencionisme, com les puncions guiades.

El sistema lineal o sectorial, es tracta d'un videoecoendoscopi amb un transductor convex de 100º situat a la punta del tub. Les imatges anatòmiques obtingudes són de més difícil comprensió, pel que la seva corba d'aprenentatge és més exigent. Permet realitzar les puncions guiades per USE amb una finalitat intervencionista diagnòstica (ex. PAAF) o terapèutica (ex. drenatge de col·leccions, injecció de substàncies). El canal de treball dels ecoendoscopis lineals i terapèutics sol ser ampli, d'uns de 3.7 mm.

En l'actualitat, tots els sistemes van acopats a una consola ecogràfica que disposa d'un senyal Doppler color i pulsativa, que permet identificar vasos de diferent mida. Les freqüències dels ecoendoscopis convencionals solen ser de 5, 6, 7.5, 10 i 12 MHz. Amb freqüències menors, la penetració serà major i al contrari (1,2).

1.2 Tècnica i aprenentatge

Per l'exploració es requereix un des dejuni de 6-8 hores. El pacient es col·loca habitualment en decúbit lateral esquerra. Requereix d'una sedació profunda per part d'un equip explorador (endoscopista i infermeria) entrenats en sedacions, o la presència d'un anestesiòleg. La duració del procediment varia depenent de la indicació: uns 30 minuts en indicacions diagnòstiques, de 45-60 minuts en intervencionismes diagnòstics o terapèutics (ex. PAAF, o drenatges), aproximadament.

Per l'obtenció de imatges ecogràfiques de bona qualitat és imprescindible obtenir una bona finestra acústica. L'aire artefacta molt la imatge USE, per tant és important insuflar-lo el mínim possible. A més, a l'estómac, duodè i recte es sol instil·lar aigua per a millorar la transmissió de les ones dels ultrasons. Els models d'ecoendoscopi ofereixen l'opció de col·locar un baló de plàstic que cobreixi el transductor i es pugui omplir d'aigua, millorant així la finestra acústica.

La USE és una de les branques de l'endoscòpia més difícils d'aprendre, a més si ha d'afegir la dificultat de trobar centres amb programes de formació especialitzats. L'experiència prèvia amb endoscòpia, maneig del

videoduodenoscopi de visió lateral i en ecografia són essencials. La comprensió de la localització i orientació dels diferents talls ecogràfics és difícil degut als múltiples talls creats i els constants canvis amb el moviment del tub.

L'aprenentatge ha d'incloure una formació teòrica amb llibres de text específics, atles anatòmics aplicats a la USE en format CD o DVD; i una formació pràctica amb un ecoendoscopista experimentat durant un període aconsellat de 6 mesos o un mínim de 150 proves supervisades incloent 75 estudis biliopancreàtics i 50 PAAF (3) .

La figura 1 mostra com es visualitza la via biliar extrahepàtica i regió de cap pancreàtic amb el conducte pancreàtic principal, per imatge USE radial des de el bulb duodenal (1A) i comparat amb la imatge (1B) obtinguda d'una Colangiopancreatografia Retrógrada Endoscòpica (CPRE).

Figura 1A: imatge USE radial des del bulb duodenal. S'identifica, la via biliar extrahepàtica (CBD), la vesícula biliar (GB), i el tram distal del conducte pancreàtic principal (PD).

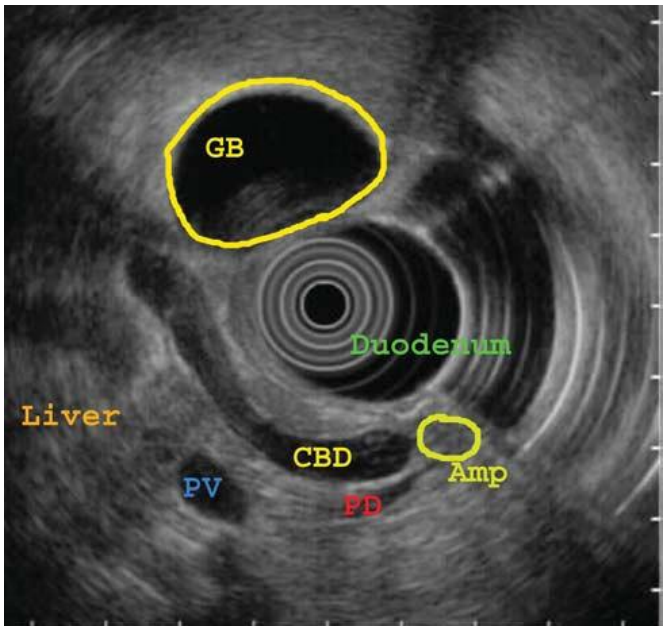
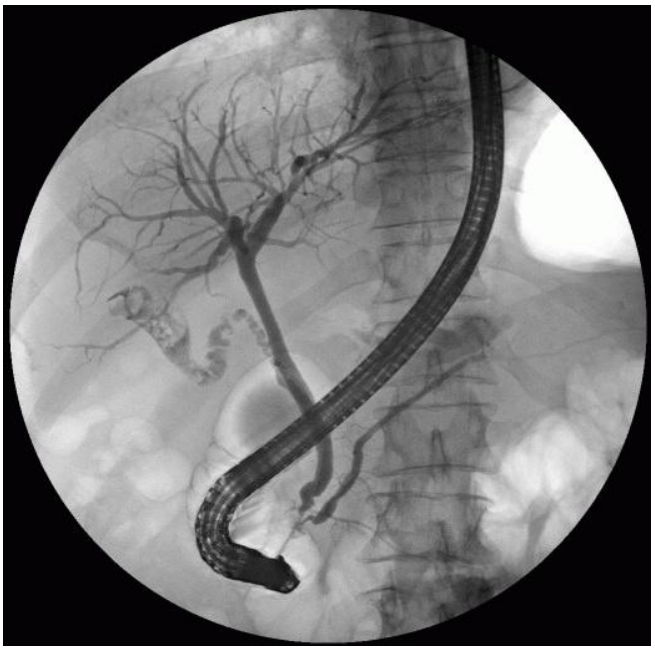


Figura 1B: imatge d'una CPRE amb la via biliar extra- intrahepàtica, el conducte cístic i la vesícula biliar amb litiasis al seu interior. El conducte pancreàtic principal també es visualitza amb un trajecte perpendicular a la columna vertebral.



*Imatges adaptades de Bhutani. Digital Human Anatomy and Endoscopic Ultrasonography.Hamilton, Ontario: BC Decker Inc, 2005.

1.3 Indicacions generals

Per les característiques descrites, la USE és una tècnica idònia per estudiar les diferents capes que formen la paret del tub digestiu i les estructures del seu voltant. La USE està indicada en l'estudi de lesions (o tumors) subepitelials, l'estudi d'extensió locorregional (TN) del càncer d'esòfag, càncer gàstric, limfoma gàstric (ex. MALT), patologia maligna biliopancreàtica, càncer rectal, càncer de pulmó i patologia del mediastí, en patologia benigna biliopancreàtica, estudi de plecs gàstrics gegants, incontinència fecal, patologia perirectal i una miscel·lània àmplia (ex. lesions hepàtiques, suprarenals, quists de duplicació). En varis estudis prospectius, la USE ha demostrat tenir un bon impacte en el diagnòstic i maneig d'aquestes patologies, i està ben establert en diverses guies internacionals. A més, la USE-PAAF, permet l'obtenció de mostres de lesions subepitelials, extramurals i adenopaties. Varis estudis han demostrat que la USE és millor a altres proves d'imatge en l'estudi TN de tumors del tracte digestiu i biliopancreàtics.

En el camp terapèutic, a pesar de ser molt més novell, ja existeixen una sèrie d'indicacions descrites en la literatura com el drenatge transmural, el bloqueig del plexe celíac en dolors intractables, la injecció de substàncies (ex. fàrmacs, virus atenuats) o la colangiografia i pancreatografia guiada per USE.
Així i tot, a pesar de ser un procediment segur, la seva implementació en la pràctica clínica depèn de la superació de vàries limitacions com són els costos dels equips i la corba d'aprenentatge significativa per arribar a un nivell d'excel·lència (4,5).

1.4 Indicacions en la patologia biliopancreàtica

L'ecoendoscopi permet visualitzar un àrea peridigestiva d'uns 6-8 cm al voltant del tram de tub digestiu explorat. D'aquesta manera es permet explorar correctament la relació de les neoplàsies amb altres estructures annexes, i identificar adenopaties regionals. Respecte a les patologies biliopancreàtiques, la USE és una prova excel·lent ja que ens permet estudiar tota la via biliar extrahepàtica, regió papil·lar i glàndula pancreàtica de forma que el procés uncinat, el cap i l'àrea papil·lar s'exploren des de el duodè, en canvi el cos i la cua des de la cavitat gàstrica. Les indicacions de la USE en la patologia biliopancreàtica inclou: càncer de pàncrees, tumors ampul·lars, tumors de la via biliar (vesícula biliar o colangiocarcinomes distals), tumor neuroendocrí (TNE), pancreatitis crònica, pancreatitis aguda, sospita de coledocolitiasis, tumors quístics pancreàtics i pancreatitis autoimmune.

En l'estudi de lesions quístiques pancreàtiques, la imatge USE i l'obtenció de líquid mitjançant USE-PAAF per ser analitzat, pot oferir un rendiment diagnòstic proper al 80-90%. És important l'estudi citològic, sobretot per descartar malignitat; i l'estudi bioquímic, per poder tipificar la natura del tipus de lesió, ja sigui inflamatòria (ex. pseudoquist) o neoplàsica (ex. tumor quístic pancreàtic mucinós o no mucinós). L'estudi del CEA comporta un alt rendiment diagnòstic: valors superiors a 192 ng/ml són diagnòstics d'un tumor quístic de natura mucinosa (premaligna), amb una S del 73% i una E del 84% (4,6).

En l'estudi de tumors sòlids pancreàtics, la USE pancreàtica té una resolució de 2-3 mm, i localitza lesions focals de 2-3 cm en més del 95% dels casos amb major precisió que la resta de proves d'imatge. Per tant, té un paper

en l'estudi locorregional TN, i també pronosticar la seva ressecabilitat mitjançant l'estudi de relacions vasculars. La USE-PAAF obté material amb una eficàcia que varia entre el 79-96 %, amb una sensibilitat del 64 al 91% i una especificitat del 97 al 100%, segons les sèries estudiades (6). En els tumors pancreàtics ressecables, que directament poden beneficiar-se d'una cirurgia, no està consensuat que s'hagi de realitzar una USE-PAAF, ja que un resultat negatiu no exclou la possibilitat d'un diagnòstic de lesió maligna donat l'existència de falsos negatius. La indicació clara d'USE-PAAF es troba en lesions que comportin dubtes diagnòstics i plantegin un diagnòstic diferencial (ex. TNE, limfoma, tuberculosis, pancreatitis autoimmune focal, pancreatitis crònica), en tumors irressecables i en tumors potencialment ressecables en protocol de neoadjuvància, prèviament a rebre el tractament oncològic. (6)

En el cas dels TNE, poden aparèixer al tub digestiu i/o la glàndula pancreàtica. En un 20% dels TNE pancreàtics, les proves d'imatge convencionals no poden identificar-los. La USE pancreàtica, pot ser útil en aquests casos de TNE sospitats i no localitzats, amb una S i E superiors al 80%. En casos de dubtes diagnòstics, en que es requereixi l'obtenció d'una mostra, es pot valorar la realització d'una USE-PAAF amb estudi immunocitoquímic de la mostra (2).

1.5 Punció guiada per USE: rendibilitat, complicacions

La USE PAAF intervencionista s'ha de realitzar amb l'ecoendoscopi lineal o sectorial ja que permet visualitzar l'agulla en tot el seu trajecte durant la punció. Es realitza una punció amb agulla fina guiat per USE en temps real des de l' interior del tub digestiu i obtenció de material citològic pel diagnòstic

d'adenopaties abdominals o mediastíniques, lesions pancreàtiques, adrenals, hepàtiques, tumors subepitelials o altres lesions extra luminals (7,8, annex 1). Existeixen diferents tipus d'agulla en quan a mida (25, 22, 19 G) i model (Trucut, PAAF, PRO-CORE).

Una vegada localitzada la lesió, es revisa per Doppler la no existència de vasos interposats al trajecte de l'agulla i es punciona amb l'agulla escollida. L'ús d'un elevador específic, permet canviar de direcció l'agulla i aspirar material de diferents zones. S'aplica aspiració amb una xeringa connectada a l'agulla, i es realitzen vàries passades amb l'agulla dins la lesió. Posteriorment es prepara, en un ambient estèril, una part de la mostra obtinguda damunt uns *portas*, per realitzar una valoració *in situ* en tinció ràpida (ex. Diff-Quik) per part de l'equip de citopatologia, i l'altra meitat de la mostra es guarda per a estudi posterior (ex. tinció Papanicolaou).

En mans d'un ecoendoscopista experimentat, el rendiment diagnòstic descrit pot arribar a ser del 90-95 % en adenopaties i tumors pancreàtics, sobre tot si el citopatòleg es troba present a la sala d'exploració i dictamina la viabilitat de la mostra. La tècnica de la USE-PAAF és segura, i s'ha descrit un percentatge global de complicacions baix (< 2%), habitualment en forma de sagnat (1,3%), pancreatitis (<2%) o infeccions, sense risc vital per el pacient (9). Per disminuir el risc d'hemorràgia, existeixen unes recomanacions internacionals específiques segons la ASGE, en les quals es recomana, substituir els anticoagulants orals per heparina de baix pes molecular, i suspendre solament antiagregants plaquetaris del tipus clopidogrel o ticlopidina 7 dies abans de la prova, sobretot en lesions de natura quística (10). La profilaxi antibiòtica es recomana en pacients amb risc d'endocarditis infecciosa i

si la lesió a puncionar és quística o de localització perirrectal. A més, en lesions quístiques s'aconsella realitzar una aspiració total del líquid per reduir al màxim el risc hipotètic d'infecció.

La sembra de cèl·lules tumorals en el trajecte de punció guiat per USE s'ha descrit només en casos puntuals (11, 12). Encara que és un fet poc freqüent i el risc de disseminació és menor respecte a puncions percutànies, en casos de tumors pancreàtics localitzats a cap i cos, s'ha d'intentar realitzar la punció via transduodenal ja que el trajecte de l'agulla s'extirparia en una eventual intervenció quirúrgica. Per altra banda no s'ha de puncionar a través d'un teixit tumoral (ex. ganglis peritumorals) pel risc significatiu de fals positiu.

Les limitacions més importants seran les estenosis del tub digestiu (benignes o malignes) o canvis anatòmics post-quirúrgics, que no permetin accedir o apropar-se a la lesió a estudiar.

2. Colangiopancreatografia endosonogràfica (CPES)

La CPRE és el procediment d'elecció pel drenatge de la via biliar o del conducte pancreàtic obstruïts. Però, fins a un 10-15 %, aquest drenatge transpapilar pot ser fallit. Un percentatge creixent d'aquests casos, són papil·les inaccessibles després d'intervencions quirúrgiques (ex. cirurgia de l'obesitat mòrbida, Y de roux) o per estenosis del tub digestiu. Els casos de cannulació fallida solen ser deguts a papil·les peri o intradiverticulars, infiltració tumorals de l'àrea ampul·lar, estenosis infranquejables dels conductes distals o litiasis impactades.

Davant d'aquesta situació, en que el drenatge transpapil·lar no és possible, els pacients habitualment són remesos a la unitat de radiologia intervencionista per realitzar un drenatge percutani o a cirurgia. Però aquestes dues alternatives s'associen a un percentatge significatiu de morbiditat (10-32% el drenatge percutani; 17-37% el drenatge quirúrgic) i mortalitat (2-5% la cirurgia) (13). En els darrers 10 anys, ha aparegut una nova tècnica per accedir i drenar els conductes biliars i pancreàtics mitjançant l'ecoendoscòpia. Utilitzant un ecoendoscopi lineal, es pot identificar els conductes biliar o pancreàtic dilatats i accedir-hi per punció guiada per USE en temps real. (13)

Després de la seva primera descripció a l'any 1996 com una colangiografia guiada per USE amb finalitat diagnòstica (14), l'any 2001 Giovannini et al. (15) va publicar el primer drenatge biliar guiat per USE. Des de llavors, ja s'han descrit a la literatura més de 200 casos de drenatges biliars i més de 80 casos de drenatges pancreàtics. La terminologia emprada ha sigut diversa, encara que a dia d'avui es tendeix a definir-la com Colangiopancreatografia anteròg rada guiada per USE (*EUS-guided*

anterograde cholangiopancreatography, **EACP**) o Colangiopancreatigrafia endosonogràfica (*Endosonography-guided cholangiopancreatography,* **ESCP**) (16,17).

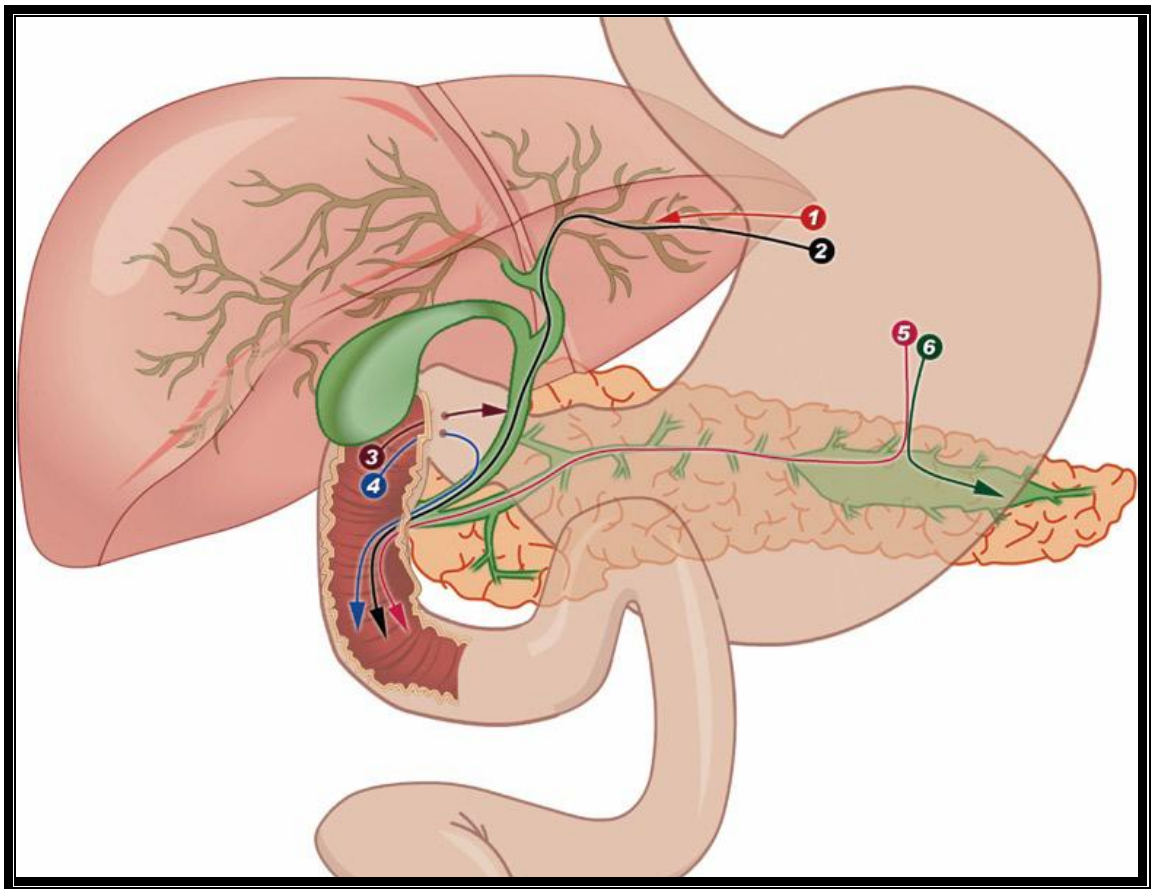
Existeixen 9 possibles variants de la tècnica, fruit de la combinació de 3 rutes i 3 tipus de drenatge. (figura 2). Les rutes d'accés són: intrahepática, extrahepàtica i pancreàtica. El drenatges poden ser: transmural, transpapil·lar o sobre una guia intraductal (Retròg rada per *Rendezvous* o anteròg rada). Les anastomosis endosonogràfiques més comunes s'anomenen coledocoduodenostomia, hepaticogastrostomia i pancreaticogastrostomia.

Els resultats dels estudis publicats demostren un èxit clínic del 75-100% en els drenatges biliars, i del 25-75% en els drenatges pancreàtics. El percentatge de complicacions és del 10-36% en els biliars (fuites biliars, coleperitoneu, peritonitis, perforació, pneumoperitoni, hemorràgia, colangitis) i del 40% en les pancreàtiques (pancreatitis severa, perforació, hemorràgia) (13,17).

Per tant, encara que el seu futur és esperançador, a dia d'avui presenta una sèrie de limitacions com és un èxit clínic al voltant del 75%, i un % de complicacions greus del 20-30%. Per altra banda, encara no disposem d'un material específic dissenyat per ser visible per imatge USE i manejable amb l'ecoendoscopi.

Figura 2. Les 3 potencials rutes d'accés de la tècnica CPES: intrahepàtiques (1, 2), extrahepàtiques (3, 4) i pancreàtiques (5, 6).

Després de realitzar-se l'accés per qualsevol de les rutes definides, el drenatge pot ser transmural sobre una guia intraductal prèviament col·locada per CPES (1,3,6) *via* hepaticogastrostomia (1), coledocoduodenostomia (3) o pancreaticogastrostomia (6). Per altra banda, la col·locació o avançament per CPES d'una guia transpapil·lar (2,4,5), permet accedir via rendezvous (i prosseguir per CPRE) o també de forma anteròg rada amb la col·locació d'una pròtesi biliar (2,4) o pancreàtica (5). La tècnica rendezvous requereix l'existència d'una papil·la accessible i és preferible en patologia benigna. La via anteròg rada transpapil·lar, és una opció en anatomies post-quirúrgiques, sobre tot en casos de drenatges biliars pal·liatius.



Adaptada de Perez-Miranda M, et al. (17).

3. Antecedents actuals del tema

3.1Tumors neuroendocrins (TNE)

Els TNE de pàncrees son infreqüents, ocupant només el 1-5% del total de tumors malignes de la glàndula pancreàtica (18). Així i tot, la seva incidència ha anat augmentant fins a un 1-1,5/100.000 en les últimes 2 dècades (19). Deriven del sistema cel·lular endocrí difús i contenen grànuls electrodensos amb hormones, cromogranines, sinaptofisina i altres (18, 20). Són un tipus de tumor heterogeni en quant al seu comportament biològic i al seu pronòstic, diferent respecte a l'adenocarcinoma pancreàtic (21, 22). La OMS classifica els TNE en ben diferenciats de probable comportament benigna, ben diferenciat de comportament incert, carcinoma ben diferenciat, i carcinoma indiferenciat (23).

Des d'un punt de vista clínic, es classifiquen en no funcionants i funcionants. El diagnòstic clínic dels funcionants és relativament fàcil, ja que presenten una clínica o síndromes (Zollinger-Ellison en gastrinomes, hipoglicèmies en insulinomes, eritema necrolític migratori en glucagonomes) relacionades amb les hormones secretades (insulina, gastrina, polipèptid pancreàtic, pèptid intestinal vasoactiu, somatostatina) pels tumors. Per altra banda, els no funcionants solen ser els més freqüents, i poden presentar lesions a distància. La clínica dels no funcionants inclou, al igual que la resta de tumoracions pancreàtiques, dolor abdominal, icterícia, hemorràgia o obstrucció digestiva alta. A més, amb la millora de la qualitat de les proves d'imatge i programes de *screening*, la troballa accidental de TNE no funcionant ha fet augmentar la seva incidència en pacients asimptomàtics. En general, el diagnòstic dels TNE requerirà una anamnesis detallada, exploració física,

estudis analítics generals i específics, proves d'imatge i la presa de mostres (24).

Els TNE poden ser esporàdics, o associats a síndromes genètics com la Neoplàsia Endocrina Múltiple tipus I (MEN I), la malaltia de von Hippel-Lindau i de von Recklinghausen (25).

La imatge habitual de un TNE pancreàtic, és una lesió tumoral sòlida, ben definida i hipervascular. Altres signes com àrees quístiques, calcificacions, i necrosis s'han descrit en tumors de mida gran (26).

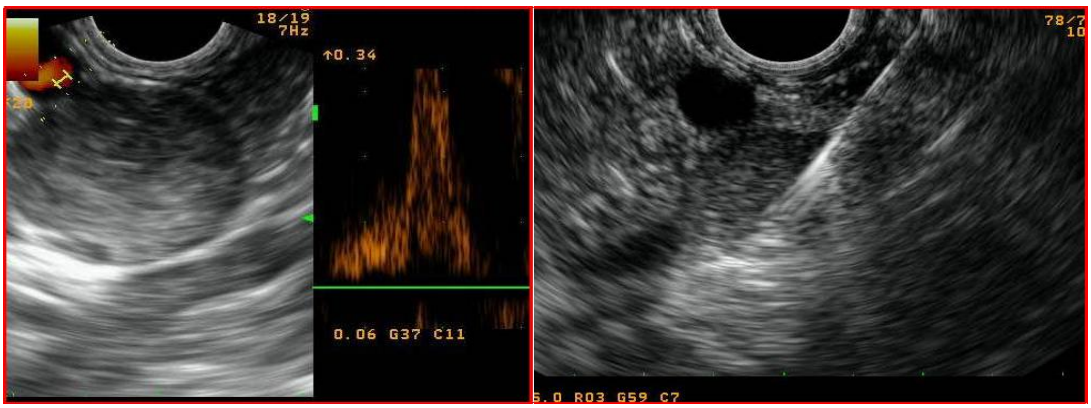
En l'estudi anatomopatològic, els TNE presenten unes característiques citològiques concretes, però a vegades no són tan clares i s'ha de plantejar un diagnòstic diferencial amb altres entitats com una pancreatitis crònica amb hiperplàsia neuroendocrina, adenocarcinoma ductal, tumor sòlid pseudopapilar, carcinoma de cèl·lula acinar o pancreatoblastoma. (27).

Les proves d'imatge que s'utilitzen en la detecció dels TNEs són la TCMD, la RM, la ecografia abdominal i el rastreig de receptors de somatostatina. La més habitual i primera en sol·licitar-se és la TC. La USE, que es considera una prova 'invasiva ' i que requereix sedació profunda, sol ser una prova complementària en conjunció amb altres proves. En casos de sospita clínica de TNE funcionant, precisar la localització exacta en la glàndula pancreàtica pot ser difícil amb les proves d'imatge habituals. La USE és una de les tècniques diagnòstiques capaç de diagnosticar tumors menors de 1 cm (fins a 3 mm), localitzats a cap i cos pancreàtic amb una sensibilitat major del 90 % (28, 29). A part, permet realitzar una PAAF guiada dels TNE, obtenint material per citologia i/o histologia, amb una rendibilitat propera al 90% en els TNE (28) segons una sèrie recent (28). A més, en les mostres obtingudes es pot realitzar

immunocitoquímica o inmunohistoquímica per determinar cromogranina, sinaptofisina, citoqueratina 19, i altres hormones o pèptids, amb un diagnòstic confirmatori de TNE proper al 95% (29, 30). Els TNE són un tipus de lesió poc freqüent. Per aquest motiu l'experiència descrita en USE-PAAF i TNE fins a l'actualitat és limitada, i en forma de sèrie de casos.

Les figures 3,4 i 5 mostren la USE-PAAF d'un tumor sòlid a cua pancreàtica diagnosticat de TNE per l'estudi citològic (fig.4) i immunocitoquímic (fig.5).

Figura 3: Imatge USE lineal de tumoració sòlida hipoecoica a regió de cua pancreàtica (esquerra) que contacta amb l'arteria esplènica; i punció guiada amb agulla fina.



Imatges de l'autor i publicadas, JB.Gornals et al. Rev Esp Enferm Dig. 2011(estudi 1 de la Tesi)

Figura 4: (Papanicolaou,x 400): grup de cèl·lules cohesives i no cohesives amb nucli rodó, citoplasma fràgil i formació de rosetes.

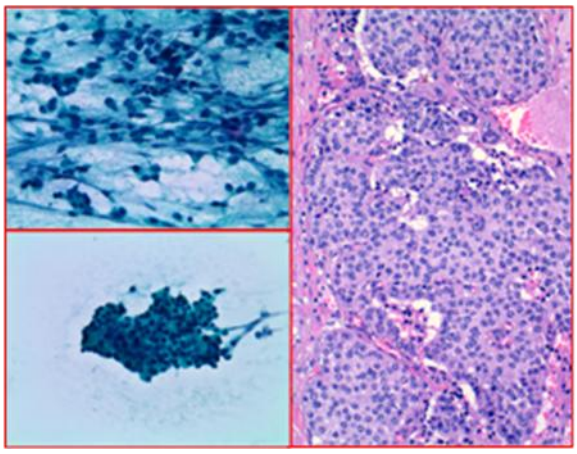
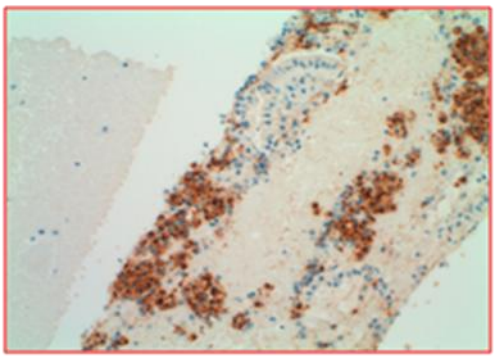


Figura 5: (H&E, x400): cèl·lules neuroendocrines en forma de nius sòlids.



Cortesia de la Dra. Isabel Català, Anatomia Patològica, Hospital Universitari de Bellvitge.

3.2 Drenatge de col·leccions pancreàtiques guiat per USE

En els darrers anys 10-12 anys, s'han publicat experiències de sèries de casos fent referència al seu potencial terapèutic com són el drenatge de col·leccions properes al tub digestiu, teràpia vascular o drenatge biliopancreàtic guiat per USE en cas de CPRE fallida o papil·les duodenals no accessibles. Aquestes experiències són limitades, i el material emprat prové del camp de la CPRE.

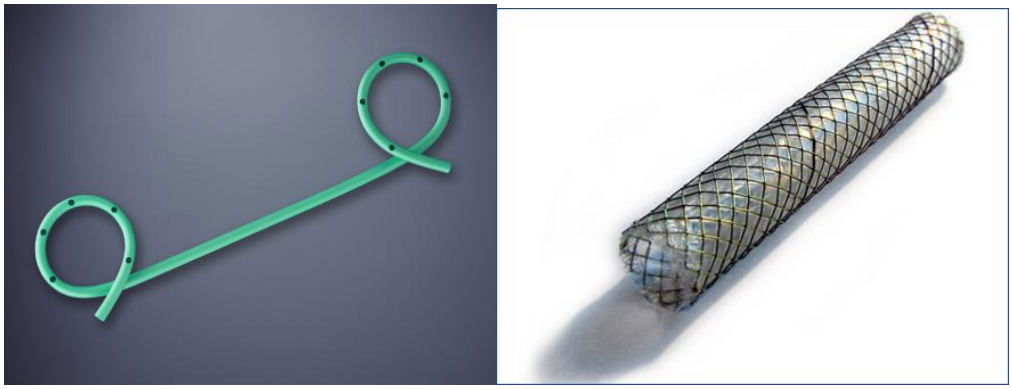
En l'actualitat, el drenatge de col·leccions pancreàtiques guiat per USE s'ha convertit en una primera opció, envers d'altres opcions terapèutiques associades a una major morbiditat, com la cirurgia o la percutània (31, 32). La USE permet descriure de forma acurada el gruix de la paret, l'existència de vasos interposats i ajudar a escollir el punt òptim d'accés a la col·lecció. A més, fa possible la pràctica d'un drenatge transmural en casos de no existir una imatge endoscòpica de compressió luminal o d'hipertensió portal amb vasos col·laterals (33). L'èxit, complicacions, i mortalitat descrits en el drenatge de col·leccions pancreàtiques guiat per USE és de 87-97%, 6-34% i 0-1% respectivament. L'hemorràgia i el pneumoperitoni són les complicacions majors descrites (32,34); i està reportat un 17% de complicacions relacionades amb les pròtesis. La migració o l'oclusió d'una pròtesi plàstica està reflectit en varies publicacions, comportant una recurrència clínica, generalment associada a infecció i inclús algun cas de perforació (32, 34, 35).

Revisant la literatura, no existeix un consens clar respecte al número i tipus de pròtesis que s'haurien d'emprar. Des de que es va associar les pròtesi plàstiques rectes a un percentatge superior de complicacions, s'ha establert entre els endoscopistes intervencionistes una preferència a col·locar 1 o més

pròtesis doble *pigtail* (34). Però l'eficàcia d'aquests tipus de pròtesis plàstiques desperta controvèrsies, degut al seu diàmetre intern reduït (màxim de 10 Fr.=3.3mm), si es compara amb les pròtesis biliars metàl·liques autoexpandibles (SEMS) (ex. 10mm). Només en 3 sèries de casos s'ha descrit la utilització de pròtesis metàl·liques parcial o totalment cobertes en el drenatge de col·leccions (36-38). En aquesta experiència també es descriuen una sèrie de limitacions: el seu disseny tubular està pensat en ser col·locat a conductes (ex. via biliar); la falta d'ancoratge entre col·lecció i paret del tracte digestiu presenta un alt risc de fuita de líquids a cavitat peritoneal; existeix un risc de migració tant a l'interior de la cavitat com a la llum gastrointestinal (32, 36); i els seus extrems metàl·lics poden causar lesions, comportant complicacions sèries com sagnat o perforació (figura 6).

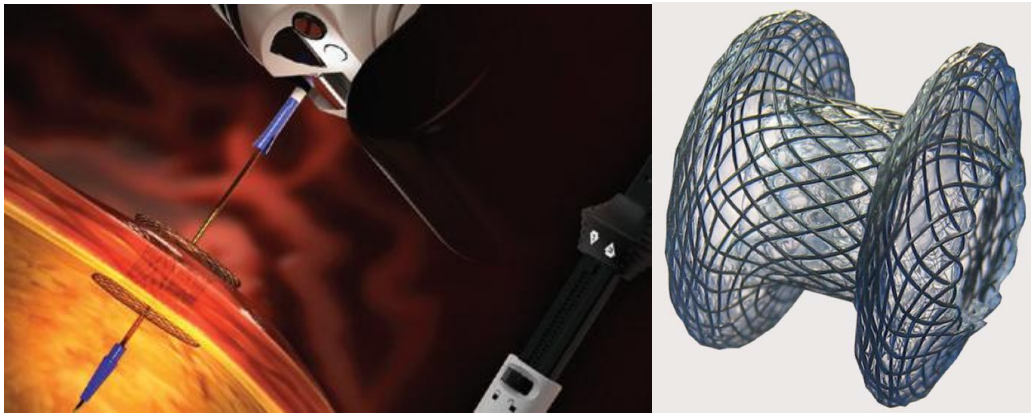
El disseny d'una pròtesi metàl·lica autoexpandible amb morfologia *'diàbolo'* permetria prevenir migracions i evitar la fuita de líquids, oferint un drenatge major que les plàstiques i, alhora, amb un menor nombre de complicacions que les metàl·liques estàndard (figura 7). Recentment, Itoi i col. han descrit una primera experiència clínica amb aquest nou tipus de pròtesis en drenatges guiats per USE de pseudoquists pancreàtics i vesícules biliars (39). Anteriorment, Binmoeller va publicar una primera experiència amb animals, utilitzant aquest nou model dissenyat de forma específica per drenatges de col·leccions adherides o no adherides a la paret del tracte digestiu (39, 40). En aquesta Tesi es descriu la nostra experiència amb aquest tipus de pròtesi en el drenatge de col·leccions pancreàtiques, en termes de seguretat i reproductibilitat, i es compara amb una sèrie prèvia de drenatges transmurals amb pròtesi plàstiques del nostre centre.

Figura 6: pròtesi plàstica doble pigtail (esquerra); i pròtesi metàl·lica autoexpandible (SEMS) totalment coberta.



Adaptació de URL: http://www.bostonscientific.com/global-endoscopy/product-image (pàgina consultada al desembre 2012)

Figura 7: AXIOS™, pròtesi metàl·lica autoexpandible totalment coberta de disseny 'diàbolo', específica per drenatges transmurals**.**



Adaptació de Xlumena. URL: http://www.xlumena.com/international/home_nonus.html (pàgina consultada al desembre del 2012)

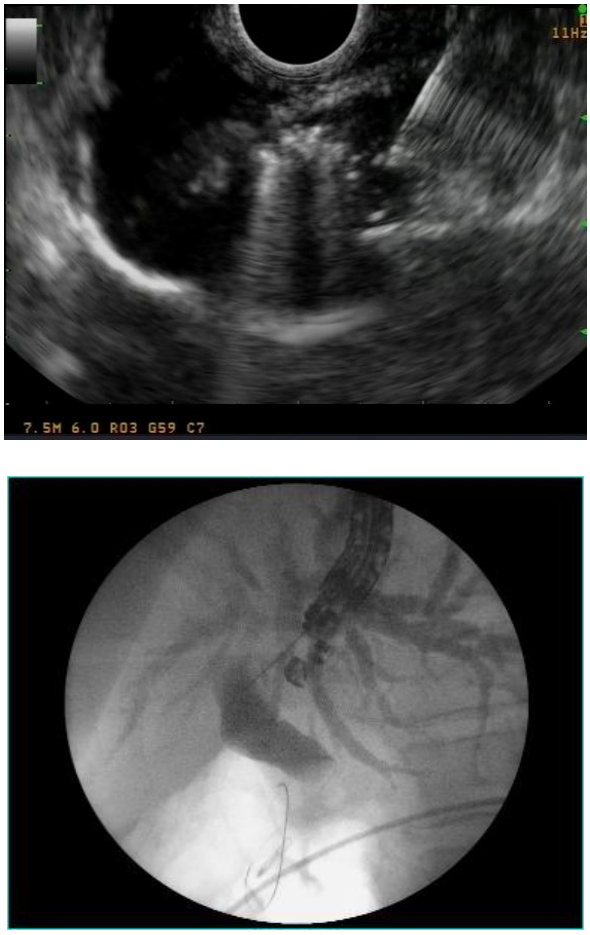
3.3 Combinació de la USE i la CPRE en una sola sessió

L'experiència clínica de combinar dos tècniques d'endoscòpia avançada, USE+/-PAAF i CPRE en una sola sessió, es troba poc descrita en la literatura i no és habitual a la rutina assistencial. En canvi, si és freqüent que ambdues tècniques siguin requerides alhora en el maneig de pacients afectes d'una patologia biliopancreàtica benigna o maligna, i es programin i realitzin en 2 procediments separats per diversos factors (41). La USE és una tècnica segura i útil en l'avaluació de malalties biliopancreàtiques, especialment per la seva elevada sensibilitat en la detecció de coledocolitiasis de mida petita, o de tumors pancreàtics de reduïda mida, oferint a la vegada un estudi d'extensió (ex. afectació vascular) i una obtenció de mostra citològica mitjançant una PAAF guiada (42, 43). La CPRE, en l'actualitat hauria de participar en el drenatge biliar amb un paper terapèutic, amb o sense col·locació de pròtesis.

En casos que la canul·lació transpapil·lar via CPRE fos fallida o no possible, una intervenció guiada per USE permetria accedir a la via biliar tal com es va descriure per primera vegada al 1996, aprofitant així el seu potencial terapèutic (44). Per tant, combinar les 2 tècniques en una sola sessió, ofereix l'avantatge de sumar el potencial d'ambdues modalitats, oferint a la vegada un diagnòstic acurat i enfortint l'aportació terapèutica del drenatge endoscòpic intervencionista (45). A pesar de l'existència teòrica d'aquesta avantatge d'una estratègia combinada envers a separada, la seva pràctica clínica es troba poc descrita a la literatura en una sèrie limitada de publicacions (46-55) (taula 1). L'aplicació d'aquesta estratègia a la rutina assistencial diària no ha de ser fàcil, per l'existència d'obstacles logístics, i el plantejament de varis dubtes com: un

possible increment del percentatge de complicacions; quin procediment hauria de ser el primer; qui o quin nombre (1 o 2) d'endoscopistes és l'ideal; si la col·locació d'una pròtesi biliar prèvia distorsionaria la imatge USE; si és una estratègia cost-efectiva i ofereix una qualitat assistencial; o si davant un drenatge fallit per CPRE, s'ha d'intentar un accés biliar guiat per USE. A dia d'avui, no existeix una evidència clínica suficient per respondre aquestes qüestions.

Figura 8: accés biliar per punció transduodenal guiada per USE de la via biliar extrahepàtica (esquerra); fluoroscòpia del colangiograma obtingut per USE (CPES), i pas d'una guia via anterògrada transpapil·lar a segona porció duodenal.



Imatges de l'autor. JB. Gornals, Unitat Endoscòpia Digestiva, Hospital Universitari de Bellvitge.

Taula 1: Resum dels principals treballs descrits a la literatura sobre els procediments combinats de USE-CPRE.

Author year (n)	Combined procedures (EUS FNA)	Study	Pathology	FNA Accuracy (%)	ERCP details	Duration (min.)	Complications
Liu 2005	70(-)	Prospective randomized	Benign (acute biliary pancreatitis)	NA	14% of unsuccessful BD cannulation	-	7% (SSG)
Rocca 2006	19 (-)	Observational	Benign	NA	94% BD cannulation rate (successful in 15 of 16)	27(22-36)	None
Tarantino 2007	72 (25)	Prospective observational	Malignant and benign (76-24%)	92	'All ERCP completed' (1 precut)	58.6±9 (30-91)	8% 2 mild bleeding
Ross 2008	114 (87)	Retrospective	Malignant and benign (70-30%)	87.8	84% B stent placement (in 96 patients) 51 sphincterotomies	73.6±30 (25-148)	10.5% 6 pancreatitis
Fabbri 2009	40(-)	Prospective randomized	Benign (choledocholi-thiasis)	NA	96% (24/25) BD cannulation	59.3±8.9 (45-90)	1 mild pancrea titis
Ascunce 2010	35 (28)	Prospective observational	Malignant and benign (80/20%)	96	97.1% BD cannulation rate 5 precut 82.9 % stents deployed (29 patients)	83.7	2% 1 bleeding
Vila 2011	39 (19)	Comparative retrospective	Malignant and benign (55-45%)	90.6	-	93±32.78	5% (SSG) 1 pancreatitis, 1 bleeding
Aslanian 2011	29 (24)	Comparative retrospective	Malignant	92	72% B stent placement	75 (60-90)	3.4% (SSG) 1 bleeding
Iles-Shih 2012	206 (110)	Retrospective	Malignant and benign (70-25%)	-	-	56±2.1 58±1.8	1 immediate AE 20 long-term AE (9%)

AE: adverse event; B: biliary; BD; biliary duct; NA: not applicable; SSG: single session group.

Taula publicada a JB. Gornals et al. Digestive and Liver Disease 2013 (material suplementari, TableS3 disponible online a http://dx.doi.org/10.1016/j.dld.2013.01.023, estudi 3 de la Tesi*)*

II. SITUACIÓ ACTUAL

JUSTIFICACIÓ DE LA TESI

II. SITUACIÓ ACTUAL I JUSTIFICACIÓ DE LA TESI

L'evolució de l'endoscòpia en els darrers temps està sent molt important sobretot per les aportacions de les diferents innovacions tecnològiques que han anat apareixent. L'ecoendoscòpia digestiva està inclosa dins la denominada endoscòpia d'alta complexitat, degut a la seva corba d'aprenentatge i el seu potencial intervencionista. Revisant l'evolució històrica de la tècnica, ha passat de tenir només una funció diagnòstica per la imatge en si, a tenir una indicació diagnòstica-intervencionista gràcies a la possibilitat d'obtenir mostres per punció guiada per USE. En els darrers anys, s'han publicat experiències de sèries de casos fent referència al seu potencial terapèutic com són el drenatge de col·leccions annexes al tub digestiu, la terapèutica vascular o el drenatge biliopancreàtic guiats per USE. Aquestes experiències són limitades, i el material emprat prové del camp de la CPRE.

La pràctica de la USE-PAAF sí que es troba àmpliament descrita i publicada englobant varis tipus d'entitats patològiques i de dianes. Així i tot, en algunes tipus de lesions, com els tumors neuroendocrins, aquestes experiències són més limitades.

En el cas dels drenatges transmurals la gairebé totalitat de les sèries publicades, han utilitzat pròtesis plàstiques doble *pigtail*, les quals presenten un diàmetre limitat i una morfologia tubular que s'associen a major risc d'obstrucció i migració.

I per altra banda, la USE i la CPRE mantenen una relació estreta al compartir gran part de les indicacions de la patologia biliopancreàtica com és el cas de l'estudi de la icterícia obstructiva per tumoració pancreàtica o

peripapil·lar; en riscs intermitjos de coledocolitiasis o altres entitats de la via biliar. Aquests procediments, una vegada es troben indicats en un mateix pacient, es realitzen separats en diferents dies de forma rutinària degut a les pròpies limitacions logístiques de les tècniques (2 sales diferents, necessitat de sala amb fluoroscòpia, no disponibilitat d'un endoscopista que domini les 2 tècniques, dificultat de la programació) i la poca experiència publicada de la combinació de les 2 tècniques en un mateix procediment.

Justificació dels estudis realitzats:

- Els resultats dels estudis inclosos en aquesta Tesi aporten una informació addicional del paper de la USE-PAAF en l'estudi diagnòstic dels tumors neuroendocrins, confirmant que l'estudi immunocitoquímic necessari per el diagnòstic definitiu dels TNE és possible amb la PAAF.

- En el camp terapèutic, es descriu l'experiència inicial i pionera amb una nova pròtesi metàl·lica autoexpandible de disseny 'diàbolo' d'aposició luminal (AXIOS™) juntament amb un nou sistema d'accés (NAVIX™) en el drenatge transmural de col·leccions annexes al tub digestiu. Aquesta experiència es compara amb un grup de casos previs drenats amb pròtesi plàstiques doble *pigtail*. Els resultats d'aquest estudi aporten informació rellevant sobre la innovació tecnològica en el camp del drenatge transmural mitjançant l'ecoendoscòpia intervencionista i terapèutica.

- El domini de les 2 tècniques (USE i CPRE) per part del doctorand, ha permès portar a terme el projecte de combinar-les en un sol procediment en els casos de patologia biliopancreàtica que comparteixen indicació. En aquest darrer estudi, s'han revisat els aspectes clínics, tècnics i econòmics dels procediments combinats realitzats. Pensem que els resultats derivats d'aquest estudi aporten una informació rellevant que ajuden a aclarir els potencials beneficis de l'estratègia de combinar les 2 tècniques.

III.HIPÒTESI

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Les hipòtesis de les quals partíem per la realització d'aquesta Tesi eren les següents:

1. La punció amb agulla fina guiada per USE és útil per la obtenció d'una mostra òptima per realitzar estudi immunohistoquímic, necessari per el diagnòstic definitiu dels tumors neuroendocrins (ESTUDI 1).

2. La utilització de les noves pròtesis metàl·liques autoexpandibles de disseny 'diàbolo', permeten realitzar un drenatge transmural eficaç i segur de col·leccions pancreàtiques al tub digestiu (ESTUDI 2).

3. La combinació de la USE i la CPRE és segura i comporta uns beneficis clínics i econòmics, sense alterar el rendiment d'ambdós procediments per separat (ESTUDI 3).

IV. OBJECTIUS

IV. OBJECTIUS

Els objectius d'aquesta tesi doctoral han sigut:

Estudi 1: avaluar la utilitat clínica i **rendiment diagnòstic de la USE-PAAF** en el diagnòstic diferencial i confirmació dels **tumors neuroendocrins.**

Estudi 2: avaluar **l'eficàcia i seguretat** clínica d'una nova **pròtesis metàl·lica** coberta **d'aproximació luminal** (AXIOS™) en el **drenatge guiat per USE de col·leccions pancreàtiques** amb o sense necrosis.

Estudi 3: avaluar els resultats clínics i costos econòmics de **combinar l'ecoendoscòpia i la colangiografia retrògrada endoscòpica** en un mateix procediment en la patologia biliopancreàtica.

V. MÈTODES I RESULTATS. PUBLICACIONS

V. MÈTODES I RESULTATS. PUBLICACIONS

Els resultats dels estudis que constitueixen la base de la present tesi doctoral s'han recollit en les següents publicacions:

ESTUDI 1

Estudi per avaluar la utilitat clínica de la PAAF guiada per ultrasonografia endoscòpica en el diagnòstic de tumors neuroendocrins

Gornals J, Varas M, Catalá I, Maisterra S, Pons C, Bargalló D, Serrano T, Fabregat J. *Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography.* **Rev Esp Enferm Dig 2011; 103: 123-8.** (Factor d'impacte: 1,548)

ESTUDI 2

Estudi per avaluar el drenatge de col·leccions pancreàtiques guiat per ecoendoscòpia mitjançant una pròtesis metàl·lica d'aproximació luminal

Gornals JB, De la Serna-Higuera C, Sanchez-Yague A, Loras C, Sanchez-Cantos A, Perez-Miranda M. *Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent*. **Surgical Endoscopy 2012, dec 12 (Epub ahead of print).** (Factor d'impacte: 4,013)

Cas clínic directament relacionat en l'estudi i anterior publicació:

Gornals JB, Loras C, Mast R, Botargues J, Busquets J, Castellote J**.** *EUS-guided transesophageal drainage of a mediastinal pancreatic pseudocyst using a novel lumen apposing metal stent*. **Endoscopy 2012; 44: E1-E2.** (Factor d'impacte: 6,096)

ESTUDI 3

Estudi per avaluar la combinació de l'ecoendoscòpia i colangiografia retrògrada endoscòpica en un mateix procediment en patologia biliopancreàtica: impacte clínic i econòmic.

Gornals JB, Moreno R, Castellote J, Loras C, Barranco R, Catala I, Xiol X, Fabregat J, Corbella X. *Single-session endosonography and endoscopic retrograde cholangiopancreatography for biliopancreatic diseases is feasible, effective and cost beneficial*. **Digestive and Liver Disease (2013)**. http://dx.doi.org/10.1016/j.dld.2013.01.023 (Factor d'impacte: 3,054)

ESTUDI 1

Gornals J, Varas M, Catalá I, Maisterra S, Pons C, Bargalló D, Serrano T, Fabregat J. *Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography.* Rev Esp Enferm Dig 2011;103: 123-8.

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ORIGINAL PAPERS

Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography

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ABSTRACT

Background: the detection and diagnosis of neuroendocrine tumors (NETs) is challenging. Endoscopic ultrasonography (EUS) has a significant role in the detection of NETs suspected from clinical manifestations or imaging techniques, as well as in their precise localization and cytological confirmation using EUS-Fine-needle aspiration-puncture (FNA).

Objective: to assess the usefulness and precision of EUS-FNA in the differential diagnosis and confirmation of NETs, in a retrospective review of our experience.

Patients and methods: in a total of 55 patients with suspected NETs who underwent radial or sectorial EUS, 42 tumors were detected in 40 cases. EUS-FNA using a 22G needle was performed for 16 cases with suspected functional (hormonal disorders: 6 cases) and non-functional NETs (10 cases). Ki 67 or immunocytochemistry (ICC) testing was performed for all.

There was confirmation in 9 cases (5 female and 4 male) with a mean age of 51 years (range: 41-81 years).

All tumors were located in the pancreas except for one in the mediastinum and one in the rectum, with a mean size of 19 mm (range: 10-40 mm).

Results: there were no complications attributable to FNA. Sensitivity was 100% and both precision and PPV were 89%, as a false positive result suggested a diagnosis with NET during cytology that surgery finally revealed to be a pancreatic pseudopapillary solid tumor.

Conclusions: EUS-FNA with a 22G needle for NETs has high sensitivity and PPV at cytological confirmation with few complications.

Key words: Fine-needle aspiration-puncture (FNA) guided by endoscopic ultrasonography (EUS) or echoendoscopy. Neuroendocrine tumors (NETs). Pancreatic endocrine tumors (PETs). Immunocytochemistry. Immunohistochemistry. Chromogranin. Synaptophysin. Cytokeratin 19. Vimentin. Ki 67. CD56.

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Gornals Joan, Varas Modesto, Catalá Isabel, Maisterra Sandra, Pons Carlos, Bargalló Domingo, Serrano Teresa, Fabregat Joan. Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography. Rev Esp Enferm Dig 2011; 103: 123-128.

INTRODUCTION

The preoperative diagnosis and precise localization of neuroendocrine tumors (NETs), particularly pancreatic NETs (PNETs), is challenging, and vital for a definitive cure of patients (1). For non-functioning cases, confirmation by histology is most necessary because of potential differential diagnoses. PNETs share histological properties with carcinoids: both are considered to derive from the diffuse endocrine cell system; they unusually exhibit mitotic features (assessable using the Ki-67 index); they usually show electrodense granules that contain hormones and various peptides, chromogranins (A, B, C), neuron-specific enolase (NSE), and synaptophysin (2,3).

PNETs are clinically classified as functional (Zollinger-Ellison syndrome, etc.) and non-functional. The clinical diagnosis of functional PNETs is relatively straightforward.

Most are benign (no metastases) and small, and may be associated with multiple endocrine neoplasia (MEN). Non-functional tumors are most common among PNETs, and have a high incidence of metastatic disease.

Their precise localization in the pancreas is difficult. Echoendoscopy or endoscopic ultrasonography (EUS) is a rather recently introduced diagnostic technique, and may diagnose tumors smaller than 1 cm (up to 3 mm) in the pancreas head and body with a sensitivity above 85% (93% in the larger series), whereas those in the tail are harder to assess (1).

EUS allows fine-needle aspiration-puncture (FNA) under ultrasound (US) guidance (4), and the collection of material for cytology and histology with a yield nearing 90%. In addition, immunocytochemistry (ICC) and immunohistochemistry (IHC) tests may be performed on obtained samples for chromogranin (C-A), synaptophysin, cytokeratin 19, and various hormones or peptides, with diagnoses that may reach 100% for cystic PNETs (5).

A recent classification proposed by WHO (2) assigned three categories to NETs: well-differentiated tumor, well-differentiated carcinoma, and poorly differentiated carcinoma based on histology, size (limit: 2 cm), and proliferation index (Ki-67 = 2%).

A TNM (tumor, node, and metastasis) classification has also been suggested for PNETs based on the WHO classification (3).

OBJECTIVE

To assess the usefulness and precision of EUS-FNA in the differential and confirmatory diagnosis of NETs using a retrospective review of our team's experience.

PATIENTS AND METHOD

For a total of 55 patients with suspected PNETs who underwent radial or sectorial EUS, 42 tumors were identified in 40 patients. Inclusion criteria for EUS-FNA: patients with presumed NET diagnosis with EUS, uncertain or non-functional.

For 16 cases (8 women and 8 men with a mean age of 56, range: 41-92 years with suspected functional (6 cases) and non-functional (10 cases) tumors, none of them cystic, EUS-FNA was performed using a 22 G needle (Echotip Ultra, Cook Medical) with conventional technique. All cases underwent Ki67 testing or immunocytochemistry for chromogranin, synaptophysin, and various hormones or peptides.

There was surgical confirmation (the gold standard) in 9 patients; in the remaining cases imaging techniques and 12-month follow-up (the gold standard) were used to reach a definitive diagnosis.

From all 16 patients 9 (5 women, 4 men) were selected with a mean age of 51 years (range: 41-81 years).

All tumors were in the pancreas, and one was in the mediastinum and one in the rectum, with a mean size of 19 mm (range: 10 to 40 mm) (Table I).

Regarding pancreatic tumors, three were in the head, two in the tail, and two in the body. Only two patients had metastases.

All examinations (EUS-FNA) were performed after collecting an informed consent, with prior coagulation testing, and using sedation (propofol) by an anesthetist.

A cytologist was in all cases present in the examination room where EUS-FNA procedures were carried out.

Diagnostic precision (P), sensitivity (S), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) were all analyzed using standard formulas.

RESULTS

There were no EUS-FNA-related complications (hemorrhage and perforation).

In the total series (16 cases) S was 100% with a Sp of 67%, P and PPV of 93 and 92%, respectively.

In patients with surgical confirmation (9 cases) sensitivity (S) was 100%, and precision (P) and PPV were 89%, as cytology yielded a false positive result that was eventually diagnosed as a solid pancreatic pseudopapillary tumor following surgical excision and tail pancreatectomy plus IHC.

DISCUSSION

EUS-FNA has been performed for PNETs for slightly over 10 years now. In earlier works both sensitivity and precision were low, with a specificity of 100% (6); however, they gradually increased, and sensitivity reached about 90% (94% in the most extensive series in the literature) (6-22) (Table II).

Our findings are consistent with those in the literature (S: 100%).

Typical EUS findings include homogeneous pancreatic nodules or lesions that are hypoechogenic, solid, hypervascular, and encapsulated with well-delimited borders (1,22,29), even non-functional ones (most of them) (22). NFPETs show the greatest sizes and are more advanced (Fig. 1).

The use of ICC techniques (chromogranin, synaptophysin, etc.) (cytokeratin 19) (23) considerably improves sensitivity on cytology material (Fig. 2).

The Ki 67 index (24-26) and microsatellite instability have also been assessed in samples (27,28) to establish the benign or malignant nature of tumors, and hence their prognosis.

Algorithms are similar for PNETs and pancreatic cancers (PCs) (4,29) (Fig. 3).

When a tumor is resectable according to computed tomography plus EUS, and both clinical and morphological features are consistent, laparoscopic or open surgery may be readily performed. For uncertain or non-functioning tumors EUS-FNA may be used to confirm diagnostic suspicion.

Sometimes a histological differential diagnosis is difficult between pancreatic endocrine tumors, solid pseudopapillary tumor, acinar cell carcinomas, mucinous tumors, and lymphoma/plasmocytoma. In recent years various cases of solid pseudopapillary tumor have been described where ICC reached the right diagnosis on EUS-

Table I. Case report

N.°	*Age/Sex*	*Diagnosis*	*Size*	*FNA*	*ICC/IHC*
1	41/M	Insulinoma, nody-tail:	12-15 mm	FNA +	V + ICC
2	49/M	NF, head	23 x 25	FNA +	V + ICC
3	42/F	PET, tail (pseudopapillary)	12 x 14	FNA +	F + ICC e IHC
4	46/M	PET, tail (Ki 67:10%)	13 x 14	FNA +	V +ICC
5	45/M	I-G, head	40 mm. B	FNA +	V +
6	50/F	Insulinoma, head-body	5.5 x 10.2	FNA +	V +
7	48/M	MEN-1/Uncinate-tail	20 mm	FNA +	V + ICC + Gastro-duodenal < 10 mm: Biopsias + e ICC Ki 67 < 5% Non-op.
8	79/M	NF, head (CT: casual)	12 by 16	FNA +	V + ICQ. No Op.
9	41/F	NF, body (NFM on CT)	12 by 14	FNA +	V + ICQ
10	75/F	Mediastinal (PC) Ki 67 8%	66-70 B	FNA +	V + ICC. Non-op.
11	68/F	Mediastinal (PC)	12-16	FNA +	V + IHC. T4N2
12	81/F	Rectal carcinoid (41) (42)	30 mm B	FNA +	V + ICC
13	55/M	Pancreatic gastrinoma, head	<10 mm	FNA –	No Op.
14	47/F	NF PET US/CT: body	9 mm	FNA –	V – . No Op.
15	45/M	MEN-1/Retro/Ca-body 5-10-20-40		FNA +	V + ICC Gastro-duodenal C-A & serotonin + < 5 mm Non-op.
16	92/F	NF PET on CT, head	23-26 mm	FNA +	V + ICC. Non-op.

NF PET: Non-functional pancreatic endocrine tumor. PC: Pulmonary carcinoid. Non-op.: Non-operated
ICC/IHC:
1. C-A: Chromogranin +
2. Chromogranin +
3. Vimentin +
4. Ki 67 10%
5. Chromogranin, insulin & glucagon +
6. Insulin +
7. Ki 67 < 5%, chromogranin, synaptophysin & gastrin +
8. Synaptophysin, chromogranin, CD 56 & CAM 5-2 +
9. CD 56, synaptophysin & chromogranin +
10. Chromogranin +, Ki 67 8%
11. Chromogranin +
12. Chromogranin +
15. Chromogranin & serotonin +
16. Synaptophysin, CD56, chromogranin & CEA expression, & keratin 5D3.

Table II. Literature overview

Ciaccia 1998 (6)	19 c. TNEs	S: 84% ? 0% F + (Sp: 100%)
Voss 2000	15 c. in 99 patients (15%)	P: 46.7% NET vs. 81% Adenoca.
Gress 2002	1 c. Tattooed insulinoma	
Jhala 2002	9 c. citology & ICC +	S. 100% (2/2)
Ginès 2002	10 c. with 14 NETs	P: & S: 90% Sp: 100% 7 c. surgical confirmation
Santo 2002	76 c. (47 F)	P: 94% S: 96%
Ardengh 2004	30 c. with 33 NETs	P y S: 83% Sp: 85.7%
Gu 2005	30 c. IHC (C-A) + in all	100%
Chang 2006	9 c. FNA & ICC	89% (8/9)
Baker 2007-8	13 c./ 9 C with ICC (C-A & synaptophysin)	9/9 100%
Pais 2007	76 c. FNA	S: 86%
Jani 2008	41 c. in 4 a. FNA: 8% C, 15% F & 85% NF	
Chatzipantelis-08	48 c. (40/48 ICC: 83%)	83% 7% inadequate
Kongkam 2008	9 c. Qysctic (9%) FNA & ICC + C & S:	100%
Alsohaibani 2008	14 c. EUS: 100%	FNA: 90% (9/10)
Charfi 2009	6 c. Q with ICC + in all	100% (6/6)
Figueiredo 2009	86 c./ 77 c. (90%) FNA & ICC. 9% C & 14% F 100% (10c.)	
Piani 2008	18 c. FNA & Ki 67 < 2%: 89%	
Alesiev 2009	15 c. ICQ & Ki 67	
Chatzipantelis-09	35 c. Ki 67: prognosis marker	
Fasanella 2009 (28)	29 c. Microsatellites. FAL<0.2 benign	
Gornals 2010	16 c (9 with surgical confirmation) PPV: 89% S: 100% (9c.)	
Summary:	> 500 c	P: 81% S: 94% Sp: 95%

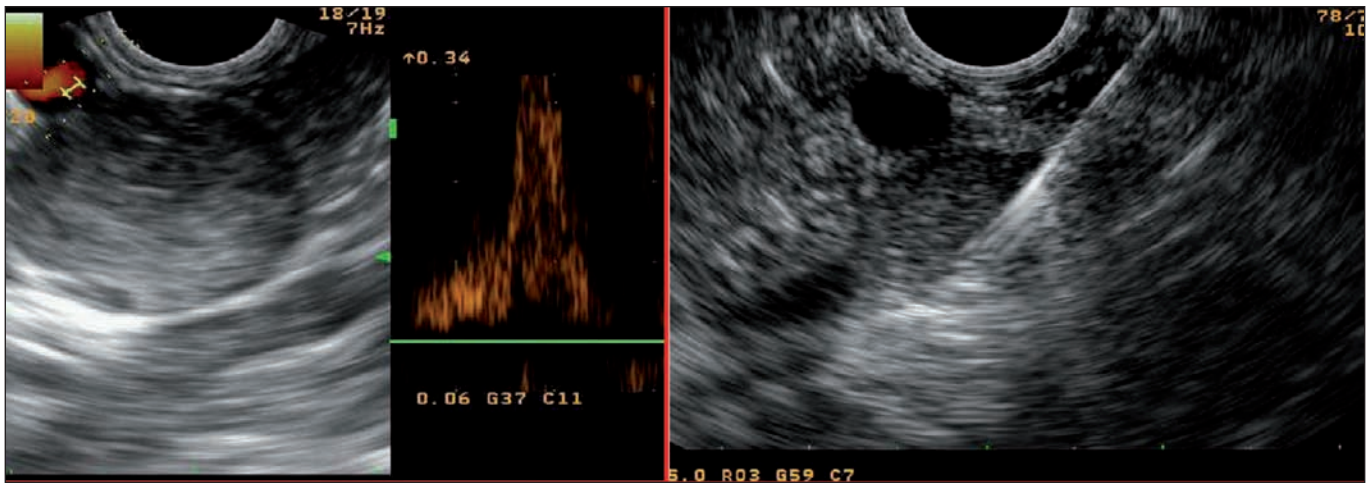

Fig. 1. Pancreatic EUS: PET and EUS-FNA.

FNA-collected samples (30-33): most were vimentin+ and cytokeratin+, whereas chomogranin and NSE were negative (they may be focally positive though) (34).

In this multicenter study in 28 patients with pseudopapillary tumors (34) a preoperative diagnosis was reached for 21 cases (75%); vimentin, alfa1-antitrypsin, CD10, and beta-catenin were positive in all cases, whereas chromogranin was positive in just 1/20 (5%) and synaptophysin in 10/17 (59%); however, the best marker to tell endocrine tumors from solid pseudopapillary tumors was E-cadherin/B-catenin/CD10 according to a recent study (35).

In our case with a solid pancreatic pseudopapillary tumor IHC was key for a definitive diagnosis. False positive results have been described in other series (12,18).

A recent Japanese study (36) reviewed 455 pancreatic FNA procedures: 28 were rare pancreatic tumors (no ductal adenocarcinomas). EUS-FNA with cytology, cell-block, and immunocytochemistry correctly diagnosed tumor type in 19 patients 19 (68%).

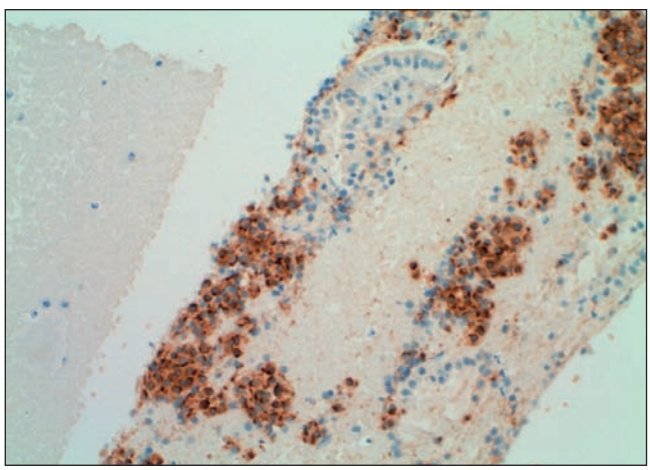

Fig. 2. ICC: chomogranin A+.

In differentiating benign from malignant tumors it had a sensitivity of 69%, a specificity of 100%, a PPV of 100%, a NPV of 79%, and a precision of 86%. None of the three malignant pancreatic endocrine tumors was diagnosed as such. EUS-FNA changed the presumed diagnosis in 11 cases (39%).

Four cases have been recently reported (37) where small (8-16 mm), non-functioning pancreatic endocrine tumors were found together with intraductal papillary mucinous neoplasms. PNETs remained undetected by common imaging techniques (CT and MRI); 3/4 were diagnosed using EUS, and only 1/3 using EUS-FNA.

To conclude, ICC on cytology samples collected by EUS-FNA is key for a definitive diagnosis of PNETs. Our study (S: 100%) (PPV: 89%) confirmed the findings in the literature (mean sensitivity of 94%, mean specificity of 95%) (Table II).

Notwithstanding, the diagnostic panel is increasingly greater, and novel markers emerge including SERPINB8 (38), which is as sensitive as C-A and synaptophysin, or CDX-2, PDX-1, NESP-55 and TTF-1, which may help in the differential diagnosis between gastrointestinal and pulmonary carcinoids, and pancreatic endocrine tumors (39), with CK 19 being an independent prognostic factor for PNETs, particularly non-insulinomas according to a recent review (40). However, chromogranin and synaptophysin remain the key markers since many years ago (43) to this day (44).

Thus, believe that ICC is key for a definitive diagnosis of NETs (45), a statement not fully shared by other teams (44).

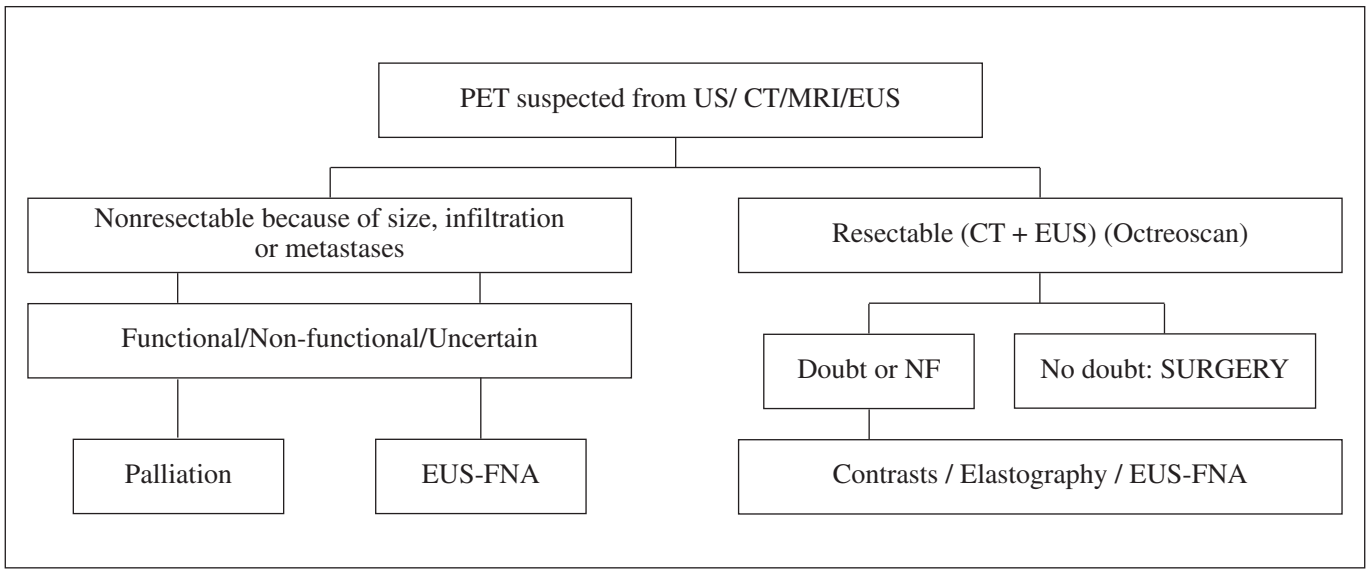

Fig. 3. Algorithm.

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ESTUDI 2

Gornals JB, De la Serna-Higuera C, Sanchez-Yague A, Loras C, Sanchez-Cantos A, Perez-Miranda M. *Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent*. Surgical Endoscopy 2012; dec 12 (Epub ahead of print).

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DYNAMIC MANUSCRIPT

Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent

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Abstract
Background The purpose of this study is to report our initial experience with a new fully covered metallic stent with a novel design (AXIOS) to prevent migration and fluid leakage, in the drainage of pancreatic fluid collections (PFC).
Methods We included nine patients from four Spanish centers undergoing endoscopic ultrasound (EUS)-guided drainage of PFC with placement of an AXIOS stent. The lesions were accessed via transgastric ($n = 7$), transesophageal ($n = 1$), and transduodenal ($n = 1$) by using a novel access device (NAVIX) in six cases or a 19-G needle in three. Patients were individually followed prospectively for procedure indications, demographic data, previous imaging techniques, technical aspects, clinical outcomes, complications, and follow-up after endoscopic drainage.
Results The mean size of lesions was 105 ± 26.3 mm (range, 70–150). In six cases, cystoscopy was performed through the stent, including necrosectomy in two. Median procedure time was 25 ± 13 min. A median number of two sessions were performed. The technical success rate was 88.8 % (8/9) due to one failure of the delivery system. One patient developed a tension pneumothorax immediately after transesophageal drainage. No migrations were reported, and all stents were removed easily. All patients had a successful treatment outcome achieving complete cyst resolution. Mean time to stent retrieval was 33 ± 40 days. Mean follow-up was 50 ± 1.3 weeks (range, 45–55), and only one patient presented a recurrence 4 weeks after the stent removal. Furthermore, comparison with ten previous consecutively recruited PFC cases drained by EUS-guided using plastic pigtail stents was done. Technical and clinical successes were similar. However, two stent migrations, two recurrences, and two complications were found. The number of stents used ($n = 15$) and the median procedure time (42.8 ± 3.1 min) were significantly higher.
Conclusions Drainage of PFC using dedicated devices as this novel metallic stent with special design seems to be an effective, feasible and safe alternative technique.

Keywords Pseudocyst · Transmural drainage · Endosonography · Pancreatobiliary · Endoscopy · Therapeutics

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In recent years, endosonography-guided drainage of pancreatic fluid collections (PFCs) has become an established procedure and a first choice of treatment in many centres,

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instead of other therapeutic options with higher morbidity rates, such as surgical and percutaneous drainage [1, 2].

Endoscopic ultrasound (EUS) has the ability to assess the wall thickness, avoid vessels, and find the closest area to access the lesion. Furthermore, it makes possible transmural drainage in those patients without luminal compression and patients with intervening vessels [3, 4]. The success, complication, and mortality rates for EUS-guided drainage of PFCs ranges from 87 to 97, 6 to 34, and 0 to 1 %, respectively. Bleeding, pneumoperitoneum and infection are the major complications described [1, 2, 5].

A stent-related complication rate of 17.7 % has been reported. The migration or occlusion of plastic stent is described in many series, developing symptomatic recurrence, generally with secondary infection [5, 6]. In a case series, a late double-pigtail stent migration was reported, resulting in small-bowel perforation that required surgery [3].

There is no clear consensus regarding the type and number of stents that should be used. Since it was discovered that straight stents can be associated with complications, endoscopists prefer the placement of one or more plastic double pigtails rather than straight stents [5]. Additionally, the efficacy of plastic stents remains controversial, due to their limited diameter compared with the large diameter of biliary self-expandable metallic stents (SEMSs).

In only three previous small case series (25 patients total) has the use of uncovered, partially covered, and fully covered SEMSs in the drainage of PFCs been reported [7, 8]. For a number of reasons, these stents have several limitations when used for transmural drainage: (1) their design is intended for use as tubular ducts in the biliary tree; (2) they do not facilitate anchorage between the lesion and gastrointestinal wall, with a commensurately high risk of fluid leak into the peritoneum; (3) stent migration into the pseudocyst or gastric lumen has been reported [3, 7]; and (4) the exposed metallic stent end can injure tissues, causing major complications.

The drainage of PFCs using a fully covered metallic stent with a novel design to prevent migration and fluid leakage could provide faster drainage with fewer complications. Recently, Itoi et al. described an experiment with pseudocysts and gallbladder drainage using a novel lumen-apposing stent that was first reported by Binmoeller and that was specially designed for transluminal drainage of nonadherent fluid collections [9, 10].

The purpose of this article is to report our initial experience with this new EUS-guided drainage of PFCs with a novel lumen-apposing stent, in terms of feasibility and safety, and further compare it to a retrospective plastic pigtail stent group.

Patients and methods

We included nine patients from four Spanish tertiary centers undergoing EUS-guided drainage of PFCs with placement of a novel fully covered metal stent with bilateral flanges, between May and September 2011. All patients underwent a blood test and computed tomography scan to assess accessibility of the PFCs before the procedure. Written, informed consent was obtained for EUS-guided drainage of the lesions before the intervention.

Patients were individually researched prospectively for procedure indications, demographic data, previous imaging techniques, technical aspects, clinical outcomes, complications, and patient follow-up after endoscopic drainage.

Materials

All interventions were performed under general anaesthesia: six patients in the fluoroscopic room and three in the EUS room. Patient was on the left side or prone position and in two procedures orotracheal intubation was performed by an anesthesiologist.

All procedures were performed using curvilinear array echoendoscopes (GF-UCT140, Olympus; EG-530UT, Fujinon). A fully covered expandable metallic stent (AXIOS^{TM}, Inc., Mountain View, CA) was used in all patients. This stent contains a nitinol wire covered with a diabolo-shaped silicon membrane with bilateral flanges (Fig. 1). Two different sizes were used: 10 × 10-mm and 10 × 15-mm in diameter and length, respectively. In six cases, a novel access device (NAVIX^{TM}, Xlumena Inc.) was used. It enables access, tract dilation, and guidewire placement, reducing device exchanges due to its special design: an anchor balloon to secure access and appose structures, and a dilation balloon to expand the tract to 10 mm. In three cases, a 19-G needle and a TTS balloon dilator were used. A prophylactic dose of intravenous antibiotics was administered before the procedure, followed by 5–7 days of oral antibiotics.

Techniques

Endoscopic ultrasound-guided drainage was performed by three experienced endoscopists, according to the accepted guidelines [11]. Seven procedures were performed in the stomach, one in the distal esophagus, and one in the proximal duodenum. Special attention was paid to finding areas with a distance of less than 1 cm, and color Doppler was used to avoid visible vessels. Two different procedures were used to access the lesions and create a fistula between the PFCs and the gastric lumen: (1) in six patients NAVIX access device was used and a 0.035-inch guidewire was inserted into the lesion (Fig. 2A); (2) in three cases, a 19-gauge needle (EUSN-19-T, Cook Endoscopy, Winston Salem, NC) was used to puncture the PFC and a 0.035-inch guidewire was introduced through the needle. The tract was dilated by a 10- to 12-mm balloon.

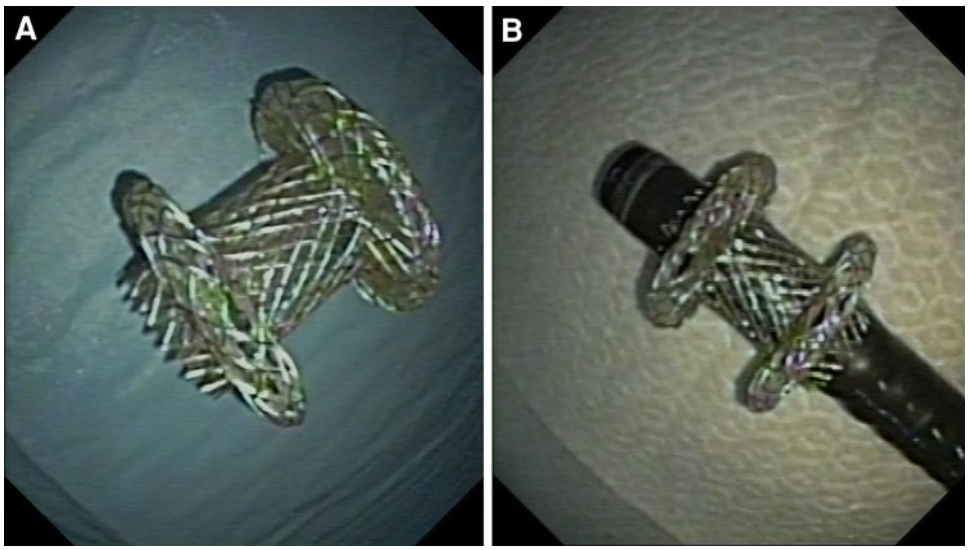

Fig. 1 Images of the stent. A novel fully covered metallic stent with bilateral flanges (**A**); a standard upper endoscope through a 10 mm-diameter AXIOS stent (**B**)

In all procedures, the guidewire placed was used to introduce the AXIOS stent, across the ostomy and deployed under only EUS view in three patients (Fig. 2B) and with fluoroscopy and EUS guidance in the other six patients (video).

In six cases, cystoscopy was performed through the AXIOS stent by using a standard upper endoscope (Fig. 2C) or a pediatrical scope. Cyst fluid was aspirated and sent for chemical analysis and culture.

In two cases of PFC with necrosis areas, double plastic pigtail stents (10 Fr per 5–7 cm) were inserted through the AXIOS stent by decision of the endoscopist to guarantee better drainage of the dense fluid. During the endoscopy control, necrosectomy and lavage were performed through the stent in two patients.

Definition of events

Pancreatic fluid collections term is categorized according to the Atlanta Classification [12]. Technical success was defined as accurate placement of the stent across the intestinal wall to the pseudocyst, with visualization of cyst fluid flow through the stent.

Clinical success was defined as complete resolution of clinical symptoms with at least a >40 % decrease in size at 1 month following treatment. Procedural times were calculated as minutes from beginning of sedation until withdrawal of echoendoscope.

Results

Patient characteristics

A total of nine patients (seven male, two female) with a mean age of 55.5 ± 1.36 years (range, 36–79) underwent EUS-drainage using AXIOS stent. Etiology for lesions was alcohol ($n = 6$), gallstone ($n = 1$), hyper-triglyceridemia ($n = 1$), and idiopathic ($n = 1$).

The mean PFC size was 90 ± 24.42 mm (range, 70–150). The PFCs were located in the pancreatic head ($n = 1$), body ($n = 5$), and tail ($n = 3$). In five lesions necrosis areas were reported by CT scan (walled-off pancreatic necrosis, WOPN), and in two these were confirmed by cystoscopy. Four lesions were defined as pseudocysts (PSC). The indications for drainage were abdominal pain ($n = 7$), infection ($n = 2$), food obstruction plus biliary obstruction ($n = 1$), and size increase ($n = 2$).

Only four patients presented bulging lesions. Table 1 shows the etiology, lesion characteristics, technical aspects, and clinical outcomes of the nine patients.

Observations

Median procedure time was 25 ± 13.2 min (range, 10–55). A median number of two sessions were performed (range, 1–3) to achieve total drainage, with a total of 16 procedures. In cases where NAVIX system was used, median procedure time was 22 min (range, 10–30) versus 40 min (range, 25–55) in cases with device exchanges.

The stent was successfully positioned in all patients except one, due to a failure of the delivery system. PFC drainage of this failure case was completed by placing two plastic double pigtails stents. Technical success rate was 88.8 % (8/9) using AXIOS stent. The clinical success rate was 100 % and the eight patients experienced immediate symptom relief after the interventions.

Mean time to stent retrieval was 33 ± 40 days (range, 7–108). To date, all AXIOS stents were removed easily using a standard polypectomy snare (Fig. 2D) or rat-tooth forceps.

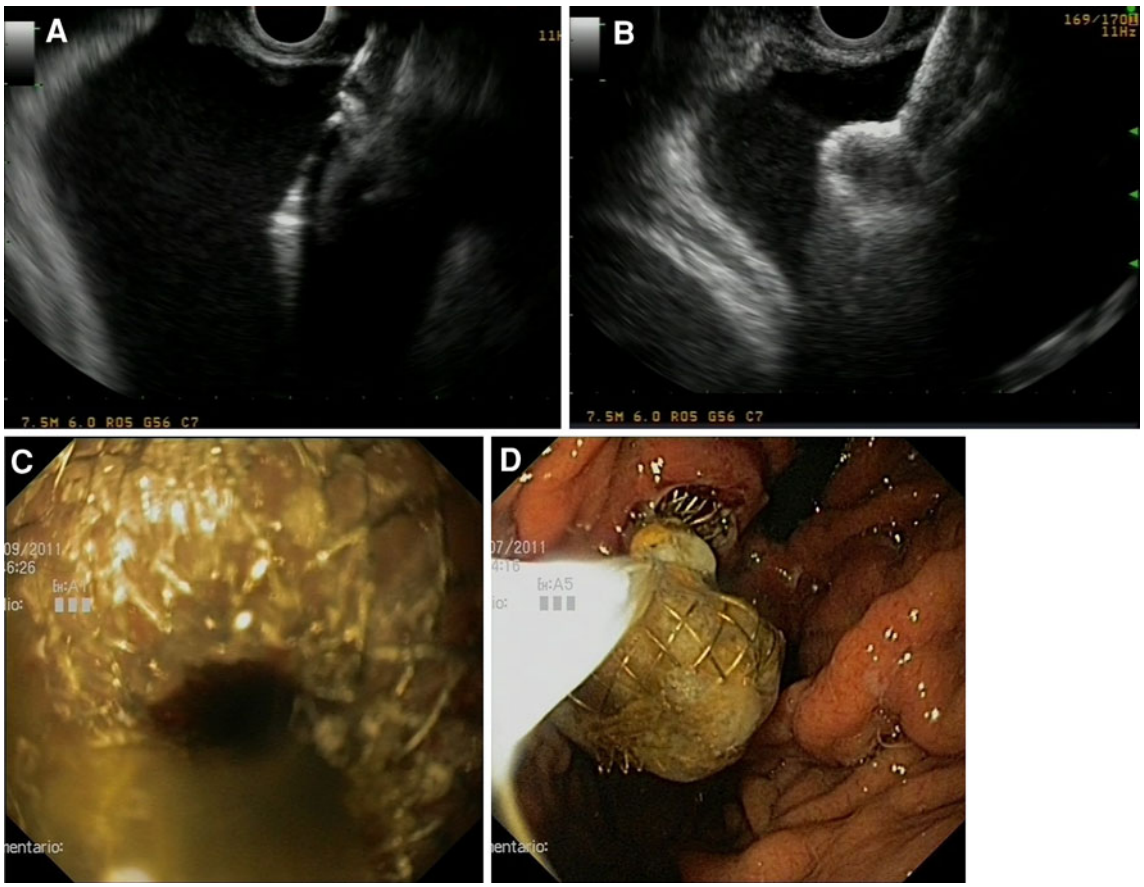

Fig. 2 Steps of a EUS-guided PFC with single-step using the NAVIX access device and placement of an AXIOS stent. Access into the lesion with the insertion of the trocar into the lesion under EUS guidance (**A**). Images of AXIOS stent deployment under EUS guidance (**B**). Endoscopic view across the AXIOS stent using an upper endoscope (**C**). Retrieval of the stent using a polypectomy snare (**D**)

Table 1 Patients demographics, lesions characteristics, technical aspects, and outcomes

Patients	Age (year)/sex	Etiology	Lesion type	Bulging, Y/N	Drainage site	Access technique	Stent size (mm)	Complications, Y/N	Outcome
1	52/M	Alcohol	Simple PSC	Y	Transgastric	NAVIX	10 × 10	N	Resolution
2	66/M	Alcohol	Simple PSC	N	Transgastric	NAVIX	10 × 10	N	Resolution
3	45/M	Alcohol	WOPN	Y	Transgastric	NAVIX	10 × 10	N	Resolution
4	48/M	Alcohol	Infected WOPN	Y	Transduodenal	NAVIX	10 × 15	N	Resolution
5	53/M	Alcohol	WOPN	N	Transgastric	19 G + Balloon	10 × 10	N	Resolution
6	79/F	Idiopathic	Simple PSC	N	Transgastric	19 G + Balloon	10 × 10	N	Resolution
7	64/F	Lithiasis	WOPN	N	Transgastric	19 G + Balloon	10 × 10	N	Technical failure
8	57/M	Hypertrig	WOPN	Y	Transgastric	NAVIX	10 × 15	N	Resolution
9	36/M	Alcohol	Simple PSC	N	Transesophageal	NAVIX	10 × 10	Pneumothorax[a]	Resolution

F female, *M* male, *Y* yes, *N* no, *Hypertrig* hypertriglyceridemia, *PSC* pseudocyst, *WOPN* walled-off pancreatic necrosis

[a] Pneumothorax as acute complication

Complications

One patient developed a tension pneumothorax immediately after transesophageal drainage, which required 9 days of intercostal drainage. Patient had a history of right spontaneous pneumothorax on the same side, and the thoracic surgeon directed the case as a complication during orotracheal positive pressure. No other major complications were observed in any patient. There was no procedure-related mortality.

Recurrence

The mean time until PFC total resolution was 5.3 ± 1.36 weeks (range, 1–12). Patients were followed up prospectively after stent retrieval for a mean time of 50 ± 1.3 weeks (range, 45–55). Only one lesion presented a recurrence, 4 weeks after the stent removal.

Comparison group (plastic stent)

Ten cases (6M, 4F) of PFCs (one WOPN, nine PSC) previously drained by EUS guidance using plastic pigtail stents were recruited consecutively and used as a comparison group. The mean age was of 60 ± 5.9 years and mean PFC size was 90 ± 13.7 mm (range, 45–160).

In all procedures, a transgastric approach was performed to access the lesions and create a fistula between the PFCs and the gastric lumen. The standard technique, which implies device exchanges (19-gauge needle plus cystotome, or needle-knife, and balloon dilation), was used in all interventions with a median procedure time of 42.8 ± 3.1 min (range, 35–70). The technical and clinical successes were 90 and 88.8 % respectively. One patient developed a pneumoperitoneum without peritoneal signs and was managed conservatively. There were two stent migrations: one occurred few days after the drainage, into the gastric lumen, and the simple PSC was converted to an infected PSC, requiring an immediate EUS-guided drainage; and one was an immediately internal migration into the cyst, requiring a rescue technique of tract dilation and cystoscopy to achieve the relocation. Median follow-up was 126 ± 19.2 weeks (range, 52–208) and two lesions presented a recurrence.

The analysis of the difference between the two groups found that the number of stents and the mean procedure time were significantly higher in the plastic stent group than in the AXIOS stent group ($p = 0.01$ and 0.049 respectively). General results are summarized in Table 2.

Table 2 Results of EUS-guided drainage of PFCs

	AXIOS™ stents	Plastic double-pigtail stents	*p* value*
No. of cases	9	10	NA
Type of PFC, PSC/WOPN[a]	4/5	9/1	0.057
Technical success, % (*n*/N)	88.8 (8/9)	90 (9/10)	1
Clinical success, % (*n*/N)	100 (8/8)	88.8 (8/9)	1
No. of stents	9	15	0.049
No. of sessions	16	16	1
Cystoscopy (*n*/N)	6/8	2/9[b]	–
Necrosectomy (*n*/N)	2/8	1/9	–
Time procedure (min ± SD)	25 ± 13.2	42.8 ± 3.1	0.01
Stent migration	0	2	0.47
Complications	1/8	2/9	1
Infection	0	1	–
Bleeding	0	0	–
Pneumoperitoneum	0	1	–
Pneumothorax	1	0	–
Recurrence, % (*n*/N)	12.5 (1/8)	22.2 (2/9)	1
Mean follow-up period, week;year (range)	50 ± 1.3 (45–55)	126 ± 19.2 (52–208)	0
Mean time to stent removal, day (range)	33 ± 40	NA	NA

PSC pseudocyst, *WOPN* walled-off pancreatic necrosis, *NA* not applicable

* *p* obtained by Student's *t* test and χ^2 test or Fisher's test. Statistical significance established at $p < 0.05$

[a] Terms categorized according to the Atlanta Classification

[b] Cystoscopy: one internal migration of a plastic stent; one WOPN case

Discussion

Endoscopic ultrasound drainage of PFCs is technically challenging, time consuming, and demanding of experience in the procedure [13, 14]. Development of large-channel (3.7 mm) linear echoendoscopes, which enable insertion of any kind of "through the scope" (TTS) stents, has opened new frontiers in the field of therapeutic endoscopy. There are still unanswered questions regarding what kind of stent should be placed. Although the placement of one or more plastic stents has been used in most of the important reports, this implies a limited diameter of the tract and related complications, such as migration or stent occlusion, as described.

As in the biliary obstruction field, in a few case series the utility of conventional or special customized SEMS have has been proven to overcome this limitation, ensuring a wider-diameter fistula in the drainage of PFCs [7, 8, 15]. But these metallic stents have a tubular morphology and are not specifically designed to be used for transmural drainage. They are not good options in cases when the cyst is not firmly attached to the gastric wall, because they do not apply any anchorage force and as a result the risk of leakage is high. Additionally, the metallic ends can cause significant bleeding [1].

For this reason, with the intention of investigating specific devices in this field, Binmoeller and co-workers [9, 10] reported first an ex vivo and animal experience and secondly a small case series of ten patients (eight PFCs) using the AXIOS stent and the conventional access tools. In the same line, a new access device (NAVIX) designed to reduce the need for device exchanges was studied [16].

In our experience, the use of this new stent has several advantages: (1) easy deployment leading to a reproducible procedure. Technically, it is easy to use and the only failure was due to a problem in the final stage of stent deployment system; (2) good EUS imaging could help to avoid the use of fluoroscopy guidance because not all endoscopy units have fluoroscopy in the EUS room as in three cases in our study [17]; (3) it is less time-consuming, as is shown in our series with a median procedure time of 25 min including six procedures of less than 30 min; (4) and similar clinical success has been reported to date by others without major complications. In addition, the stent's large diameter facilitates faster drainage and enables diagnostic (cystoscopy) and therapeutic interventions. Cystoscopy was performed in six patients, with a standard video gastroscope passing through the stent without dislodging the stent and allowing the practice of necrosectomy in two cases.

Finally, no migration or fluid leaks were observed in our experience, but this potential benefit has to be confirmed with a greater number of patients. Regarding the benefits of using NAVIX access device, we observed a reduction in median procedure time in cases when it was used, with respect to others in which devices exchanges were carried out.

Comparing these results with ten previous PFC drained using plastic pigtail stents, it is worth noting the statistically significant difference of the procedure time due to the necessity of device exchanges performing the "ostomy" and the technical complexity to deploy more than one plastic stent in the same session. Two cases of migration were detected, thus both requiring extra interventional procedures, which is significantly time-consuming. Additionally, two cystoscopies were performed in one WOPN case and one internal migration of the stent. These procedures required a stent exchange, aggressive tract dilation, and restenting the ostomy with a new plastic stent, implying an important time of intervention.

The small number of cases and the heterogeneity between both groups (more WOPN cases in the AXIOS stent group) are the main limitations of this study. This fact may explain the similar number of sessions (16 vs. 16) in both groups, understanding that a WOPN requires a more aggressive endoscopic management, such as more number of cystoscopies and necrosectomies. In terms of economy, at first sight, the use of SEMSs stent may seem that the costs are higher, but if it reduces procedure time and entails fewer interventions, the end costs will be lower [18].

Conclusions

Drainage of PFCs using dedicated devices, such as this novel metallic stent with a special design, is feasible and safe. Larger, prospective and randomized studies to validate and confirm these findings are needed.

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Disclosures Drs. Gornals, De la Serna, Sanchez-Yague, Loras, Sanchez-Cantos, and Pérez-Miranda have no conflicts of interest or financial ties to disclose.

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Endoscopic ultrasound-guided transesophageal drainage of a mediastinal pancreatic pseudocyst using a novel lumen-apposing metal stent

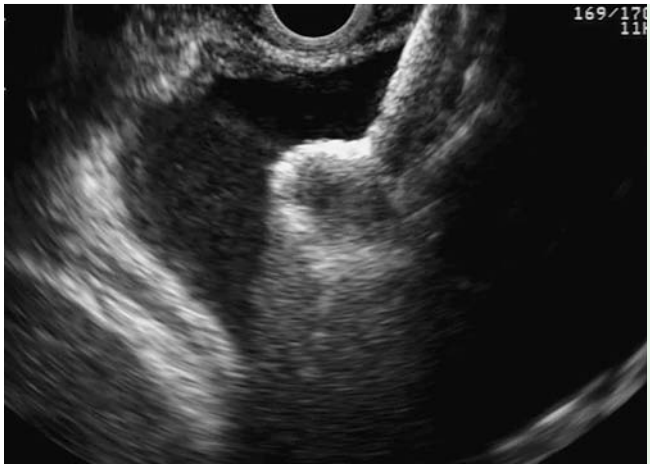

Fig. 1 View during endoscopic ultrasound (EUS)-guided placement of a lumen-apposing metal AXIOS stent across the cystoesophagostomy.

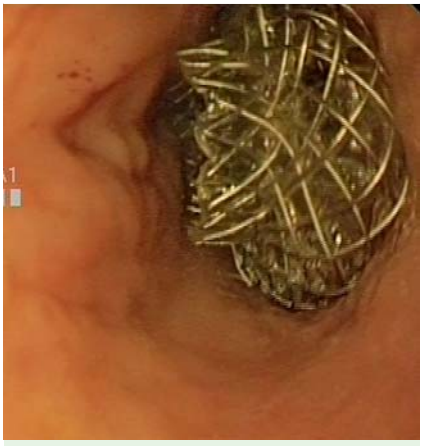

Fig. 2 Endoscopic view of the intraluminal end of the stent within the lower esophagus.

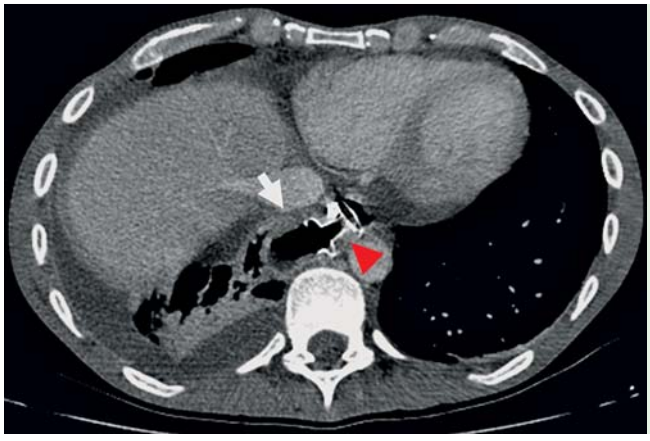

Fig. 3 Follow-up computed tomography (CT) scan after 7 days showing the AXIOS stent (arrowhead) still in place with significant resolution of the lesion (arrow).

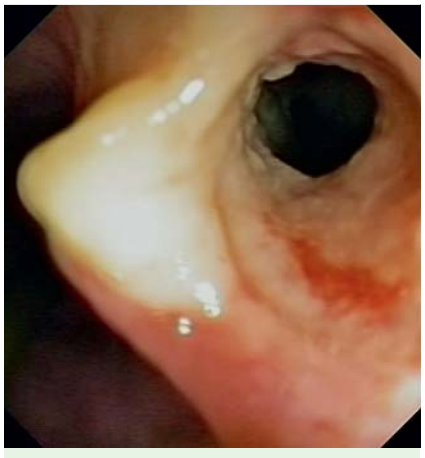

Fig. 4 Endoscopic view of the cystoesophagostomy after the stent had been removed.

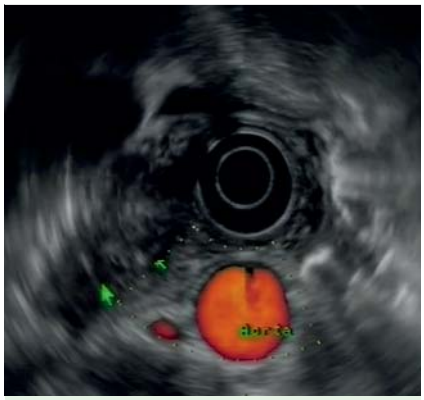

Fig. 5 Follow-up endoscopic ultrasound (EUS) image 6 weeks later showing complete resolution of the lesion.

There have been a few previous reports of transesophageal endoscopic ultrasound (EUS)-guided drainage of pancreatic fluid collections (PFC). In these reports the drainage modality has been a single aspiration or deployment of a plastic stent [1–4]. We report a patient who underwent transesophageal EUS-guided drainage of a mediastinal PFC using a novel lumen-apposing metal stent.

A 37-year-old man with a history of right-sided pneumothorax and four episodes of acute pancreatitis was referred for drainage of a PFC. He was experiencing abdominal pain and cysts of increasing size had been seen on his imaging procedures. Computed tomography (CT) scanning revealed an 80×50-mm PFC, which had herniated into the mediastinum adjacent to the lower esophagus.

The PFC was accessed from the lower esophagus using a linear echoendoscope and a novel access device (NAVIX; Xlumena Inc., Mountain View, California, USA) that enables dilation of a tract up to 10 mm and placement of a guide wire. Once the cystoesophagostomy had been created, a fully covered metal stent with bilateral anchor flanges that can appose nonadherent lumens (AXIOS, 10×10 mm; Xlumena) was placed across the tract (**Fig. 1**, **Fig. 2** and **Video 1**) and 900 mL of fluid was aspirated. An immediate chest radiograph revealed a tension pneu-

mothorax on the right side, which required intercostal drainage. The thoracic surgeon who performed the drainage procedure felt that this was a complication of the orotracheal positive pressure.

By day 7, the patient reported resolution of his abdominal pain and a repeat CT scan revealed a marked reduction in the size of the PFC (**Fig. 3**). The AXIOS stent was removed (**Fig. 4**) and the patient was discharged with marked improvement in the pneumothorax. Follow-up imaging after 6 weeks showed complete resolution of the lesion by both EUS and CT scanning (**Fig. 5**). The patient remains asymptomatic 4 months later.

EUS-guided transesophageal drainage of PFCs has become an alternative to surgery or percutaneous drainage [1 – 4]. We describe the first case of transesophageal EUS-guided drainage of a PFC using a novel lumen-apposing metal stent. The procedure was technically successful and led to complete resolution of the lesion, although a pneumothorax occurred as an immediate complication.

Video 1

Transesophageal endoscopic ultrasound (EUS)-guided mediastinal pseudocyst drainage using a lumen-apposing metal AXIOS stent.

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ESTUDI 3

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Digestive Endoscopy

Single-session endosonography and endoscopic retrograde cholangiopancreatography for biliopancreatic diseases is feasible, effective and cost beneficial

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ABSTRACT

Background: Endoscopic ultrasonography (EUS) and Endoscopic Retrograde Cholangiopancreatography (ERCP) are often required in patients with pancreaticobiliary disorders.
Aims: To assess the clinical impact and costs savings of a single session EUS-ERCP.
Methods: Patient and intervention data from April 2009 to March 2012 were prospectively recruited and retrospectively analyzed from a database at a tertiary hospital. Indications, diagnostic yield, procedure details, complications and costs were evaluated.
Results: Fifty-five scheduled combined procedures were done in 53 patients. The accuracy of EUS–fine needle aspiration for malignancy was 90%. The main clinical indication was a malignant obstructing lesion (66%). The ERCP cannulation was successful in 67%, and in 11/15 failed ERCP (73%), drainage was completed thanks to an EUS-guided biliary drainage: 6 transmurals, 5 rendezvous. Eight patients (14%) had related complications: bacteremia ($n = 3$), pancreatitis ($n = 2$), bleeding ($n = 2$) and perforation ($n = 1$). The mean duration was 65 ± 22.2 min.

The mean estimated cost for a single session was €3437, and €4095 for two separate sessions. The estimated cost savings using a single-session strategy was €658 per patient, representing a total savings of €36,189.
Conclusion: Combined EUS and ERCP is safe, technically feasible and cost beneficial. Furthermore, in failed ERCP cases, the endoscopic biliary drainage can be completed with EUS-guided biliary access in the same procedure.

1. Introduction

Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) and endoscopic retrograde cholangiopancreatography (ERCP) are often required in the evaluation and treatment of patients with pancreaticobiliary disorders and are most commonly performed as separate procedures [1].

EUS is a safe and useful technique for the assessment of benign or malignant pancreaticobiliary disease, including a higher sensitivity for the detection of choledocholithiasis, or small pancreatic tumours, and providing vascular staging and tissue sampling thanks to guided FNA [2–4].

Additionally, ERCP plays a key role in the treatment of biliary drainage (BD), allowing the placement of stents [5]. Furthermore, in the event of ERCP failure, EUS-guided interventions have allowed access or direct therapy since the procedure was first described in 1996 [6].

Combining these procedures in a single session takes advantage of the strengths of both modalities, providing diagnostic and therapeutic possibilities [7,8]. Despite the numerous potential advantages without compromise in diagnostic accuracy of the

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Table 1
Demographic data and clinical indications.

Variables	N (%)
Male sex	29 (54%)
Median age, y (range)	67 (36–90)
ERCP success rate	33/49 (67%)
EUS-guided BD success rate	11/15 (73%)
Total cannulation rate	44/49 (89%)
Sphincterotomies precut/papilloplasties	46 29/2
Stents	32
Metallic	20
Plastic biliar/pancreatic	12 10/2

Clinical indications	N (%)
Pancreatic mass	31 (54%)
Ampullary mass	2 (3.5%)
Abnormal imaging	2 (3.5%)
CBD stricture	5 (8.7%)
Choledocholithiasis	13(23%)
Cystic pancreatic lesión	4(7%)
Total	57[a]

y, years; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; BD, bile duct; CBD, common bile duct.
[a] 2 patients had pancreatic cystic lesion and concomitant choledocholithiasis.

combined strategy in some early reports [8–16], implementation in clinical practice can encounter important obstacles [9,13], and concerns do remain [1,7], including the development of complications, the question of which procedure should be the first, the question of whether biliary stent can alter the accuracy of EUS, and the worry as to whether EUS-guided BD should be attempted after a failed ERCP. Yet to date there are no studies with scientific evidence substantiating that this combined strategy is cost-effective.

Therefore, the aim of the present study was to report our experience and to assess the clinical impact and the cost savings of a single session EUS–ERCP for patients undergoing evaluation of pancreaticobiliary diseases in our centre and to help clarify the benefits of this approach.

2. Materials and methods

The study took place at Hospital Universitari de Bellvitge, an 850-bed tertiary-care public institution for adults in Barcelona, Spain. The hospital provides acute care to a population of 1.5 million and attends 33,000 annual inpatient admissions. Annually, more than 500 ERCP and 300 EUS procedures are performed in our endoscopy unit.

Patient and procedural data from April 2009 to March 2012 were prospectively recruited and analyzed retrospectively from an EUS–ERCP database. The following information was collected: demographic data, presenting symptoms, indications, procedure characteristics and complications. Procedure details included diagnostic yield, bile duct cannulation rate, success at BD, duration and complications. Indications and demographics are detailed in Table 1.

The decision to arrange a combined procedure was made by the referring physician and the endoscopist, and it depended on scheduling availability. The main factors in scheduling patients for a single-session strategy were: suspicion of low-intermediate risk of choledocholithiasis (same session EUS–ERCP) and FNA indication (e.g. tumour) plus the need for BD. In cases of failed ERCP in patients with unresectable tumours or poor surgical candidates, an EUS-guided BD was considered. In addition, all cases initially considered as resectable pancreatic cancers were excluded from EUS-guided BD. All these items were used as search criteria during the retrospective analysis.

All patients provided written informed consent prior to the procedure and the study was approved by the ethics committee of our centre.

2.1. Procedures and technical aspects

The patients were placed in a prone position in a dedicated fluoroscopy room. All procedures were performed under profound sedation administered by an anaesthesiologist using propofol with supplementary fentanyl administered according to each patient's compliance.

All procedures were performed by a single interventional endoscopist (J.G.). EUS procedures were done using a radial echoendoscope in 6 cases (Olympus/Aloka GFUE160-AL5, Aloka Medical Device Co., Tokyo, Japan) and a linear-array device (GFUCT140-AL5) in the remaining cases. In all cases, an EUS evaluation of the biliary tree, liver, pancreas and ampulla (if this was accessible) was made. In 4 cases with intermediate risk of common bile duct stones (CBDs), the EUS was normal and no subsequent ERCP was done.

When a pancreatic mass or other suspicious image was seen, an EUS-guided FNA (routinely 2 passes) was performed using a fine needle (Echo-1-22; CookMedical, Winston-Salem, NC, USA). The specimens were assessed by a cytotechnician and stained with Diff-Quik stain to establish a diagnosis. Tissue processing and interpretation took 10–25 min, with results being relayed over the phone by the cytopathologist. Depending on the outcome, the need for a third pass was assessed. Atypia on cytology was considered suspicious but not positive for cancer.

While the FNA specimens were being evaluated, an ERCP was performed using a duodenoscope (TJF160, Olympus) with a sphincterotome preloaded with a 0.035 in. guidewire. If cannulation was not achieved after 3–5 attempts, a precut was made using a needle-knife. Biliary and duodenal samples were obtained using cytobrush and/or biopsy forceps in 6 cases.

In 15 cases, in which ERCP cannulation was unsuccessful ($n = 13$) or the papilla could not be reached with a duodenoscope ($n = 2$), direct EUS-guided BD was performed in the same session. The decision to do this was made by the endoscopist on a case-by-case basis considering the underlying clinical indication and patient condition.

The biliary access involved different approaches: transgastric (1 intrahepatic; 1 extrahepatic from distal antrum) and transduodenal (13 extrahepatic).

In patients with an accessible papilla, an EUS-guided rendezvous was preferred, because the final stent position is more physiologically correct for the BD.

EUS-guided ductal puncture was performed using a 19-gauge needle. Colour Doppler was used to avoid vascular structures. Upon removal of the stylet, bile was aspirated to confirm the intraductal location, and contrast was instilled under fluoroscopic guidance to obtain a ductogram. If transpapillary wire placement was achieved, a rendezvous procedure was performed. The echoendoscope was removed leaving the guidewire in place, and a duodenoscope was inserted. Once the ampulla was reached, a sphincterotome was used for cannulation alongside the wire (parallel rendezvous), or if this was not possible, the transpapillary wire was grasped using a biopsy forceps and classic rendezvous ERCP was carried out (Fig. S1).

When anterograde transpapillary wire placement was not possible because the wire could not be advanced across the obstruction, or in cases of non-accessible papillas, upstream transmural drainage was attempted and a transenteric fistula was created using a needle-knife over the wire. If necessary, a balloon dilation was used for dilation. A tranduodenal/extrahepatic route was preferred due to the superior technical control by the endoscopist

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using this route. Finally, depending on the specific anatomy and approach, a covered metal or plastic stent was placed.

Procedure time was calculated as the time from the insertion of the first scope to the withdrawal of the last. All patients received prophylactic antibiotics.

2.2. Cost analysis

The financial study was based on data provided by the finance department. A cost-minimization analysis was done since differences in the outcome of the two strategies being compared are minor, meaning that the effectiveness of treatment in the two cases was the same.

The analysis of direct cost included: professional fees, cost of the material used, type of procedure and expected costs of hospital stay.

Material costs were subdivided into endoscopic instruments, non-reusable endoscopic devices and anaesthetic drugs. Depending on the type of combined procedure, costs were divided into different groups: A (EUS only); B (EUS and ERCP, benign lesions); C (EUS–FNA and ERCP, mostly malignant lesions) and D (attempted EUS-BD when ERCP failed). The average procedure duration and hospitalization days for all procedures were calculated in order to estimate the costs of hospital stay for each group. Indirect costs such as central services were also included.

Final estimated costs were compared with the estimated costs of a separate session strategy. For this reason, an extrapolated calculation was made of the hospitalization costs of a double-step strategy, according to the routine hospitalization protocol of our centre in this type of procedure.

2.3. Statistical analysis

For variables following a normal distribution, results were expressed as mean value ±SEM and range. Proportions are given as numbers and percentages. In univariate analysis the χ^2 test and Fisher exact test were used to compare proportions, and the Student t test was used to compare quantitative variables. The odds ratio (OR) and its 95% confidence interval (CI) were calculated to assess the strength of each significant association.

Statistical significance was established at $p < 0.05$ for all the analyses. The data were analyzed using the program SPSS 13.0 (SPSS Inc.).

3. Results

A total of 53 patients were included during the study period and they underwent 55 scheduled combined procedures. Patient characteristics and clinical indications are summarized in Table 1. In 45 cases EUS was the first procedure. A total of 48 EUS-guided punctures were made, including 15 for therapeutic purposes. Six patients underwent 'triple' procedure: EUS–FNA, ERCP and EUS-guided BD. A flow diagram representing all the procedures is included in Fig. 1.

FNA was performed in 33 (60%) of all EUS procedures. The average number of needle passes was 2 (range 1–3) based on sample adequacy evaluated by the cytopathologist.

These specimens were positive for malignancy in 24, suspicious in 2, negative in 4 and non-representative in 3. Excluding the suspicious cases, EUS–FNA had a sensitivity of 88%, a specificity of 100%, and accuracy in differentiating cancer from non-malignant lesions of 90%.

During ERCP, brush cytology was obtained in 6 patients. The brushings were positive for malignancy in 3, and of the 3 patients with negative results, EUS–FNA was positive.

Table 2
Factors evaluated for their relationship to complications.

	Cases with complications ($n = 8$)	Cases without complications ($n = 47$)	p value
Male sex (%)	62.5	57.4	1
Mean ± SEM age (years)	67.5 ± 4.2	67.7 ± 1.68	0.97
No of punctures (1/>1) (%)	50/50	20/80	0.38
Stent placement (%)	62.5	51	0.70
Precut (%)	37.5	57.4	0.56
Success of BD (%)	85.7	72	0.70
Groups of procedure (%)	31.2	8.5	0.09
Duration time (min)	60.63 ± 6.64	65.66 ± 3.34	0.55

BD, biliary drainage.

Excluding group A (only EUS), ERCP cannulation rate was 67% (33/49).

Forty-six endoscopic sphincterotomies or precut were performed. In 28 cases, 32 stents were successfully placed, including 2 plastic pancreatic, 19 biliary metallic and 1 duodenal metallic. EUS-cholangiography was obtained in 86.6% (13/15) of procedures with definition of the relevant anatomy, but BD was successfully performed in only 11 (73%) of the 15 patients (6 transmurals and 5 biliary rendezvous procedures). Thanks to the EUS-guided BD, the total biliary cannulation rate increased up to 89% (44/49).

The mean (SD) total procedure time was 65.5 ± 3 min. The range was wide, from 25 to 120 min. The mean procedural time of an EUS–FNA plus ERCP was 65.4 ± 3.7 min, and EUS plus ERCP was 53.4 ± min. In contrast, mean procedural time of EUS-guided BD was 78.4 ± 5.9 min, which was significantly higher compared to the other types of procedure ($p = 0.010$).

Complications occurred in 9 patients, and 8 were directly related to the procedures (14%). One patient with a cardiac history had an arrhythmia during the procedure which was resolved conservatively. Six were outpatients and required hospitalization for the complications. The majority of complications were associated with an EUS-guided BD, and only 3 complications were in the combined EUS ± FNA plus ERCP. One duodenal perforation was resolved satisfactorily with an Over-The-Scope-Clip system. It was caused by the tip of the echoendoscope before attempting puncture for biliary access, in a pancreatic cancer case. No surgical intervention was required to deal with the complications. Two cholangitis events delayed the oncologic management. No contrast leak was observed during ERCP when FNA was performed. The mortality rate was 0%, as no procedure-related deaths occurred. Various procedural features were evaluated for their relationship to overall complication. None of them was significantly related to the complications in the univariant analysis (Table 2), although a trend towards a higher rate of complications was observed in group D (OR4.84; 95%CI 0.99–23.7).

Duration data and complications are summarized in Table S1.

3.1. Cost results

Overall hospitalization days for each group of procedures included in this study were 0 days (A), 1.78 days (B), 4.4 days (C) and 4.2 days (D). In contrast, the hospital stay for a double-step strategy extrapolated by our finance department for each group was 0 days (A), 1.78 days (B), 5.9 days (C), and 8.6 days (D). Table 3 shows all calculated costs for each strategy.

The mean unit cost for a single-session procedure was €3437, lower compared to the separate session strategy, at €4095. Therefore, the estimated saved cost per procedure performed with the one-step strategy was €658, and the overall cost saving

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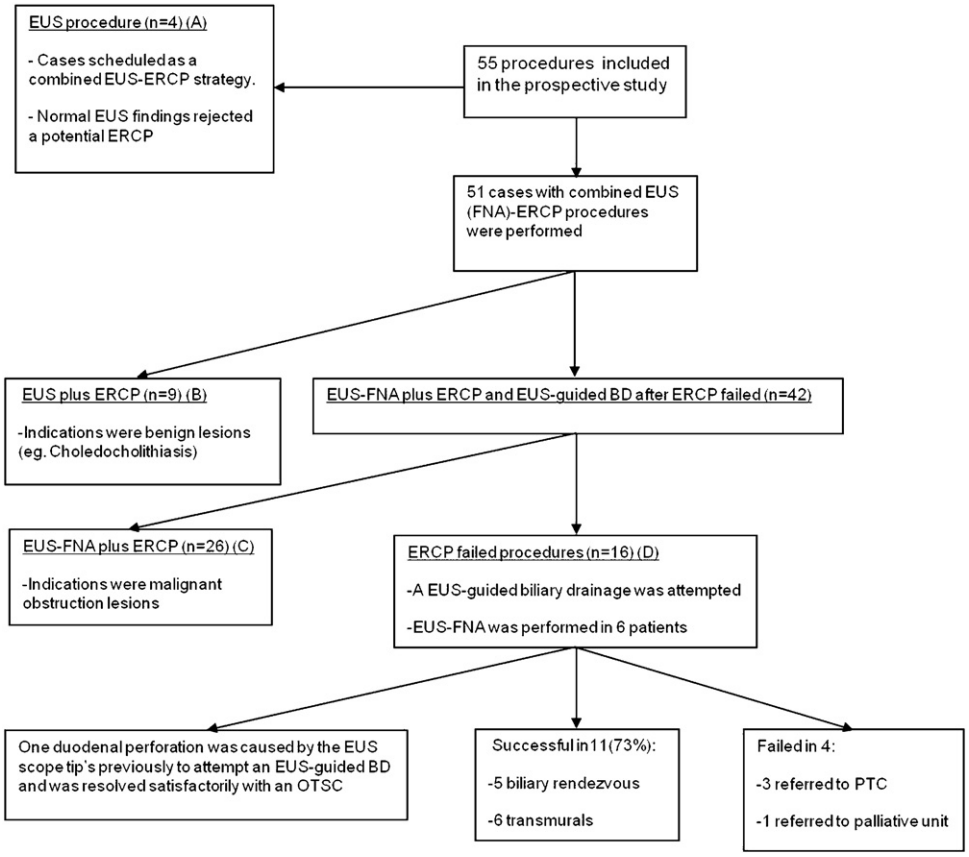

Fig. 1. Flow diagram of the procedures. EUS, endoscopic ultrasound; FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; BD, biliary drainage; OTSC, Over-The-Scope-Clip system; PTC, percutaneous transhepatic cholangiography.

including all the procedures was €36,189. In large measure this was due to a reduction in hospitalization days, procedure duration and professional fees. The global cost analysis by type of procedure combination is summarized in Table S2.

Finally, if we analyze the results of therapeutic procedures (group D), we estimate that in 11 cases with technical success, the subsequent practice of a percutaneous transhepatic cholangiography (PTC) was avoided. If the estimated cost of a PTC in our centre

Table 3
Calculated costs for each strategy.

Variables	Single-session strategy				Double-step strategy (expected costs)			
Groups	A ($n=4$)	B ($n=9$)	C ($n=26$)	D ($n=16$)	A′	B′	C′	D′
Professional fees	101.59	135.45	227.89	295.62	101.59	237.04	295.62	388.74
Endoscopist	29.03	38.71	58.07	77.42	29.03	67.74	77.42	104.03
Anaesthesiologist	29.03	38.71	58.07	77.42	29.03	67.74	77.42	104.03
Registered nurse	22.94	30.59	45.89	61.18	22.94	53.53	61.18	82.21
Assistant nurse	13.94	18.58	27.87	37.16	13.94	32.52	37.16	49.93
Cytotechnologist	–	–	10.20	10.20	–	–	10.20	10.20
Cytopathologist	–	–	12.90	12.90	–	–	12.90	12.90
Indirect costs	6.95	8.86	14.91	19.34	6.65	15.51	19.34	25.43
Health supplies	71.29	622.85	1145.91	2524.91	71.29	622.85	1145.91	2524.91
Endoscopic devices	67.26	587.60	1081.05	2381.99	6726	587.60	1081.05	2381.99
Indirect costs	4.04	35.26	64.86	142.92	4.04	35.26	64.86	142.92
Stents	–	47.51	561.93	465.32	-	47.51	561.93	465.32
Anaesthesia drugs	3.07	14.56	15.44	23.85	3.07	14.56	15.44	23.85
Endoscopic equipment maintenance	12.58	12.58	12.58	12.58	12.58	12.58	12.58	12.58
PTC in failed ERCP	–	–	–	648.04	–	–	–	648.04
Hospitalization costs	32.27	520.05	1293.88	1246.91	32.27	520.05	1731.78	2518.50
Stay (days)	0	1.78	4.42	4.26	0	1.78	5.92	8.61
Cost (*per* day)	–	292.53	292.53	292.53	–	292.53	292.53	292.53
Recovery	32.27	–	–	–	32.27	–	–	–
Central services	15.46	57.43	136.58	231.68	15.46	64.54	141.32	238.20
Unit cost	236.26	1410.44	3394.22	5448.91	236.26	1519.14	3904.58	6820.14
Total cost	945.06	12,693.93	88,249.74	87,182.58	945.06	13,672.23	101,519.13	109,122.30

Groups: (A and A′) EUS; (B and B′) EUS plus ERCP; (C and C′) EUS–FNA plus ERCP; (D and D′) EUS-guided biliary drainage after failed ERCP.
EUS, endoscopic ultrasound; FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography.
All costs are in € for 2012.

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is €2073, completing the endoscopic BD with the help of EUS in the same session involved a total estimated savings of €22,803.

4. Discussion

Initially, early experiences raised concerns about the safety of performing EUS ± FNA plus ERCP procedures in a single session, with reports of contrast leak and pneumoperitoneum at the time of ERCP [17,18]. Recently, series of single-session experiences involving 19–110 patients [8–14,25,26] demonstrated that the approach is feasible with no additional complications, reporting a complication rate ranging from 2% to 10.5% (Table S3). In our study, the overall complication rate was 14%, including those related to the EUS-guided BD procedures. If we do not consider these, the complication rate decreases to 8%, similar to the range for the individual procedures.

Previous studies have suggested that elderly patients may be at increased risk of myocardial injury in longer ERCPs [19], but other authors have rejected these findings [10,14]. In our study, one elderly patient experienced a ventricular tachycardia that resolved spontaneously. This complication was not considered to be directly related to the procedure. In addition, duration time was not associated with the complication rate (no significant differences). The mean global procedure duration of our study was 65 and 78.4 min for the EUS-guided BD group. These times are similar to or better than those of other reports [10,19,20].

Regarding which procedure should be the first, some authors have commented that beginning with ERCP with stent placement could improve the EUS study of the biliary system, because the stent could be used as a guide [1]. Based on our experience, we prefer to use the 'EUS-first' approach in malignant diseases for several reasons: is more accurate for cancer staging [21,22]; if FNA confirms malignancy we can obviate the need for biliary brushing, and in some cases this helps us to decide between plastic or metallic stent. Meanwhile tissue processing can be started with ERCP, gaining procedural time. Moreover, the performance of EUS–FNA and its diagnostic yield were not altered. Rocca et al. [8] reported an experience using an echoendoscope to perform BD evaluation and simultaneous treatment with cannulation and sphincterotomy. In our experience, we tried to cannulate the BD using the echoendoscope in all the accessible papilla cases; it was only possible, however, in 3 interventions (6%). The concept of a single scope is attractive but is still far off, and we think that it awaits the development of new technology.

The main indication for a BD was suspicion of jaundice malignancy (66%). This explains the level of difficulty of biliary cannulation in all the cases, and it is the main reason for the lower ERCP success rate (67%) in a referent endoscopy unit with a regularly high success rate. Fifteen patients underwent EUS-guided BD procedures and the majority of them were performed as a palliative manoeuvre. All these cases, except two, had duodenoscope-accessible papilla, and precut access was attempted in all of them. This point may explain why the overall complication rate related to EUS-guided BD increased to 31%, almost reaching significance ($p < 0.09$). We believe that 1 incidence of bleeding was likely related to the ERCP procedure rather than the EUS-guided intervention. So, a more accurate complication rate specific to EUS-guided BD would be approximately 25%, similar to the complication rate reported for other groups, ranging from 10% to 36% [16,23]. Three cholangitis cases were seen in 3 EUS-guided transmural BD and none with a EUS-guided rendezvous. We agree, then, with Shah et al. [16], that surely the final stent position in transmural drainage does not preclude the intended use of tubular stents for lumen recanalization across stenotic areas. The final stent position via rendezvous is identical to the position in which it would be placed via ERCP.

Success rates for EUS-guided BD of 67–100% have been reported in several series in which procedures were performed in a second session after initial failed ERCP. In our study, we had a similar success rate of 73.3% among 15 patients, excluding a perforation case explained above which occurred before attempting the biliary access technique. This technique helps us to increase the biliary cannulation rate from 66% to 89% in patients, the majority with jaundice malignancy.

Nowadays, interest in carrying out a financial assessment arises from the necessity to administer resources, which are scarce, in line with needs, which are limited or at least greater than the resources. Cost-minimization analyses have been reported in the field of strategies in diagnosing pancreatic cancer [24]. Regarding the single-session strategy, it has been suggested as being cost-effective but it has not been specifically studied in a cost-minimization analysis. In the authors review of the literature we found two randomized studies by Fabbri et al. [25,26] comparing EUS plus ERCP during the same endoscopic session or in two separate sessions for the management of patients with low risk of choledocholithiasis and acute biliary pancreatitis. In the Fabbri study, a financial analysis was conducted, reporting a lower total cost for the single-session (€3474) compared to the separate session (€4771) mainly due to lower hospital stay costs.

To our knowledge, we present herein the first cost-minimization analysis in this field. In our study, besides encountering support for previous data, we also evaluated other financial variables such as professional fees, endoscopic devices, and indirect costs including central services. The existence of various combinations of procedures has been taken into account, arranging them in 4 groups to facilitate understanding of the study. The single-session strategy showed a reduction of total costs mainly as a result of a reduction in procedure time, professional fees and hospital stay, without variations in the technical or clinical success.

Small sample size and selection bias are possible limitations, because this study was carried out in a tertiary centre and by a single operator experienced in both ERCP and EUS, which may limit generalizability to some extent. Logistical difficulties must be considered as significant limitations in that they prevented us from designing a prospective study with inclusion criteria. In our clinical practice, scheduling of combined procedures is challenging, because of coordination of equipment, fluoroscopy and personal schedules. These obstacles could explain a possible selection bias, excluding certain patients for these types of procedures, and could explain why this type of approach was not used in all consecutive patients during the study period. Some complex financial issues were not taken into account. We focused only on the hospital cost and did not take into account the financial aspect of the post-discharge period. Factors in support of this study include a clinical and financial analysis from a specific database of a heterogeneous group of patients, covering a period of 3 years and single interventional endoscopist, providing fewer potential confounding factors.

In conclusion, combined EUS–ERCP as a one-step intervention is safe, technically feasible, effective and cost beneficial, with a reduction in procedure duration and hospitalization days. It provides an accurate diagnosis and BD, improving the quality of life of the patient. Furthermore, in failed ERCP or inaccessible papilla cases, the drainage can be completed in the same procedure. We can recommend this strategy in hospitals without logistical difficulties, when the two procedures are indicated, thereby increasing the efficiency of the centre and improving the management of patients. In addition, based on our results, we believe that tertiary centres should strive to promote the training of qualified endoscopists to perform EUS and ERCP. Finally, the development of more advanced therapeutic echoendoscopes and specific devices to simplify and facilitate EUS-guided BD is needed.

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Conflict of interest

The authors declare that they have no conflict of interest or financial ties to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2013.01.023.

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Material suplementari (article de l'estudi 3) accessible *online:*

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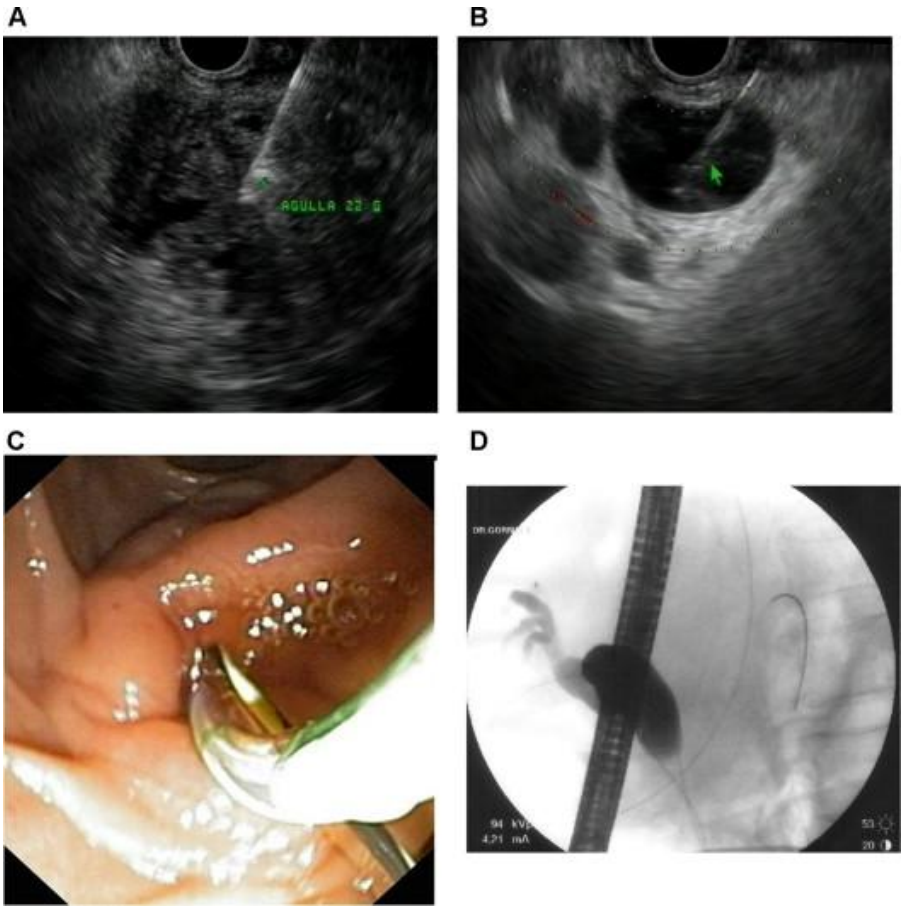

Supplementary Fig. S1. Endoscopic ultrasound-guided fine needle aspiration (EUS–FNA) and EUS-guided biliary via rendezvous in a patient with malignant biliary obstruction and failed endoscopic retrograde cholangiopancreatography in the same session. (a) EUS–FNA confirmed malignancy for a hypoechoic tumour in the pancreatic head. (b) EUS-guided transduodenal puncture and advance of a wire into a dilated common bile duct. (c) Endoscopic view of a transpapillary wire (arrow) placed under EUS-guidance and a sphincterotome used for cannulation alongside the wire (parallel rendezvous). (d) Cholangiographic view obtained after contrast injection under previous EUS guidance. The echoendoscope has been replaced by a duodenoscope. Rendezvous of two guidewires advanced across the distal biliary stricture via anterograde (arrow) and retrograde (arrowhead) respectively

Material suplementari (article de l'estudi 3) accessible *online:*

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Table S1: Complications and duration times

Complications	**Scenario**	**Outcomes**
*Arrythmia (n=1)	During a combined EUS-FNA and ERCP procedure in an elderly patient with cardiac history	Resolved conservatively. PTC for biliary drainage
Perforation (n=1)	Duodenal perforation with the tip of the echoendoscope before attempting a puncture	Resolved endoscopically with an OTSC clip
Bleeding + transfusion (n=2)	After precut during an ERCP; after unsuccessful EUS-guided intervention	Transfusion and 1 needed embolization
Mild pancreatitis (n=2)	After precut during ERCP	Resolved conservatively, <5-day hospitalization
Cholangitis/ Bacteriemia (n=3)	After 3 successful EUS-guided biliary transmural drainage	Antibiotics
Groups (n)	**Duration mean ±SEM and range (min)**	**Related complications**
A (4)	33.7 **±** 4.2 (25-45)	0
B (9)	53.4 **±** 3.7 (36-70)	3/35 (8%)
C (26)	65.4 **±** 3.7 (25-95)	
D (16)	78.4 **±** 5.9 (35-120)	5/16 (31%)
Total	64.9 **±** 3 (25-120)	8/55 (14%)

Groups: (A) EUS; (B) EUS plus ERCP; (C) EUS-FNA plus ERCP; (D) EUS-guided Biliary drainage after failed ERCP

* Complication not directly related to the EUS or ERCP procedure

EUS: endoscopic ultrasound; FNA: fine needle aspiration; ERCP: endoscopic retrograde cholangiopancreatography; OTSC: over-the-scope-clip; PTC: percutaneous transhepatic cholangiography

Material suplementari (article de l'estudi 3) accessible *online:*

J.B Gornals et al. Dig Liver Dis (2013), http://dx.doi.org/10.1016/j.dld.2013.01.023

Table S2: Total saved costs summarized by type of combination procedure

		Cost of single session		Estimated cost of separate session			
	N	**Unit**	**Total**	**Unit**	**Total**	**Single vs Separate Total cost saving**	**Individual cost saving**
A	4	236	945	236	945	0	0
B	9	1,410	12,693	1,519	13,672	- 979	-109
C	26	3,394	88,249	3,904	101,519	-13,269	-510
D	16	5,448	87,182	6,820	109,122	-21,939	-1,371
Total	**55**		**189,071**		**225,258**	**-36,189**	**-1.990**
Mean cost		**3,437**		**4,095**		**-658**	

Costs are in € for 2012

RESUM DELS RESULTATS

Les hipòtesis plantejades van ser testades a partir de 3 estudis que han donat lloc a les publicacions descrites prèviament, amb un factor d'impacte global de: 14,711

En resum, els resultats més rellevants dels estudis són els següents:

ESTUDI 1: Estudi per avaluar la utilitat de la PAAF guiada per ultrasonografia endoscòpica en el diagnòstic de tumors neuroendocrins

Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography. Rev Esp Enferm Dig 2011 Mar;103(3):123-8.

Es tracta d'un estudi descriptiu i retrospectiu mitjançant la revisió d'un protocol específic i les dades informatitzades que consten a les bases dels sistemes d'informació de 2 centres.

D'un total de 55 pacients amb sospita de TNE, es practicà USE radial o sectorial, i es varen detectar 42 tumors en 40 pacients. Es realitzà USE-PAAF utilitzant una agulla 22 G en 15 casos amb sospita de TNE (8 funcionants, 7 no funcionants). Totes les lesions foren sòlides. Es va poder practicar l'estudi immunocitoquímic (cromogranina i/o sinaptofisina, CD56 vs. altres) (taula I) de les mostres obtingudes per USE-PAAF en 12 casos, i es va poder determinar l'índex mitòtic de Ki-67 en 3 casos. La confirmació quirúrgica mitjançant l'estudi anatomo-patològic va ser possible en 9 casos (5 dones, 4 homes). Tots els tumors estaven localitzats a la glàndula pancreàtica (3 a cap, 2 a cua i 2 a cos), excepte un situat a mediastí i un altre a recte. La mida mitja dels tumors, fou de 19 mm (interval de 10-40 mm). Dos casos presentaren metástasis hepàtiques, el que implica un 12% de la sèrie. En 1 cas de TNE funcionant amb sospita

d’insulinoma, les proves d’imatge prèvies a la USE, no varen identificar una tumoració de 5 x 10 mm

La sensibilitat va ser del 100%, la precisió, i el valor predictiu positiu del 89%. Es donà un cas de fals positiu de TNE a l’estudi citològic, diagnosticat a la peça quirúrgica de tumor sòlid seudopapil·lar de cua pancreàtica. No es varen descriure cap tipus de complicacions significatives relacionades amb la tècnica de USE-PAAF.

ESTUDI 2: Estudi per avaluar el drenatge de col·leccions pancreàtiques guiat per ecoendoscòpia mitjançant una pròtesis metàl·lica d'aproximació luminal

Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. Surgical Endoscopy 2012, dec 12 (Epub ahead of print).

EUS-guided transesophageal drainage of a mediastinal pancreatic pseudocyst using a novel lumen apposing metal stent. Endoscopy 2012; 44: E1-E2.

Estudi multicèntric descriptiu prospectiu que inclou 4 centres terciaris de l'estat espanyol, els quals han realitzat drenatges transmurals de col·leccions pancreàtiques guiades per USE amb una pròtesi específica per comunicacions internes intraluminals. Elaboració d'un protocol de recollida de dades informatitzades que consten als sistemes d'informació de cada centre.

Comparació dels resultats amb una sèrie prèvia de 10 drenatges amb pròtesi plàstiques del nostre centre. Anàlisi estadística amb el sistema informàtic SPSS 13.0. Inclusió de 9 pacients, entre maig i setembre del 2011. Recollida prospectiva de dades dels pacients en fitxes individuals. Variables registrades: indicacions, dades demogràfiques, tècniques d'imatge prèvies, aspectes tècnics, resultats clínics, complicacions i el seguiment després del drenatge endoscòpic.

Detalls tècnics d'utensilis: pròtesi metàl·lica autoexpandible, format per filament de nitinol (níquel i titani) recoberta per una membrana de silicona i amb una morfologia novadora en forma de diàbolo (AXIOS™, Xlumena Inc, Mountain View, CA) per aconseguir una aposició luminal i evitar migracions. Utensili

d'accés i creador d'ostomia format per un trocar de punció-accés i un baló dilatador fins a 10mm, que permet la introducció de 2 guies dins la cavitat (NAVIX™, Xlumena Inc, Mountain View, CA).

Detalls tècnics dels procediments: sis drenatges amb control per fluoroscòpia i 3 només per visió USE. Dimensions utilitzades de la pròtesis AXIOS: 10 x 10mm i 10 x 15mm. En 6 casos l'accés i l'ostomia, es realitzà amb el sistema NAVIX. En 3 casos, l'accés i creació de la comunicació es realitzà amb la tècnica estàndard d'agulla de 19 gauges i baló dilatador. En tots els casos, s'administraren dosis d'antibiòtics profilàctics. El punt d'accés fou a l'estómac en 7 casos, esòfag distal en 1 (cas clínic referit i publicat), i duodè en 1. En 6 procediments, es realitzà una exploració de la cavitat (quistoscòpia) a través de la pròtesis metàl·lica alliberada. En 2 casos, es realitzà necrosectomia de fragments sòlids necròtics no adherits.

Es defineix com èxit tècnic, la col·locació tècnica correcta de la pròtesis entre la col·lecció i la llum del tub digestiu, i la visualització d'un drenatge òptim del líquid de la lesió a través de la pròtesis. L'èxit clínic, es defineix com la resolució total de la simptomatologia del pacient i una reducció >40-50% per prova d'imatge en el primer mes de seguiment.

Nou drenatges amb pròtesi AXIOS comparats amb 10 drenatges de pròtesi plàstiques. Temps mitjà del procediments-AXIOS, 25±13min. Èxit tècnic del 88,8%(8/9). Una complicació significativa (pneumotórax). No migracions i retirada de les pròtesis sense incidències. Bona evolució clínica i resolució

complerta en tots els casos. Temps mig de retirada de pròtesis, de 33±40 dies. Seguiment, 50±1,3 setmanes (45-55). Un cas de recidiva a les 4 setmanes de la retirada. En la comparació d'aquests resultats amb 10 drenatges de pròtesi plàstiques, el nombre de *stents* (n=15) i duració del procediment (42,8±3.1min) foren significativament superiors en el grup de *stents* plàstics incloent 2 migracions, 2 recidives i 2 complicacions.

ESTUDI 3: Estudi per avaluar la combinació de l'ecoendoscòpia i colangiografia retrógrada endoscòpica en un mateix procediment en patologia biliopancreàtica: impacte clínic i econòmic.

Single-session endosonography and endoscopic retrograde cholangiopancreatography for biliopancreatic diseases is feasible, effective and cost beneficial. Digestive Liver Disease (2013), http://dx.doi.org/10.1016/j.dld.2013.01.023

Estudi descriptiu i observacional amb inclusió prospectiva en una base de dades específica, dels 55 procediments combinats USE-CPRE realitzats entre abril 2009 fins març 2012, seguint un protocol de recollida de dades informatitzades que consten als sistemes d'informació del nostre centre.

Variables registrades: dades demogràfiques, indicacions, característiques dels procediments i complicacions. Detalls dels procediments inclosos: precisió diagnòstica PAAF, canul·lació biliar, drenatge biliar, duració. La decisió de realitzar el procediment combinat, fou discutida entre el metge responsable del pacient i l'endoscopista intervencionista, i segons la disponibilitat assistencial de la programació diària. Principals factors per programar el procediment combinat: sospita baixa- intermèdia de coledocolitiasis, i la indicació de USE-PAAF més la necessitat de drenatge biliar (ex. icterícia obstructiva per càncer de pàncrees) en un mateix pacient.

Detalls tècnics: tots els procediments es realitzaren amb sedació profunda i en una sala amb fluoroscòpia disponible. En 6 casos només s'utilitzà ecoendoscopi radial, i en la resta l'ecoendoscopi sectorial (terapèutic). En tots els casos, es realitzà un estudi USE de la via biliar, glàndula pancreàtica i regió

papil·lar (en cas de ser accessible). En 4 casos amb risc entremig de coledocolitiasis, la USE fou normal, i no es realitzà la CPRE. En els casos d'identificar una tumoració sòlida amb semiologia USE sospitosa de malignitat, es realitzà USE-PAAF amb la tècnica estàndard utilitzant agulla de 22 gauges (mitjana: 2 passades). L'atípia es considerà sospitosa però no positiva a malignitat. Mentrestant el material obtingut era processat i avaluat, es procedia a iniciar una CPRE amb el duodenoscopi. En 6 casos, obtenció de mostra citològica addicional mitjançant raspallat de la via biliar. En 15 casos de canul·lació no possible per CPRE (o la papil·la no accessible), es realitzà un accés biliar guiat per USE en la mateixa sessió.

Anàlisi econòmic: dades obtingudes amb la col·laboració del departament econòmic i finançer del nostre centre. Es realitzà un estudi de costos, atenent a que els resultats obtinguts de les 2 estratègies (combinar els procediments vs. estimació de procediments separats) són iguals o amb diferències mínimes. L'anàlisi de costos directes inclou: salaris professionals, costos dels materials, tipus de procediment i costos de l'hospitalització estimada. Els costos dels materials inclouen: instrumental endoscòpic, material no reutilitzable i anestèsia. Depenent del tipus de procediment combinat els costos derivats foren dividit en diferents grups: A (USE); B (USE i CPRE); C (USE-PAAF i CPRE) i D (intent d'accés biliar per USE en CPRE fallida). La mitja de la duració dels procediments i dies d'estància hospitalària, foren calculats per estimar els costos de l'hospitalització en cada grup. Els costos indirectes com els serveis centrals també es varen incloure. Els costos finals estimats foren comparats amb els costos de l'estratègia de procediments separats. El càlcul

de l'hospitalització d'aquesta estratègia es va extrapolar, segons el protocol d'estància hospitalària del nostre centre.

Anàlisi estadística: per les variables que segueixen una distribució normal, els seus resultats s'expressen com mitja i error estàndard de la mitja, i rang estadístic. Les proporcions s'expressen en números i percentatges. A l'anàlisi univariant, s'utilitzà la χ^2 i el test exacte de Fisher per variables qualitatives, i la t de *Student* en variables quantitatives. Per l'avaluació de l'associació significativa entre variables, s'utilitzà la *odds ratio* i el seu interval de confiança S'estableix que l'anàlisi és significatiu quan $p<0.05$. S'ha utilitzat el programa informàtic SPSS 13.0 per l'anàlisi estadística.

En total es van realitzar 55 procediments combinats en 53 pacients, incloent 16 intents d'accés biliar guiat per USE en CPRE fallides. Es manté l'eficàcia i seguretat d'ambos procediments realitzats en 1 sessió combinada. En 11 casos de CPRE fallida, el drenatge es completà amb un accés biliar per USE. Mitjana global de duració dels procediments de 65±22,2 min. Mitjana del cost estimat per procediment combinat de 3.437€ i de 4.101€ per procediments separats. Estalvi de costos estimat, amb l'estratègia combinada, de 663€ per procediment; representant un estalvi total en els casos estudiats.

VI. DISCUSSIÓ

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Els resultats d'aquesta tesi manifesten en primer lloc que l'ecoendoscòpia intervencionista és una tècnica efectiva en el diagnòstic de tumors neuroendocrins; en segon lloc, que l'aportació de la nova tecnologia en el camp de l'ecoendoscòpia intervencionista incrementa la seguretat i eficàcia en el drenatge de col·leccions intrabdominals; i finalment, que és factible combinar l'ecoendoscòpia amb la colangiografia retrògrada endoscòpica mantenint l'eficàcia i seguretat de cada prova per separat, oferint unes avantatges des del punt de vista clínic, terapèutic i econòmic.

ESTUDI 1:

El primer estudi d'aquesta tesi doctoral demostra que la USE-PAAF presenta un elevat rendiment en el diagnòstic diferencial i confirmació de tumors neuroendocrins. Els TNE conformen un grup de tumors heterogeni, amb una presentació clínica i conducta diferent al tumor més comú: l'adenocarcinoma de pàncrees. La troballa casual d'aquests tipus de tumors en les proves d'imatge de control o *screening,* ha fet augmentar la seva incidència en els darrers anys, a expenses dels TNE no funcionants asimptomàtics (56).

En el nostre estudi, es descriu un percentatge més alt de tumors no funcionants envers a funcionants, ja descrit en alguns estudis recents (57, 58), i és una dada contrària al reportat a la literatura en estudis més inicials (59). A més, la majoria de tumors es presenten com solitaris i només en 2 casos com lesions múltiples (MEN-1). Per altra banda, també es descriuen casos amb metástasis hepàtiques, semblant al 15% descrit en sèries de la literatura més llargues (56).

A pesar de que les proves d'imatge han evolucionat molt en els últims anys, està descrit a la literatura que en TNEs de petita mida poden passar desapercebuts en l'estudi d'un TCMD (60). Recentment s'han publicat quatre casos (61) que coincidien TNE pancreàtics petits (8-16 mm) no funcionants amb neoplàsies mucinoses papil·lars intraductals. Aquests TNE no es varen detectar per les tècniques habituals d'imatge (TC i RM), 3 dels 4 mitjançant USE, i només 1 es diagnosticà per USE-PAAF.

Des de fa més de 12 anys, que es practica USE-PAAF als TNE. Inicialment la sensibilitat era baixa però s'ha anat incrementant fins a un 90% (29, 57,58, 62-77). Les troballes típiques de la USE són l'observació de nòduls pancreàtics sòlids de patró hipoecoic i homogeni, hipervascularitzats, i de límits precisos i ben definits (57). La realització de tècniques d'immunocitoquímica (cromogranina, sinaptofisina, citoqueratina19) incrementa la sensibilitat del material citològic i és necessari per el diagnòstic confirmatori de TNE. També s'ha valorat l'estudi de l'índex mitòtic Ki67 i la inestabilitat dels microsatèl·lits per avaluar la benignitat – malignitat d'aquests tumors (30, 74-79). En el nostre estudi es va poder determinar en pocs casos l'índex mitòtic de Ki-67 amb el material obtingut amb agulla 22 G, i en quasi tots els casos, l'estudi immunocitoquimic habitual per la sinaptofisina i/o la cromogranina.

En l'estudi de Larghi i col., es va poder determinar el ki-67 per USE-PAAF utilitzant agulles més gruixudes, de 19 G, en 18 (75%) de 24 casos (78). El coneixement de l'expressió Ki-67 en els TNE no funcionants, pot tenir un impacte en el seu algoritme assistencial. En TNE no funcionant de mida > 2 cm, l'actitud clarament és quirúrgica. En canvi, quan la mida és < a 2 cm, solen ser lesions de risc baix o intermig i no queda tan clar el potencial benefici d'una

resecció quirúrgica, sobre tot en localitzacions de cap pancreàtic on la cirurgia es més agressiva. Valors <2% de Ki-67 suggeriria un grau baix de malignitat, i recolzaria una actitud conservadora, de seguiment. També tindria la seva utilitat en casos de TNE no funcionants i irressecables, ja que conèixer el valor del ki-67, ajudaria als oncòlegs a escollir el tractament mèdic més apropiat (20, 80, 81).

El diagnòstic diferencial que es planteja davant una sospita de TNE, pot incloure el tumor sòlid pseudopapil·lar, els carcinomes de cèl·lules acinars, els tumors mucinosos i el limfoma/plasmocitoma. Diferenciar els tumors sòlids pseudopapil·lars dels TNE a vegades no és tan fàcil, tal com es reflexa a la nostra experiència. Estan descrits casos de tumors sòlids pseudopapil·lars en que la immunocitoquímica de les mostres obtingudes per USE-PAAF és vimentina i citoqueratina positives, amb cromogranina, ENE negatives i altres marcadors específics (30-34, 82). En el nostre estudi, vàrem tenir un fals positiu de TNE, que finalment va ser un tumor sòlid pseudopapil·lar.

La immunocitoquímica realitzada en les mostres de citologia obtingudes per USE-PAAF és fonamental per el diagnòstic definitiu dels TNE. El nostre estudi, descriu una S del 100%, E 95% i VPP del 89%. Aquestes xifres són semblants a les descrites per altres grups (73, 83). En el diagnòstic anatomopatològic, cada vegada existeixen més marcadors específics com el SERPINB8 (84), CDX-2, PDX-1, NESP-55 I TTF-1 que poden ajudar en el diagnòstic diferencial entre TNE i carcinoides GI o pulmonars (85). Així i tot, els marcadors més importants des de fa anys fins a l'actualitat són la cromogranina i la sinaptofisina (86).

Les limitacions que es poden atribuir a l'estudi, són les similars als estudis retrospectiu, com la pèrdua de certa informació que ha limitat la correlació de la USE amb les altres proves d'imatge; i un possible biaix associat a les facilitats derivades de la disponibilitat de citopatòlegs experts en el maneig de mostres obtingudes per PAAF.

Com a conclusió, en casos de sospita de TNE no funcionant o dubtes per prova d'imatge en funcionants, la USE-PAAF amb agulla 22 G permet establir el diagnòstic definitiu mitjançant l'estudi immunocitoquímic de les mostres obtingudes amb un percentatge de complicacions baix.

ESTUDI 2:

El segon estudi d'aquesta tesis doctoral ha permès avaluar una nova tecnologia dissenyada específicament per ser emprada en la USE terapèutica per la creació de comunicacions intraluminals. Fins a l'actualitat el drenatge de col·leccions annexes al tub digestiu realitzades per USE s'ha realitzat amb material 'llogat' del camp de la CPRE com són les pròtesi biliars metàl·liques o plàstiques de morfologia tubular. Aquesta estudi descriu la primera experiència a nivell europeu i nacional amb una nova pròtesi metàl·lica totalment coberta de disseny novell en forma de 'diàbolo' per prevenir el risc de migració interna o externa; de diàmetre ampli per assegurar un drenatge ràpid del fluid i que permeti accedir a les col·leccions a través de la pròtesi en cas de precisar terapèutica (ex. existència de necrosis); i totalment coberta per evitar fuites del líquid i ser fàcilment extraïble.

Aquesta experiència inicial, descriu una reducció del temps habitual del procediment amb menys nombre de complicacions com la migració i la recidiva.

Els resultats recolzen l'opció de realitzar els drenatges de col·leccions pancreàtiques guiat per USE, i la possibilitat d'utilitzar pròtesi metàl·liques, com a alternativa a les pròtesis plàstiques. En casos de col·leccions complexes (mida gran, contingut sòlid) es podria contemplar utilitzar-les de primera opció.

El drenatge transmural guiat per USE de les col·leccions comporta un grau de dificultat tècnica, implica una duració del procediment llarga i requereix d'una experiència i corba d'aprenentatge (40, 87). Amb l'aparició dels ecoendoscopis lineals amb canal de treball ampli (3,7 mm), que permeten el pas d'utensilis del tipus "through the scope" (TTS) com les pròtesis, ha obert noves fronteres en el camp de l'endoscòpia intervencionista terapèutica. Però, encara hi ha qüestions no resoltes com és el tipus i nombre de pròtesis. La col·locació de 1 o més pròtesis plàstiques és el que està més reportat a la literatura, però aquest tipus de *stent* implica un diàmetre reduït, (màxim 3,3 mm; 10 Fr.) i s'han descrit complicacions com la migració i obstrucció de la seva llum.

Recentment, en algunes sèries de casos reduïdes, s'ha descrit l'experiència de realitzar els drenatges transmurals emprant pròtesis SEMS (biliars, enterals,...), per resoldre el problema del diàmetre de l'ostomia i facilitar així el drenatge de les col·leccions (36-38, 88). Però aquest tipus de pròtesis metàl·liques presenten una morfologia tubular i no estan dissenyades per ser utilitzades en drenatges transmurals. Per tant, no són una bona opció en casos de que la col·lecció no es troba ben adherida a la paret del tub digestiu per què no realitzaran una força d'ancoratge, i s'associarà a un alt risc de possible fuita de líquid a la cavitat peritoneal. A més, els extrems d'aquest tipus de pròtesis és recte, pot causar traumes per decúbit a dins la lesió, comportant risc de

sagnat i/o perforació (31). Per aquests motius, recentment Binmoeller va descriure la primera experiència en model ex-vivo i animal, i posteriorment en una sèrie de 10 casos (8 col·leccions pancreàtiques), utilitzant una pròtesis de disseny diferent, tipus diàbolo (AXIOS™) amb l'ajuda dels utensilis d'endoscòpia habituals (39, 40).

En la mateixa línea, també es va dissenyar un nou utensili d'accés anomenat NAVIX, per facilitar la tècnica i reduir la necessitat d'intercanvi de material durant la creació de l'ostomia que comunica la col·lecció amb la paret del tub digestiu (89).

En la nostra experiència, l'ús d'aquest nou *stent* comporta vàries avantatges: 1) un sistema d'alliberació senzill i precís que facilita la seva reproductibilitat. És fàcil d'usar i només vàrem tenir una fallida del sistema d'alliberació, degut a una fallida tècnic en la fase final d'alliberació; 2) està dissenyat específicament per ser emprat amb un ecoendoscopi terapèutic (lineal), per tant la imatge USE és excel·lent i pot ser una raó per prescindir de l'ajuda de la fluoroscòpia, ja que no es troba present en totes les unitats d'endoscòpia digestiva on es realitza USE, com en 3 dels casos del nostre estudi (90); 3) és menys laboriós, i redueix el temps de duració dels procediments, amb una mitja de 25 minuts, incloent 6 procediments de menys de 30 minuts; 4) i l'èxit clínic descrit és semblant al descrit sense més complicacions significatives i 0% morbiditat.

A més, els diàmetres amplis de la pròtesis, a part de facilitar un drenatge de major dèbit, permeten realitzar exploracions de les cavitats (quistoscòpia) amb finalitats diagnòstiques i terapèutiques. En alguns casos, es varen realitzar quistoscòpies, amb videogastroscopis a través de la pròtesi, sense

descol·locar-la del seu lloc i permetent així la pràctica de necrosectomies endoscòpiques.

Finalment, no es van descriure casos de migració o fuita de líquid en la nostra sèrie. Així i tot, aquest potencial benefici hauria de ser confirmat amb un major nombre de pacients. Respecte als beneficis de l'ús del sistema d'accés NAVIX, en aquesta experiència vàrem observar una reducció en la mitja de duració dels procediments en que ho vàrem utilitzar, en comparació amb els altres en que es van emprar varis estris que requerien passos d'intercanvi d'utensilis.

Comparant aquests resultats amb casos previs de drenatges de col·leccions pancreàtiques amb pròtesis plàstiques, varen existir diferències significatives en quant al temps de duració dels procediments degut a: la necessitat d'un intercanvi laboriós d'utensilis; i la dificultat tècnica afegida alhora de col·locar més d'una pròtesi plàstica a través de l'ostomia en una mateixa sessió. En aquests casos, existiren algunes migracions que varen precisar de nous procediments. Aquests procediments, varen requerir l'extracció de les pròtesis plástiques, noves dilatacions i recol·locació dels stents amb nous models de pròtesis plàstiques, implicant per tant, un important temps per les proves.

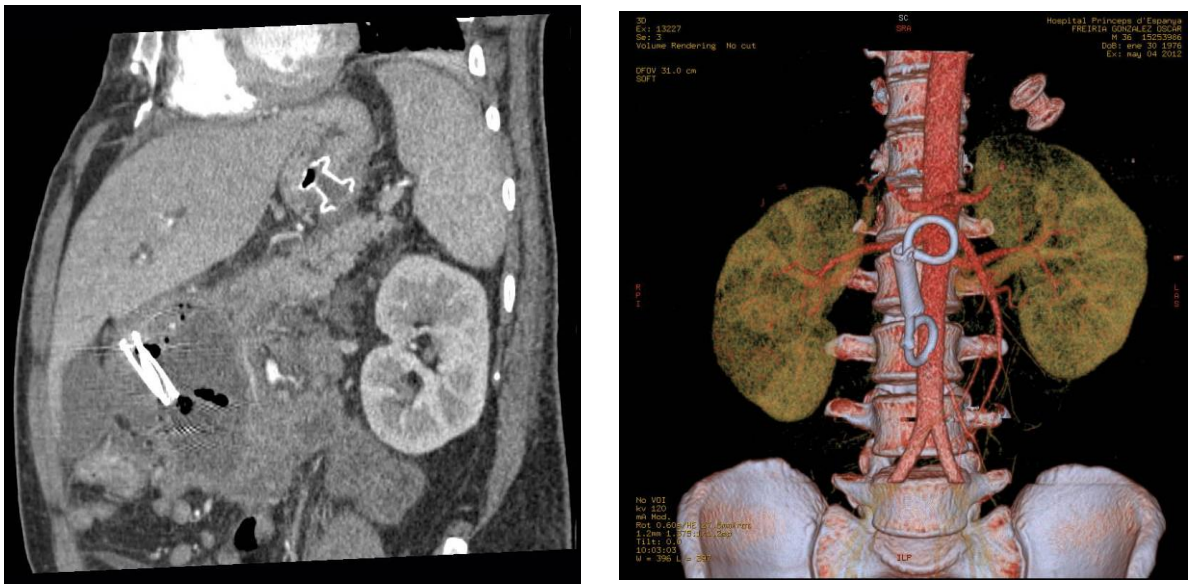
El petit número de casos i l'heterogeneïtat d'ambos grups (més casos de WOPN en el grup AXIOS), són les principals limitacions d'aquest estudi. Aquest fet, pot explicar el nombre similar de sessions en ambos grups, entenent que les WOPN per la seva complexitat, requereixen d'un maneig endoscòpic més agressiu amb més nombre de quistoscòpies i necrosectomies. En termes econòmics, a primera vista, l'ús de SEMS pot parèixer més car, però si es

redueix la duració dels procediments i, a la llarga implica menys nombre d'intervencions, el cost final serà menor (91).

A mode d'exemple, es cita un cas clínic (annex 1, 92) de 2 col·leccions pancreàtiques infectades en context d'una pancreatitis aguda necrotitzant severa que van ser tractades amb drenatges transmurals guiats per USE. La ressolució d'una col·lecció emprant un stent 'diàbolo' fou més ràpida, precisant només 1 sessió i sense cap complicació, envers a la necessitat de més sessions i recanvi de pròtesis, en la segona col·lecció tractada amb pròtesis convencionals (figura 9).

En conclusió, el drenatge de col·leccions pancreàtiques utilitzant utensilis específics, com aquest nou tipus de pròtesi amb un disseny especial és factible, més ràpid, eficaç i segur. Es necessiten estudis prospectius i randomitzats per validar i confirmar els resultats del nostre estudi.

Figura 9: tall coronal-sagital oblic de TCMD (esquerra) i reconstrucció 3D (dreta) que inclou 2 pròtesis metàl·liques autoexpandibles totalment cobertes en un mateix pla: una quistogastrostomia amb pròtesi de disseny 'diabolo'; i una quistoduodenostomia amb una pròtesi biliar totalment coberta de morfologia tubular amb pròtesi plàstica doble pigtail coaxial.



Imatges de l'autor i publicades. JB. Gornals (92). Annex1, #4: Fig. 3a i Fig. 3b.

ESTUDI 3:

Per últim, el tercer estudi d'aquesta tesi doctoral presenta l'experiència pionera en el nostre entorn, de combinar l'ecoendoscòpia i la colangiografia retrògrada endoscópica en un mateix procediment en la patologia biliopancreàtica amb la intenció: 1) d'evitar segones exploracions; 2) agilitzar la dinàmica de l'estudi diagnòstic; 3) sumar els beneficis potencials de cada prova per separat en una sessió mantenint el mateix grau de seguretat; i 4) oferir en un grup de pacients amb CPRE fallida que precisen de drenatge biliar preferent, el potencial de la USE terapèutica en accessos biliopancreàtics (CPES) per completar el drenatge en una sessió endoscòpica i estalviar així la necessitat d'una CTPH.

L'anàlisi demostra que aquesta estratègia comporta un benefici clínic amb menys estància hospitalària, menys duració global del procediment i que en casos de drenatges biliars fallits per CPRE, es poden completar per CPES.A més, l'estudi de minimització de costos realitzat, també confirma el benefici econòmic de l'estratègia combinada envers a realitzar 2 procediments per separat. Aquests resultats, recolzarien un interès d'hospitals terciaris en la formació d'endoscopistes intervencionistes competents en les 2 tècniques per poder aprofitar el potencial intervencionista i terapèutic que ofereix combinar la USE i la CPRE.

Estudis previs sobre la combinació de USE i CPRE descriuen troballes similars al nostre estudi, descrivint que realitzar una USE-PAAF i a continuació la CPRE amb col·locació d'una pròtesi biliar metàl·lica en una mateixa sessió es pot dur a terme, sense compromís del seu rendiment diagnòstic (90%) i de forma segura per el pacient. A la vegada, seguint la filosofia de '*Brothers in*

arms' esmentada per Hollerbach (45), en casos de drenatges fallits per CPRE, es poden beneficiar del potencial terapèutic derivats dels procediments intervencionistes terapèutics guiats per USE, durant la mateixa sessió (54).

Inicialment, algunes primeres experiències varen posar en dubte la seguretat de realitzar aquests tipus de procediments junts en una única sessió, en casos clínics on es referien fuites de contrast i pneumoperitoni durant la CPRE realitzada de forma consecutiva després d'una USE-PAAF (93, 94).

Recentment, vàries publicacions sobre l'experiència de combinació en una única sessió incloent sèries de 19 fins a 110 casos (46-55), intenten demostrar que l'estratègia és factible i reproduïble sense un increment significatiu de les complicacions (entre 2-10.5%). En el nostre estudi, el percentatge global de complicacions va ser del baix, incloent les associades als procediments de la USE intervencionista terapèutica (CPES). En cas de que no es considerin aquestes, el percentatge de complicacions es redueix més encara, sent similar al percentatge conegut per cada procediment per separat.

Estudis previs han suggerit que pacients d'edat avançada poden patir un increment de dany miocardi en CPRE de llarga durada (95). Per altra banda, altres autors com Iles-Shih y col. en un estudi amb 107 pacients majors de 65 anys, han confrontat aquestes troballes (47,52). En el nostre estudi, un pacient d'edat avançada va patir una taquicàrdia ventricular que es va resoldre espontàniament, però obligà a suspendre abans d'hora l'exploració. Aquesta complicació, no es considerà directament relacionada amb el procediment tècnic endoscòpic. A més, el temps global dels procediments de l'estudi, no s'associà amb el percentatge de complicacions (no diferències significatives).

Un altre punt a comentar, és que la pràctica de la USE-PAAF i el seu rendiment diagnòstic no es varen veure afectats. Per aquesta raó, estem d'acord amb altres autors (41, 47) que creuen que si la USE-PAAF no perd rendibilitat, permet estalviar la pràctica de raspallats biliars en la CPRE posterior, i d'aquesta manera es pot estalviar un temps addicional.

El temps mig del global de la duració dels procediments combinats realitzats a l'estudi foren similars o, fins i tot, millors que els descrits per altres publicacions (47, 95, 96). En el casos més intervencionistes com els drenatges biliars per USE (o CPES), la duració va ser major que la resta de procediments combinats, tal com també està reflectit a la literatura recent (54).

Respecte a quin procediment ha de ser el primer (USE o CPRE), alguns autors han comentat que començar amb la col·locació d'una pròtesi per CPRE podria millorar l'estudi biliar per part de la USE, per què la pròtesi serviria de guia o referència en la imatge (41). Altres, clamen que el rendiment diagnòstic de la imatge USE es podria veure alterat respecte a realitzar la prova en condicions naïve, podent tenir un impacte negatiu en casos d'estudi d'extensió de patologia maligna (97, 98). A partir de la nostra experiència, preferim realitzar l'estratègia 'USE-primer' en casos de patologia maligna per varis motius: si la PAAF confirma malignitat, podem obviar la necessitat de realitzar un raspallat biliar via CPRE, i en alguns casos aquesta informació de confirmació de la positivitat de la PAAF ens pot ajudar a escollir entre el tipus de pròtesi; plàstica o metàl·lica. Mentrestant, es processa el material citològic i esperem els resultats, es va iniciant la CPRE, per així guanyar temps i disminuir la duració del procediment.

Rocca i col. (49) varen publicar un estudi emprant un ecoendoscopi per avaluar la via biliar i alhora, amb el mateix tub, canular la via biliar i practicar l'esfinterotomia de la CPRE que habitualment es realitza amb un videoduodenoscopi. Suggereixen que la utilització d'un ecoendoscopi lineal podria oferir un estudi biliar per imatge USE i un tractament a la vegada, evitant l'exposició de Rx. A la nostra experiència, es va intentar canular la via biliar amb el mateix ecoendoscopi lineal en tots els casos de papil·la accessible, i només va ser possible en molts pocs casos. El concepte d'un sol endoscopi que permeti realitzar les funcions de USE i CPRE és atractiva, però encara lluny, i haurem d'esperar el desenvolupament de noves tecnologies.

La principal indicació pel drenatge biliar va ser la icterícia de causa maligna. Aquest fet, explicaria l'alt grau de dificultat en la canulació biliar en tots els casos, i la principal raó de per què el percentatge d'èxit d'accés a via biliar per CPRE fos baix en una unitat d'endoscòpia referent amb un èxit de canulació regularment alt. En un nombre significatiu de pacients es realitzà un drenatge biliar guiat per USE (CPES), i en la majoria d'ells com a actitud pal·liativa. En tots els casos, excepte dos, tenien papil·la accessible al duodenoscopi, i en tots es realitzà pretall com a intent previ d'accedir a la via biliar. Aquest punt permet explicar, un percentatge relativament alt de complicacions relacionats amb la CPES, quasi significatiu. En un cas, que presentà un sagnat a nivell papil·lar, creiem que estava més associat a la manipulació per CPRE que a la intervenció de la CPES. Tenint en compte aquest fet, el percentatge de complicacions associat a l'intervencionisme terapèutic guiat per USE seria aproximadament d'un 25%, semblant als descrits per altres grups, entre un 10-36% (54, 99). En els drenatges transmurals de la

via biliar guiat per USE s'observaren 3 colangitis, i cap per tècnica rendezvous. Per tant, estem d'acord amb Shah i col (54), quan comenten que segurament la posició final de la pròtesi en un drenatge transmural no es tan fisiològica i anatòmica que la posició aconseguida via rendezvous, idèntica a la col·locada via CPRE.

El percentatge d'èxit publicat fins a dia d'avui en sèries de casos de CPES realitzats en una segona sessió posterior a una CPRE fallida, és entre 67% i 100% (100). En el nostre estudi, l'èxit fou semblant, d'un 73.3% en 15 pacients, excloent un cas de perforació duodenal, abans d'iniciar les maniobres de la tècnica d'accés biliar guiat per USE (annexa 1; 101). La tècnica CPES, en el nostre estudi ens va ajudar a incrementar el percentatge de canulació biliar d'un 66% a un 89%, la majoria afectes d'icterícia maligna obstructiva.

A dia d'avui, l' interès de portar a terme anàlisis econòmics prové de la necessitat de gestionar els recursos de manera òptima, els quals es troben bastants necessitats i limitats en el context social actual que vivim. Algun anàlisi de costos s'ha publicat en el camp d'estratègies de maneig en el diagnòstic del càncer pancreàtic (102). Respecte a l'estratègia d'una única sessió USE-CPRE, s'ha suggerit en algun treball que podria ser una maniobra cost-efectiva, però sense estudiar-se de forma especifica en un anàlisi de minimització de costos. En la revisió de la literatura realitzada en aquesta Tesi, s'han trobat 2 estudis randomitzats per Fabbri i Liu (55, 103) comparant la USE més CPRE en un mateix procediment endoscòpic respecte a fer-ho en 2 sessions separades, en el maneig de pacients amb baix risc de coledocolitiasis i en pancreatitis aguda. A l'estudi de Fabbri, es va dur a terme un anàlisi econòmic, descrivint

un cost total més baix en el grup d'una única sessió envers al grup de 2 sessions separades, a expenses d'una estància hospitalària més reduïda.

En el nostre estudi, a part de que els resultats recolzen les dades d'aquests estudis previs, es varen avaluar una sèrie de variables noves i diferents com els honoraris dels professionals (endoscopista, anestessiòleg, equip de citopatologia i personal d'infermeria), instrumental d'endoscopia digestiva i costos indirectes incloent serveis centrals.

L'existència de vàries possibles combinacions de tipus de procediments s'ha tingut en compte, per aquest motiu s'han distribuït en 4 grups per facilitar la comprensió i lectura de l'anàlisi. L'estratègia d'una única sessió en el nostre estudi, ha demostrat una reducció dels costos globals, principalment a expenses d'una reducció en la duració dels procediments, dels honoraris i de l'estància hospitalària, sense variacions en l'èxit tècnic i clínic.

Limitacions:

Aquest estudi no està lliure de limitacions. La mida relativament petita de la mostra, així com un possible biaix en la selecció dels pacients s'expliquen en part, per què l'estudi s'ha dut a terme en un únic centre terciari i amb només un endoscopista experimentat o competent en les 2 proves, USE i CPRE. L'existència de dificultats en l'àmbit logístic i d'infraestructures derivades de ser un centre públic que posa enmarxa una técnica nova, també es poden considerar limitacions significatives. En la nostra pràctica clínica habitual, la gestió de programar de procediments combinats (USE+/-PAAF i CPRE) és autenticament un repte assistencial, per la necessitat de coordinar els 2 equips d'endoscòpia, la sala de radiologia i les agendes del personal de suport.

Aquests “obstacles” reflecteixen les condicions reals del dia a dia i, poden ser una explicació clara d’un probable biaix en la selecció dels casos, excloent així alguns pacients candidats a l’estratègia combinada per falta de disponibilitat logística, i impedint la seva aplicació de forma consecutiva a tots els possibles candidats. En l’apartat econòmic, alguns aspectes més complexes fora de l’àmbit hospitalari no es varen tenir en compte. Només es varen analitzar els costos hospitalaris, sense afegir els aspectes econòmics del període després de l’alta mèdica.

Resum de l’estudi 3:

Com a conclusió, la combinació USE-CPRE, en un únic procediment és segura, tècnicament factible, eficaç i cost-efectiva amb una reducció clara en el temps de duració del procediment i dies d’hospitalització. Alhora, ofereix un diagnòstic precís i drenatge biliar, millorant la qualitat de vida del pacient. A més, en CPRE fallides o papil·les inaccessibles, el drenatge biliar endoscòpic es pot completar amb l’ajuda de la USE, l’anomenada CPES, en la mateixa sessió. Aquesta estratègia es pot recomanar en hospitals terciaris sense problemes o dificultats logístiques, quan els 2 procediments estan indicats en un mateix pacient, optimitzant així l’eficiència del centre i millorant el maneig dels pacients. A partir d’aquests resultats, creiem que centres terciaris universitaris, haurien de promoure l’entrenament d’endoscopistes qualificats en USE i CPRE. Finalment, esmentar que és necessari encara el desenvolupament d’ecoendoscopis terapèutics més avançats i en material fungible més específics per facilitar i simplificar la tècnica del drenatge biliar guiat per USE.

VII. CONCLUSIONS

VII. CONCLUSIONS

Dels resultats obtinguts dels estudis que formen part d'aquesta Tesi, podem concloure que:

1. La punció aspirativa amb agulla fina (22 G) guiada per ecoendoscòpia en l'estudi dels tumors neuroendocrins presenta una elevada sensibilitat i valor predictiu positiu en la seva confirmació citològica, sense complicacions significatives.

2. En la nostra sèrie de tumors neuroendocrins, es recolza el fet de que la incidència dels tumors no funcionants assimptomàtics augmenta i supera als funcionants. Per tant, es reforça el paper de la punció guiada per ecoendoscòpia en el diagnòstic d'aquest tipus de lesions.

3. El drenatge transmural de col·leccions pancreàtiques amb una pròtesis metàl·lica totalment coberta de nou disseny (AXIOS), en la nostra experiència, s'ha mostrat eficaç, ràpid i segur sense observar migracions, pel que suposa una innovació tècnica per al futur.

4. La comparació de la pròtesi AXIOS amb les pròtesi plàstiques doble pigtail, destaca una reducció significativa del temps del procediment.

5. La combinació de la USE i CPRE en una mateixa sessió és efectiva, segura i ofereix uns millors resultats assistencials i econòmics.

6. En l'aspecte assistencial, aquesta estratègia combinada millora els paràmetres de qualitat del pacient: disminueix l'estància hospitalària, evita doble sedacions i revisites, facilita el maneig clínic, i millora el confort global i el cost social.

7. A més, aquesta combinació de USE i CPRE en una mateixa sessió, s'ha mostrat segura, amb un percentatge baix de complicacions. En el grup de pacients amb CPRE fallida i posterior drenatge biliar completat per ecoendoscòpia, és on hem d'esperar més nombre de complicacions, al requerir un abordatge més agressiu.

8. En l'aspecte tècnic, l'estratègia combinada en els casos de CPRE fallida va ajudar a incrementar el percentatge global assolit de drenatge biliar gràcies a l'accés biliar guiat per ecoendoscòpia.

9. En el nostre cas, en contra d'alguna experiència prèvia descrita a la literatura, no s'ha pogut completar la CPRE amb el mateix tub, o ecoendoscopi sectorial, després de realitzar la USE. Aquest fet recolza, en la nostra opinió, la necessitat d'innovar en endoscopis més específics que cobreixin les necessitats d'ambdues proves en un únic tub.

10. En l'aspecte econòmic, el cost de la combinació de la USE i CPRE en una única sessió, és inferior als costos d'ambdues tècniques sumades per separat. Aquesta reducció en el cost de la combinació en una sola sessió és atribuïble a una menor necessitat de recursos de personal, la menor duració de la prova i la disminució de l'estància hospitalària.

VIII. BIBLIOGRAFIA

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IX. ANNEXES

IX. ANNEXES

Annex 1

Altres articles publicats relacionats amb el tema de la Tesi:

1. **Gornals JB**, Varas M. J, Bhutani M.S. Novel aspects of diagnostical and interventional Endosonography. **Rev Esp Enferm Dig 2007; 99 (supl. II): 36-56** (Factor d'impacte: 1.548)
2. **Gornals JB**, Baixeras N, Paules MJ, Mast R, Pujol R. *Diagnosis of Whipple's disease by EUS-guided-FNA and endoscopic biopsy at the same procedure.* **Gastrointest Endosc 2012; 75: 895-896** (Factor d'impacte: 5.608)
3. Salord S, **Gornals JB**, Maisterra S, Pons C, Busquets J, Fabregat J. Endoscopic closure of duodenal perforation with an over-the-scope clip during endoscopic ultrasound-guided cholangiopancreatography. **Rev Esp Enferm Dig 2012; 104: 489-490** (Factor d'impacte: 1.548)
4. **Gornals JB**, Parra C, Pelaez N, Secanella Ll, Ornaque I. Double endosonography-guided transgastric and transduodenal drainage of infected pancreatic-fluid collections using metallic stents. **Rev Esp Enferm Dig 2013** (acceptat, pendent de publicació) (Factor d'impacte:1.548).

APRENDIZAJE DE USE

La ecoendoscopia es una de las especialidades dentro del mundo de la endoscopia más difíciles de aprender y manejar, junto a la dificultad de encontrar centros con un programa de formación organizado. La experiencia previa en endoscopia convencional, con duodenoscopio de visión lateral y en ecografía abdominal, son esenciales.

El aprendizaje debe incluir formación teórica con libros de texto específicos (113,114,120), atlas de anatomía para entender e interpretar las imágenes de USE (www.sepd.es/ecotest), artículos, diapositivas, CD-ROM, videocasetes, y autoestudio. Por otro lado, la formación práctica junto a un ecoendoscopista experimentado es imprescindible (114,115).

El entendimiento y comprensión de la localización y orientación de los diferentes planos ecográficos es difícil debido a los múltiples planos creados y los constantes cambios con el movimiento del tubo. El *'Digital human anatomy and endoscopic ultrasonography'* es un atlas de reciente publicación (116), con imágenes extraídas del visible *human project* (VHP) y aplicadas a los planos obtenidos por ecoendoscopia radial y sectorial. Una gran ayuda para entender mejor las imágenes ecoendoscópicas.

El VHP es una base de datos de toda la anatomía humana, promovido por la *National Library of Medicine* (117), y elaborado en la Universidad de Colorado, Center Human Simulation en 1995 (www.visiblehuman.org).

NOVEL ASPECTS OF DIAGNOSTICAL AND INTERVENTIONAL ENDOSONOGRAPHY

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INTRODUCTION

Endoscopic ultrasound (EUS) combines and integrates endoscopic and ultrasonography imaging in the same scope. It enables clinicians to obtain real-time sonographic images for diagnostic and/or therapeutic purposes.

Three different systems exist:

—Radial system: diagnostic EUS.

—Linear system: interventional EUS-FNA.

—Ultrasound probes or miniprobes:

The already large number of indications has increased in recent years (1-12). This review aims to report on the most recent advances in the field.

EQUIPMENT

Frequencies in the radial echoendoscopes have increased to as high as 20 MHz, and electronic systems and color Doppler systems, which had until now only been available for linear systems, are now on the market. Furthermore, three-dimensional EUS (13) has been implemented to evaluate volumes, by means of computers that use imaging analysis software to differentiate with reasonable accuracy between benign and malignant lymph node involvement secondary to esophageal cancer (14).

Linear echoendoscopes now have very wide working channels (up to 3.7 mm) and they are electronic, thus offering images with a better quality and resolution than mechanical systems (15).

Miniprobes have increasingly good resolution (even with 3-D) and can be used for more indications (see below).

A small-caliber echobronchoscope has recently been developed which, when introduced into the airway, provides better images of the anterior mediastinum and enables punctures guided by endobronchial ultrasound–fine-needle aspiration (EBUS-FNA) to be performed (16).

Endoscopic ultrasound elastography (EUE) has recently been introduced to avoid the practice of FNA.

DIAGNOSTIC EUS

Diagnostic EUS is, mainly performed with radial echo endoscopes (mechanical or electronic), although they are only slightly better than curved linear-array (electronic) echoendoscopes. These scopes make it possible to examine several gastrointestinal alterations (the main indications are cancer staging and submucosal tumors), although greater resolution, color Doppler, and 3-D mean that it can be used for many more indications.

It has been suggested that EUS possesses a high potential to detect cancer in patients with Barrett's esophagus, when the standard endoscopy does not detect it or biopsies reveal high-grade dysplasia. One study (17) reports a high sensitivity (100%), specificity (94%) and negative predictive value (100%) of preoperative EUS in the detection of submucosal invasion.

The pancreas has been one of the most studied organs by EUS. Acute idiopathic pancreatitis has been examined by EUS, while chronic pancreatitis has been evaluated and detected prematurely by ultrasound.

In one study (18) that evaluated 168 patients with idiopathic pancreatitis, EUS identified abnormalities in 80% of patients; 62% had diagnostic findings such as lithiasis, sludge, or microlithiasis. A comparison with the final surgical diagnosis, endoscopic retrograde cholangiopancreatography (ERCP), analysis of biliary crystals, or clinical follow up revealed that EUS had correctly determined the etiology of pancreatitis in 92% of the cases.

Another prospective study (19) with 200 patients suffering from dyspepsia showed that EUS was more accurate in the detection or exclusion of different causes of dyspepsia than ultrasound or videoendoscopy. Extraluminal lesions were identified, tumors were staged, and pancreatic-biliary diseases were excluded, with the result that EUS changed clinical management in 25% of these patients. EUS is proving increasingly useful in the evaluation of cholelithiasis.

Brugge et al (20) report the results of a multicenter prospective study involving 341 patients with cystic tumors of the pancreas. Histological diagnosis was obtained in 112 cysts. A comparison of EUS, cytology and tumor markers revealed that cyst fluid carcinoembryonic antigen (CEA) level was more accurate than the other methods.

EUS has a high accuracy (80-90%) for the diagnosis of chronic pancreatitis. This percentage decreases when FNA is used for the histopathology diagnosis, especially during the initial phases of the condition. Chong et al (21) analyze the EUS findings in patients examined for suspected chronic pancreatitis who underwent pancreatic surgery (63 cases). The results show that the combination of calcifications or more than three EUS criteria of chronic pancreatitis has a sensitivity of 87% and a specificity of 57%. This low specificity means that false positives exist, and that the diagnosis is observer-dependent. Furthermore, possible pancreatic changes can occur with age.

In 120 symptom-free patients (22) with no known pancreatic biliary disease and no relevant consumption of alcohol, eleven parameters were studied (5 parenchymal and 6 ductal) with radial EUS. Abnormalities were detected in 28% of the cases, and prevalence increased with age (39% in the over-60 group). Hyperechoic strands appeared in 18% of cases. None of them had biliary tortuosity, ductal dilation, or lithiasis.

EUS sensitivity for detecting clots in the portal system is 81% (13/16 patients) and the specificity is 93% (27/29), with a global accuracy of 89% (40/45). In some patients, CT had not provided a diagnosis (23) (Tabla I).

TABLE I

INDICATIONS FOR RADIAL DIAGNOSTIC EUS (MODIFIED AND EXTENDED FROM REF. 1)

– Staging of malignant tumors of the digestive tract and detecting relapse and response
– Staging of Non-small Cell Lung Cancer
– Staging of gastric lymphoma
– Evaluation of submucosal lesions
– Study of large gastric folds
– Diagnosis of small-scale pancreatic lesions (exo and endocrine)
– Staging of pancreatic cancer
– Study of vascular lesions
– Complications of inflammatory bowel disease
– Evaluation of non-tumoral anal sphincter abnormalities
– Evaluation of extrahepatic cholestases: choledocholithiasis and others
New indications
– Barrett's esophagus
– Dyspepsia
– Acute idiopathic pancreatitis
– Chronic pancreatitis
– Portal hypertension
– Portal thrombosis
– Staging of ampulloma and cholangiocarcinoma

MINIPROBES

A recent review (24) emphasizes that miniprobes are very useful for studying biliary, pancreatic and GI tract strictures. They also seem to be a good option in case of small-scale mucous and submucous tumors and colon cancer (Table II). The most important technological advance has been to develop a 20-Mhz over-the-wire catheter US probe (25) to be introduced into the papilla (5-8-10 Fr) and the DPR, three-dimensional system in the latest-generation miniprobes (26).

Recent prospective comparative studies have shown that miniprobes are as effective as EUS in esophageal cancer (27), papillary tumors, and gastric Malt staging (28). 20-Mhz miniprobes are also useful in probe-guided endoscopic mucosal resection and tumor resection (29). They are equally or more effective than ERCP in the diagnosis of choledocholithiasis (30-33) and obstructive jaundice (34). ERCP complemented with intraductal ultrasonography gives more reliable information when differentiating between malignant and benign lesions (34).

EUS-GUIDED INTERVENTIONS

EUS guided interventions need curved linear-array echo endoscopes (electronic) with angio or color Doppler. Major

TABLE II

INDICATIONS FOR MINIPROBES /MODIFIED FROM REF. 24)

Single indications:
– Biliary and pancreatic strictures and staging
– Colon cancer staging and inflammatory bowel disease evaluation
– Evaluation of esophageal conditions (achalasia, scleroderma, varices)
Indications where miniprobes are preferable to EUS:
– Malignant gastrointestinal strictures
– Superficial cancer
– Submucosal lesions under 3 cm.
Indications where miniprobes could be an alternative to EUS:
– Submucosal lesions
– Malignant strictures
– Staging of esophageal and gastric cancer
– Staging of low-grade gastric MALT lymphoma
New indications:
– Papillary tumors
– Choledocholithiasis

TABLE III

INDICATIONS FOR NON-THERAPEUTIC NON-INTERVENTIONAL LINEAR EUS (2,7,12)

FNA:
• Lymph node involvement
• Submucosal lesions and y large gastric folds
• Pancreas
• Mediastinum
• Cysts, duplication cysts
• Cholangiocarcinoma
• Hepatic metastases and hepatic carcinoma
• Adrenal lesions
• Ascites
• Pelvic masses
• Others
— Biopsy as an alternative to EUE

indications are staging, FNA, and biopsy (Table III). The number of traditional indications for FNA (6,7) –lymph nodes, subepithelial lesions and pancreatic tumors– has been complemented by many new ones.

Endoscopic ultrasound elastography (EUE) has been developed to help reduce the need for histologic samples. The first estudies were performed on prostate, thyroid, and breast tissue.

Giovannini et al (35) have published the first results on 49 patients. The technique is coming to be known as the virtual biopsy. In case of pancreatic tumors, sensitivity was 100% for malignancy, with a specificity of 67%, whereas a study of lymph nodes (31 of 25 cases) revealed a sensitivity of 100% and a specificity of 50%.

ENDOSONOGRAPHY GUIDED INTERVENTIONS. EUS-GUIDED FNA

The most popular instruments for EUS-guided intervention are curved linear array echo endoscopes that provide a sector scan parallel to the axis. These instruments are thus able to visualize a needle along axis as well as sonographically monitor its depth penetration. Conclusive cytologic diagnoses are achieved more frequently in the presence of an on-site cytopathologist compared with settings that have no cytopathologist (78 and 52% respectively) (36-38).

FNA lymph nodes (Fig. 1)

Despite that standard echo features can predict malignant invasion of lymph nodes, limitations have been shown. EUS-guided FNA is thus essential for determination of malignant invasion in lymph nodes in gastrointestinal, pulmonary cancers and mediastinal lymphadenopathy of unknown origin.

It has a large impact on staging malignancies. If malignant cells are revealed, these patients can avoid unnecessary surgery, or changing in clinical decisions.

On the other hand, in a recent report, 144 patients with esophageal carcinoma were prospectively evaluated by EUS. Accuracy of standard (hypoechoic, smooth border, round, or width > 10 mm) and modified (4 standard plus EUS identified celiac lymph nodes, > 5 lymph nodes, or EUS T3/4 tumor) criteria were compared. It suggests that modified EUS lymph-node criteria are more accurate than standard criteria and a selective EUS-FNA approach reduced the cost by avoiding EUS-FNA in 42% of patients with esophageal carcinoma. (39)

There is growing evidence that micrometastases are present in lymph nodes, which cannot be detected with standard pathological methods. Pellisé et al, have studied it is feasible to detect occult neoplastic cells in EUS-FNA samples by hypermethylation gene promoter analysis (58).

In the last years, papers have been reporting about the importance of the FNA technique. A prospective randomized controlled trial in 43 patients has determined the effect of suction, the site of FNA (edge or center of lymph node), number of needle passes needed, and specimen quality. It seems that suction can increase bloodiness, and the sample quality is worse. In the matter of the site of FNA within the lymph node, does not affect accuracy, and the number of passes recommended, is up to 3 FNAs without suction (first pass 78% diagnoses, third pass 100%) (40).

In another recent study, has been evaluated the role of EUS-FNA in the diagnoses of mediastinal lymphadenopathy of unknown etiology. Final diagnoses included benign/infectious lymph nodes, 26; malignant pulmonary, 24; and malignant mediastinal, 12. EUS-FNA established a tissue diagnosis in 56 of 62 patients (90%). Results influenced subsequent evaluation and therapy in 87% of patients and avoiding the need for mediastinoscopy or bronchoscopy (41).

Beside that, EUS guided FNA has shown a high yield in diagnosing sarcoidosis and qualifies as the next diagnostic step after a nondiagnostic bronchoscopy, providing a nonsurgical alternative for the demonstration of noncaseating granulomas by aspirating mediastinal lymph nodes from the esophagus (42).

FNA submucosal lesions (Fig. 2)

Evaluation of submucosal nodules is a common indication for EUS. Lesions arising in the submucosa have a broad differential diagnosis. EUS-FNA can ensure that the needle is within a lesion instead of being superficial or deeper to it. Overall accuracy seems to be lower than pancreatic or lymph nodes FNA. One explanation about that is because these lesions are normally benign, as overgowth of normal tissue, and cells on a needle aspirate could appear normal (43). If a gastrointestinal stromal tumor (GIST) is suspected, EUS cannot differentiate exactly between benign and malignant tumors, but it can guide fine needle aspiration (FNA) biopsy or histology needle biopsies, thus providing samples for cytology or histological analysis. Also offers valuable information on the clinical management, and helps to decide whether a lesion should be consequently followed, removed by endoscopy (small lesions < 1.5 cm limited to the deep mucosa or the submucosa) or by surgery. GISTs are spindle cell tumors that stain positive for immunohistochemical CD-117 (c-kit). Prognostic factors for malignancy include size (> or =4 cm), mitotic index (5 mitotic figures/50 high-powered fields), and ulcerated, cystic, or necrotic areas within the tumor. EUS-FNA with immunohistochemical staining should be performed for CD-117 (c-kit). C-kit tumors are more likely to have malignant features and should be resected or subjected to close clinical follow-up (44). Hwang et al (45) report 100 subepithelial lesions evaluated by endoscopy and EUS obtaining histologic samples in 23 cases. Standard endoscopy had high sensitivity (98%), but low specificity (64%). Size measurement by endoscopy correlated with size measurement by EUS. Presumptive EUS diagnosis correct was in only 48% of cases, compared with histologic diagnosis (by FNA or resection).

FNA pancreas tumors (Fig. 3)

EUS seems to be very effective in determining which cystic lesions have malignant potential. If a cyst appears malignant or produces symptoms, it requires resection and therefore does not require FNA. Prediction of the clinical course for cysts of indeterminate nature requires EUS-guided FNA and analysis of fluid (46,47). According to a recent multicenter study, of tested markers, cyst fluid CEA is the most accurate test available for the diagnosis of mucinous cystic lesions of the pancreas (20).

The complex regional anatomy of the pancreas makes cytologic diagnosis of malignancy at this region difficult without exploratory surgery. Although CT-guided fine-needle aspiration (FNA) is used for this purpose, reports of an increased risk of peritoneal dissemination of cancer cells and considerable false-negative rate, make this a poor choice. The ability to position the EUS-transducer in direct proximity to the pancreas by means of the stomach and duodenum, combined with the use of FNA, increases the specificity of EUS in detecting pancreatic malignancies.

EUS in combination with FNA is a highly accurate method of preoperative staging of pancreatic cancer, especially those too small to be characterized by CT or MRI, and it has the ability to obtain cytological confirmation of pancreatic cancer. Accuracy ranges from 78% to 94% for tumor staging and from 64% to 82% for nodal staging (48,49).

Detection of mutant KRAS gene at high amounts may represent pancreatic cancer, whereas its absence increased the possibility of benign lesion. When adequate specimens obtained by EUS-FNA, are not available to reach a cytological diagnosis, the addition of KRAS mutational analysis may represent the best strategy (50,51).

In the case of Neuroendocrine tumours (NETs) is very useful and a valuable method to identify the cytological features of pancreatic NETs. By adherence to the characteristic cytomorphological criteria of pancreatic NET together with collection of suitable material for ancillary immunocytochemical stains, cytopathologists could reach a correct diagnosis in most instances (52).

A retrospective multicenter study, studied the diagnosis of pancreatic metastases confirmed with EUS-FNA. This is an important cause of focal pancreatic lesions and may occasionally be discovered during EUS examination after previously negative or inconclusive CT. Use of immunocytochemistry, when available, may help to confirm a suspected diagnosis. One outstanding feature would be that these lesions are more likely to have well-defined EUS margins compared with primary pancreatic cancer (53).

In cases of potential resectable pancreatic lesions, it is important to bear in mind that a negative EUS-FNA will not rule out the presence of cancer (because of low negative predictive value of it, and in chronic pancreatitis is lower) and a surgical intervention will be undertaken anyway. Another point is about seeding risk of malignant cells. It only would be concern in respectable body/tail lesions, because in head lesions, needle track will be included in the respectable specimen. If the information ob-

tained will assist in clinical decision on resectable pancreatic lesions or the patient has to be enrolled in any protocol for neoadjuvant radiation or chemotherapy before proceeding with surgery, EUS-FNA is recommended (43).

About potentials complications, performing EUS-guided FNA of solid pancreatic masses are infrequently associated with acute pancreatitis (54). Acute intracystic hemorrhage is a rare complication too and it has a characteristic EUS appearance (55,56). Infectious complication is a known risk reported in cystic lesions and prophylactic antibiotics are recommended (56).

Pancreatic cancers are difficult to diagnose on the basis of cytology alone. To overcome these limitations, a 19-gauge Trucut needle has been developed to obtain histological samples but the diagnostic accuracy of this new EUS-Trucut Needle Biopsy is comparable to that of EUS-FNA (57).

FNA cholangiocarcinoma

Hilar neoplasia requires preoperative tissue diagnosis to avoid risk of inappropriate extensive surgery. This is commonly attempted using various techniques at ERCP, which have variable sensitivity and accuracy.

Prospective evaluations of 44 patients with strictures at the liver hilum were diagnosed by CT and/or ERCP. All were suspicious of cholangiocarcinoma but had inconclusive tissue diagnosis. They underwent EUS-FNA and adequate material was obtained in 43. Cytology revealed cholangiocarcinoma in 26 and other malignancies in 5 patients; 12 had benign results: sclerosing cholangitis, primary sclerosing cholangitis, inflammation, and sarcoid-like lesion. Finally, EUS-FNA changed preplanned surgical approach in 27 (59). In another study, 28 patients with obstructive jaundice were evaluated. All except 1, had nondiagnostic sampling of the biliary lesions and 14 had no definitive mass seen on prior abdominal imaging. They underwent EUS-FNA, and positive impact was described on patient management in 84% of patients: preventing surgery for tissue diagnosis in patients with inoperable disease, facilitating surgery in patients with unidentifiable cancer by other modalities, and avoiding surgery in benign disease (60). These results suggest that EUS-FNA is of value as a new, less-invasive approach for tissue diagnosis of hilar strictures of unknown cause or with suspected cholangiocarcinoma, when other procedures fail.

FNA liver lesions

EUS-FNA of liver tumors is a reliable and safe procedure for the diagnosis of malignant liver lesions. Optimal diagnostic results are achieved by combining cytological with histological assessment. Moreover, EUS-FNA is an alternative to percutaneous biopsy, particularly in patients at risk of bleeding or with small lesions of the liver.

A retrospective questionnaire was sent, and 21 centers reported 167 cases of EUS-FNA of the liver. Outstanding findings were: EUS-FNA diagnosed malignancy in 23 of 26 cases after nondiagnostic fine needle aspiration under transabdominal US guidance. EUS localized an unrecognized primary tumor in 17 of 33 cases in which CT had demonstrated only liver metastases. It should be considered when a liver lesion is poorly accessible to US-, or CT-guided FNA, and should be considered when US- or CT-guided FNA fail to make a diagnosis, when a liver lesion(s) is detected (de novo) by EUS, and for investigation of possible upper GI primary tumors in the setting of liver metastases (61).

In another recent study, 41 patients were prospectively studied, 33 of whom had clinical findings suggestive of liver malignancies. Transgastric EUS-FNA were performed and provided appropriate biopsy specimens in 40/41 patients. On average, 1.4 needle passes were necessary to obtain sufficient amounts of tissue, and 31 out of 33-malignancies were correctly diagnosed (62).

Besides the possibility of FNA liver metastases (61-63), EUS permits the diagnosis of hepatoma with portal thrombosis, puncturing the clot (64). A 19 gauge trucut needle is used in those patients with coagulopathy.

FNA adrenal left (Fig. 4)

EUS-guided FNA of the left adrenal gland is a minimally invasive, safe, and highly accurate method that confirms or excludes malignant adrenal involvement in patients with thoracic or GI malignancies.

Stelow et al (65) reported 24 cases of EUS-guided FNA of the adrenal gland from 22 different patients with adrenal known lesions. Almost all FNAs were of the left adrenal gland. Diagnostic material was present in all cases. Final diagnoses were: cortical adenoma 19, metastatic adenocarcinoma 3, pheochromocytoma 1, and adrenal cortical carcinoma 1.

Eloubeidi et al. (66) included 31 patients with an enlarged left adrenal gland on abdominal imaging and known or suspected malignancy. Tissue adequate for interpretation was obtained in all patients. EUS-guided FNA confirmed malignant left adrenal involvement in 13 patients. Benign masses were more likely to have preservation of the normal sonographic appearance of the adrenal gland ("seagull" configuration) compared with those with malignant masses. The accuracy of EUS imaging based on size (> or =3 cm) alone was 81%.

FNA ascites

EUS seems to be more sensitive than CT in detecting small amounts of ascites. A retrospective study of 571 pa-

tients who underwent EUS for several indications, a 15% of series were found to have ascites; in a significant number, undetectable by CT. In 5 patients, malignant ascites was diagnosed by EUS-guided FNA, in whom surgery was avoided. EUS-guided paracentesis appears to be safe and effective and can identify malignant ascites (67).

FNA gastric and rectals folds

If the standard endoscopic biopsies are non- diagnostic on prominent gastric and rectal folds, linear EUS-guided FNA of the deeper layers can help to obtain tissues for clinical diagnosis. Possibility of an infiltrating linitis plastica (gastric or rectal) or lymphoma (less common) is high when deeper layers are thickened.

In a recent paper has been studied predictive factors for malignancy in gastric folds from 61 patients with gastric folds (40 benign and 21 malignant). Several predictive factors of malignancy were evaluated. Only the enlargement of deep layers, as assessed by EUS was the only independent predictive factor for malignancy in patients with large gastric folds at endoscopy and biopsies testing negative for malignancy and EUS had a high clinical impact in these patients (68).

FNA: pelvic, kidney and gallbladder masses

Perirectal masses can also be imaged with EUS. And transrectal FNA can be performed to further characterize these lesions. Other new sites being evaluated with EUS-guided FNA reported in the literature included kidney and gallbladder masses. (69-71).

EUS-guided core-needle biopsy

A 19 gauge Tru-cut needle could improve accuracy respect EUS-FNA and may decrease procedure time, eliminating the need for an on-site cytopathologist. A follow-up human study, relates a higher accuracy with EUS-guided Tru-Cut biopsy than EUS-guided FNA with no complications (72). However, another recent study with 18 patients did not found different accuracy and two serious complications were occurred. More studies are needed before standard application (57,73).

THERAPEUTIC ENDOSONOGRAPHY (Table IV)

Endoscopic ultrasound-guided pancreatic pseudocyst drainage

It is an alternative non surgical approach. Endoscopic drainage of pseudocysts entails the creation of a fistulous tract between the pseudocyst and the gastric lumen (cystogastrostomy) or duodenal lumen (cystoduodenostomy) when a submucosal compression is present. The limitation of that technique was its relatively 'blind' approach. So, EUS-guided pseudocyst drainage can be very helpful without bulging of the gastrointestinal lumen.

Drainage is indicated to relieve symptoms, and an observation period is recommended, because there is a high probability of spontaneous resolution. The suitability for drainage includes a distance from the gut wall of < 10 mm, no major vessels by Doppler, homogeneous and unilocular cyst (74).

After the optimal site for puncture is determined, the pseudocyst is punctured. Initials reports on this technique used diathermy with a needle-knife. The standard needles that are used for FNA can be used, but the small calibre (22 or 23 G) accepts only a 0.018 in guidewire. Using a 19 G FNA needle (Wilson-Cook), a 0.0035 in guide wire can be inserted, and the tract is dilated using a 6 or 8 mm balloon over the wire.

Recently, a 'one step' device has been developed by Wilson-Cook (Giovanni needle-wire), which is composed of a needle-wire, a dilator catheter of 6.5 fr, and a stent of 8.5 or 10 fr. When the needle wire is punctured and inserted into the cyst, the internal rigid part is removed, and it becomes a soft wire that is able to insert easier. Second step is to dilate the tract using the catheter and to push the stent on the dilator (75). Recent studies have confirms the effectiveness (82 or 88% complete resolution) and safety (75,76). After cyst is punctured, a sample of the cyst contents is aspirated for biochemical, cytological, tumor markers analysis and if infection is suspected a sample

TABLE IV

INDICATIONS FOR THERAPEUTIC EUS
(MODIFIED AND EXTENDED FROM REF. 2, 6 AND 12)

- Pancreatic pseudocyst drainage
- Celiac plexus block / neurolysis
- Thoracocentesis and paracentesis
- EUS FNI:
  - Botulinum toxin injection
  - Antitumor injection therapy
  - Sclerotherapy
- Cholangiopancreatography
- Endoscopic ultrasound-guided endoscopic mucosal and tumoral resection
- Endoscopic ultrasound-guided radiofrequency ablation
- EUS suturing (gastroplexy, etc.)
- Gastrojejunal anastomosis
- Biliary anastomosis to stomach and duodenum
- Ostomy
- Resection of necrotic tissue

should be sent for cultive. A naso-cystic drain or stent is placed to drain the cyst. The choice depends on the appearance of the cysts contents. An infected cyst mandates irrigation by nasocystic catheter or 10 fr stents. Clear liquid contents can be drained with 8.5 F or 10 F alone, or with two 7 fr stents.

Complete aspiration of cyst and follow-up could be an option in some patients (eg, portal hypertension). If it recurs, continuous drainage can be performed by stent or nasocystic catheter.

In a review of literature of series published, Giovanni et al (77), EUS-guided drainage was successful in 31 patients of 35 patients (88.5%). No major complications. One patient developed a pneumoperitoneum, which was managed by conservative measures. Four patients underwent surgery. Another group, Vosoghi et al. has published a high successful rate in 14 patients (78). Sriram et al (79) with 8 patients concluded that pseudocyst and portal hypertension can be drained and guided by EUS in absence of doppler.

In the future, this technique may improve the results, if dedicated accessories are designed, like large-channel interventional echoendoscope for stent placement (80).

Comparing advantages between conventional transenteric techniques or by EUS-guided drainage, a prospective study (81) were 99 patients (bulging lesions without portal hypertension underwent CTD), received endoscopic management, and no were found clear differences in safe or efficacy. Recent survey of ASGE members shows that EUS-guided is used by 56% US endoscopists compared with 43% international endoscopists (82).

Endoscopic ultrasound-guided celiac plexus block/neurolysis (Fig. 5)

Celiac plexus block (CPB) when a steroid is injected or celiac plexus neurolysis (CPN) with alcohol, can be performed under real-time EUS in case of pancreatic pain such as pancreatic cancer or chronic pancreatitis. Using a linear array echoendoscope, a 22 G needle is advanced through the gastric wall into the peri-aortic space, where the celiac trunk take-off.

The results of CPB/CPN in pancreatic cancer have been better than in chronic pancreatitis. Gress et al (83), performed CPB in 90 patients, and reported a 55% improvement in pain scores, but this percentage decreased to 10% after 24 weeks. Young patients or those who had prior pancreatic surgery had no benefit.

In inoperable pancreatic cancer, a prospective study (84) included 58 patients underwent CPN. Improvement in pain scores was observed in 78%, but it decreased to 54% in improvement in pain scores of > 2 points using standard analog scale. Patients who had received oncologist therapy had better response. Lemelin et al compare two series of patients with abdominal pain, being more effective a bilateral injection respect a central injection (70% set against 47%) (85).

Comparing with CT-guided CPB via posterior percutaneous approach with EUS-guided, in a prospective randomized study (86), 18 patients with chronic pancreatitis pain were studied and 50% of patients underwent the EUS had improvement in pain score and medication used, and only 25% of patients in CT-guided group.

Recent case report (87), reports a significant clinical improvement after CPN, in a women who suffered pain attacks, relation to acute intermittent porphyria.

Endoscopic ultrasound-guided botulinum toxin injection for achalasia

Using a linear echoendoscope after the lower esophageal sphincter has been visualized as a hypoechoic band, a EUS-guided FNA needle may increase the efficacy of the procedure, avoiding superficial injection or only partly into the sphincter. First reported by Hoffman BJ (119), and after, Maiorana et al. (88) experience with 3 patients have been successful, but comparatives studies with and without EUS are needed.

Endoscopic ultrasound-guided cholangiopancreatography and rendezvous drainage

With the development of magnetic resonance cholangiopancreatography, the utility of EUS-guided injection into the bile duct or pancreatic duct have to be limited. But after failed ERCP cannulation, using linear EUS, these ducts can be punctured with a needle, and a passage of a wire or drainage is possible, and technically feasible.

Successful results have been reported by Burmester et al. (89) performing three stent placement of four patients with malignat pancreatobiliary strictures and previous failed cannulation. Another experience was performed with gastropancreatic duct stent placement in two patients who were affected with pancreatic duct strictures, and clinically improvement is reported (90).

Other group attempted in six patients, guidewire placement through obstructed pancreatic or bile ducts, advancing the guidewire across the papilla or surgical anastomosis. EUS-guided duct access and intraductal guidewire placement was accomplished in five patients (5/6) with successful traversal placement, and rendezvous ERCP with stent placement, in three patients (3/6) without serious complications (91,92).

An italian group, evaluated a new approach in the management of common bile duct stones, by using an oblique-viewing echoendoscope, for diagnostic and therapeutic purposes. Nineteen patients with acute abdominal pain associated with increased liver tests entered the study. Evaluation of the biliary tree was performed by using an

oblique-viewing echoendoscope. When biliary stones or sludge were found, bile duct cannulation and sphincterotomy were performed in the same session. The mean time for the whole procedure (EUS plus endoscopic retrograde cholangiography with biliary treatment) was 27 minutes (118).

Endoscopic ultrasound-guided antitumor injection therapy

Therapeutic endoscopic for gastrointestinals cancers is a reality and one of the most exciting fields. There are several options for anticancer therapeutic endoscopic as endoscopic mucosal resection, self-spending stents and ablative therapy (microwave, cryotherapy, high intensity focused ultrasound, EUS-guided radiation and radiofrequency therapy) but the emerging area will be antitumor injection therapy (93,94).

Image guided injection of alcohol has been used for local tumor ablation. Two recent case reports (solitary hepatic metastasis and a GIST) describe the feasibility of this approach (95,96).

Recent studies with pancreatic cancer are in early phase. In these trials is using allogenic mixed lymphocyte culture, adenovirus that selectively kills malignant cells (ONYX-015) combining with gemcitabine, and a novel gene transfer therapy (TNFerade) a replication-deficient adenovector containing the TNF. (97) These clinical trials are demonstrating that EUS-guided FNI is feasible but more trials and data are needed before routine clinical application.

Endoscopic ultrasound-guided radiofrequency ablation

Usually radiofrequency is performed percutaneously by ultrasound, MRI or CT-guided in primary, or metastasic liver tumors. EUS-guided radiofrequency treatment may help in cases of difficult accessible liver cancers or small pancreatic endocrine tumors. Limited experience in animals has been described (98).

Endoscopic ultrasound in the management of upper gastrointestinal bleeding

Some studies suggest that using real-time EUS-guided sclerotherapy or banding techniques can decrease the number of sessions, to obliterate the perforating veins and to confirm of total obliteration. In a recent randomized controlled trial, 48 cirrhotic patients were randomized into 2 groups, comparing standard sclerotherapy with EUS-guided sclerotherapy for esophageal varices. The results gave advantage on EUS group, because recurrence tended to be less frequent and later (99,100).

Endoscopic ultrasound-guided endoscopic mucosal resection

The ability to perform a correct endoscopic mucosa resection (EMR) depends on the 'lift' sign. EUS -guided (or using a miniprobe of 20 MHz) injection of saline into the precise layer under real-time can assure a correct placement of the injection, confirming a complete separation of the lesion from the normal tissue.

In series of 16 and 9 patients, no perforations and no recurrences were observed (101,102). Resections were complete in all cases, without serious complications

A new device has been tested on animals, which allows viewing in real-time during cutting, avoiding serosal layer inclusion, so decrease the complication rate. It consists with an end-cap, and two channels into which a miniprobe and a snare were inserted (103).

In recent series of the same group with 24 carcinoide tumors (104) and 50 submucosal tumors (105), mucosectomy guided by EUS, obtained complete resection also of almost the 100%, with scarce complications (4% bleeding).

Endoscopic ultrasound and ethanol lavage of pancreatic cysts lesions

In a clinical trial, 25 patients with pancreatic cystic lesions were evacuated with needle aspiration by EUS control. After evacuation, the cavity was lavaged with ethanol for 3 to 5 minutes. Resolution of their cysts was observed in 8 patients (35%). This procedure is safe and feasible, but further studies are needed (106).

Posterior gastropexy for reflux disease

Because with EUS is possible to visualize organs adjacent to the gastrointestinal tract such as muscles of the diaphragm, it would allow to perform selective tissue approximation. But a main prerequisite is the development of tools to perform that. Suture kit, is a new device allowing the placement of a stich to any desired depth under EUS guidance as the lower esophageal sphincter (LES) (107).

Using a linear scope, the crura and median arcuate ligament are identified by EUS, and under EUS control, one stitch is fired through the gastric wall into the diaphragmatic ligament, and a second stitch is fired through stomach wall posteriorly, just below the LES and 1.5 cm above the first stitch. Then, they are attached to each other and locked, using a pledge to spread the force. The alterations of pressure in the LES are measured by pre, intra and postoperative manometry.

It has been used only in animal's experiments, performing posterior gastropexy under EUS control without peritoneal access (108). But, more studies are needed to confirm advantages over conventional laparoscopic or current endoluminal endoscopic antireflux procedures.

Anastomosis formation: gastrojejunal, gallbladder anastomosi to stomach or duodenum and others

Intra and transluminal endosurgery is likely to be an important field in the future. EUS can play a helpful place in this advance (109,110).

Gastrojejunal anastomosis has been performed in animals, creating an anastomotic opening between 3 and 9 mm without dilatation, but using specials balloons these anastomoses measured up to 2 cm wide. No evidence of leakage or bowel perforation was described.

This kind of anastomoses could provide an alternative way in inoperable and elderly patients, in cases of an obstructing cancer in the pancreas or stomach. Under EUS guidance, target bowel can be visualized and punctured from the stomach (111,112).

TRAINING ASPECTS

EUS is one of the most difficult procedures for a clinician to learn and a skill that is difficult to acquire outside a formal training program. Previous experience in upper endoscopy with side-viewing instruments and abdominal ultrasonography will be helpful.

Training should include textbooks (113,114), atlases relearning the anatomy that is relevant to EUS image interpretation (www.sepd.es/ecotest), journal articles, slides, CD-ROM, videotapes, self-study and hands-on supervised procedures (114, 115).

A deeper understanding of the location and orientation of the image plane is difficult because the multiplicity of images planes and their constant movements with the movement of the scope. Special mention requires the 'Digital Human Anatomy and Endoscopic Ultrasonography' a recent published atlas (116) using images from the Visible Human Project (VHP) database to provide anatomic correlates of radial and linear EUS images.

The VHP is a three-dimensional computer database of human anatomy, initiated by the National Library of Medicine (117), and it was completed by the University of Colorado, Center Human Simulation in 1995 (www.visiblehuman.org).

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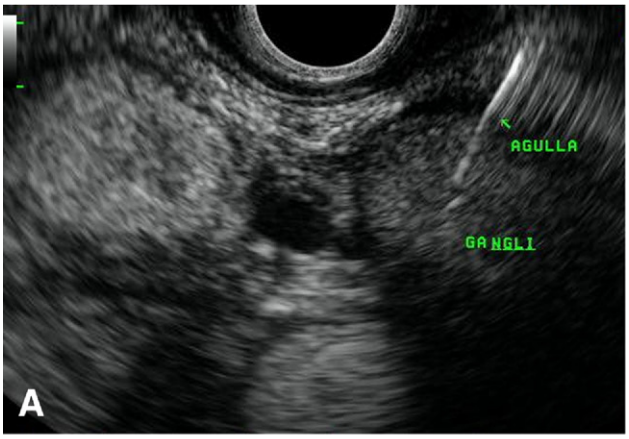
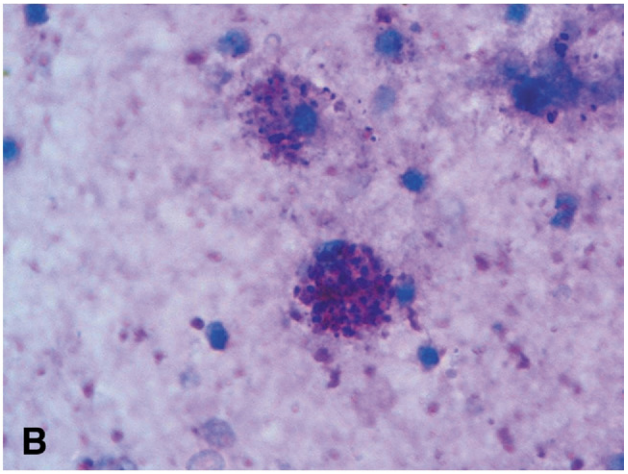
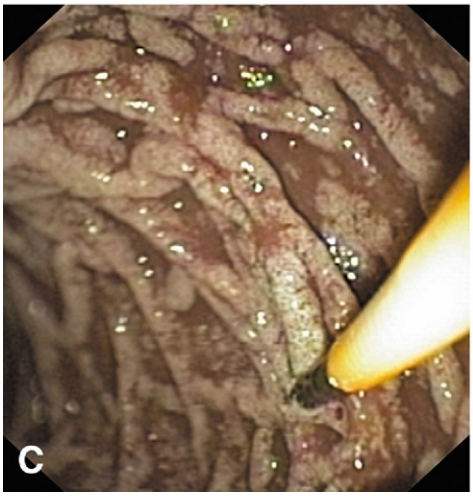
AT THE FOCAL POINT

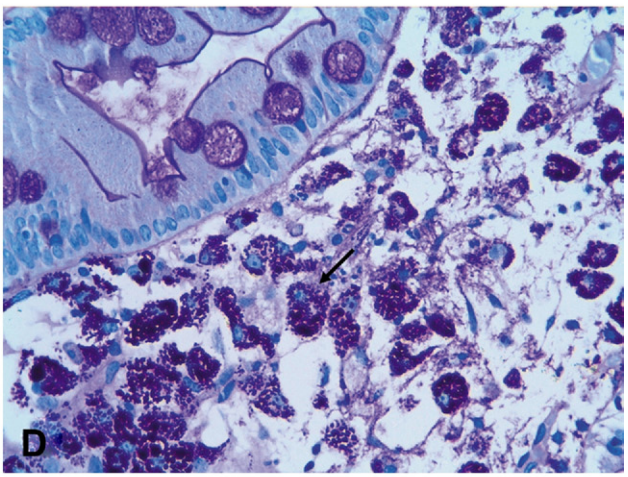
David Robbins, MD, MSc, *Assistant Editor for Focal Points*

Diagnosis of Whipple's disease by EUS-guided-FNA and endoscopic biopsy at the same procedure









A 52-year-old woman with an unremarkable medical history presented with a 4-month history of weight loss, anorexia, and diarrhea. Laboratory tests revealed leukocytosis and elevated levels of C-reactive protein. CT revealed diffuse mesenteric lymphadenopathy without other abnormalities. Based on the clinical suspicion of tuberculosis or lymphoma, an EUS was performed (**A**), revealing perigastric lymph nodes with a round or oval shape, sharp margins measuring larger than 1 cm, and a characteristic hyperechoic, homogeneous echo pattern. EUS-guided FNA of a lymph node in the celiac trunk region revealed numerous macrophages with positive periodic acid-Schiff (PAS) staining (**B**, PASD, orig. mag. ×630) and negative Ziehl-Neelsen staining. The concurrent endoscopy revealed pale yellow and shaggy duodenal mucosa (**C**) of the post-bulbar region. Mucosal biopsy specimens were similarly PAS stain positive (**D**, PASD, orig. mag. ×400). Based on these findings, a diagnosis of Whipple's disease was made and confirmed by a polymerase chain reaction assay, which was positive for *Tropheryma Whipplei* (and negative for *Mycobacterium tuberculosis*). The patient was treated successfully with long-term cotrimoxazole therapy.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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Commentary

Whipple's disease is a rare (one is more likely be struck by lightning: http://www.lightningsafety.noaa.gov/medical.htm), multisystemic, chronic, infectious disease that, like Barrett's esophagus, preferentially affects middle-aged white men ("middle age" has a dynamic definition simply calculated as twice your current age). First described by the pathologist George Hoyt Whipple in 1907, the once-fatal lightning rod-shaped organism was successfully treated with antibiotics in 1952. *Tropheryma whippelii* was so named in a nod to its proclivity for inciting GI havoc (Greek, trophe: nourishment; eryma: barrier, because of the resulting malabsorption). For the hard-core trivia buffs out there, in 2001 it was renamed *T whipplei* (Whipple had to be properly Latinized to *whippleus*, and the genitive is obviously *whipplei*!). The clinical hallmarks of Whipple's disease include polyarthralgia, weight loss, chronic diarrhea, and abdominal pain. The lymphectasia observed in this case is only rarely seen macroscopically, so multiple post-bulbar duodenal biopsies should be done in any suspected case, and endoscopy is the first-line diagnostic test. *T whipplei* is relatively ubiquitous (its natural source is unknown) and could be considered a commensal bacterium acquired through fecal-oral transmission. Disease is thought to result in the genetically susceptible host. Although clinical improvement should be seen within 2 weeks of therapy, follow-up endoscopy with biopsy (histology and PCR analysis) is advised at regular intervals (perhaps annually) after the initiation of antibiotics because relapse can occur after many years. This is, in my recollection, the first example of EUS-guided FNA confirming its diagnosis; the clinically astute authors are unlikely to ever see another case. And I'd strongly suggest they pick up a few lottery tickets.

David Robbins, MD, MSc
Assistant Editor for Focal Points

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PICTURES IN DIGESTIVE PATHOLOGY

Endoscopic closure of duodenal perforation with an over-the-scope clip during endoscopic ultrasound-guided cholangiopancreatography

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INTRODUCTION

Duodenal perforations are a rare complication during interventional endoscopy. Their mortality is high, and the treatment in most cases is surgical.

We report a case of duodenal perforation (type I, Stapfer) (1) during an interventional endoscopic ultrasound (EUS) procedure resolved using an over-the-scope Clip called OTSC®.

CASE REPORT

A 74-year-old woman presented obstructive jaundice. Computed tomography revealed a pancreatic head tumor with dilatation of the common bile duct (CBD) and pulmonary metastases. Biliary drainage by ERCP was indicated.

Papilla had tumoral signs of infiltration. Cannulation was not achieved after several attempts with a papillotome. We accessed the distal CBD after performing a pre-cut, but the guidewire could not pass deeply. After replacing the duodenoscope with a linear echoendoscope with the intention of performing biliary drainage guided by EUS, a 10 mm duodenal perforation (type I, Stapfer) was visualized in the posterior wall of the duodenal bulb (Fig. 1A), surely caused by the tip of the echoen-

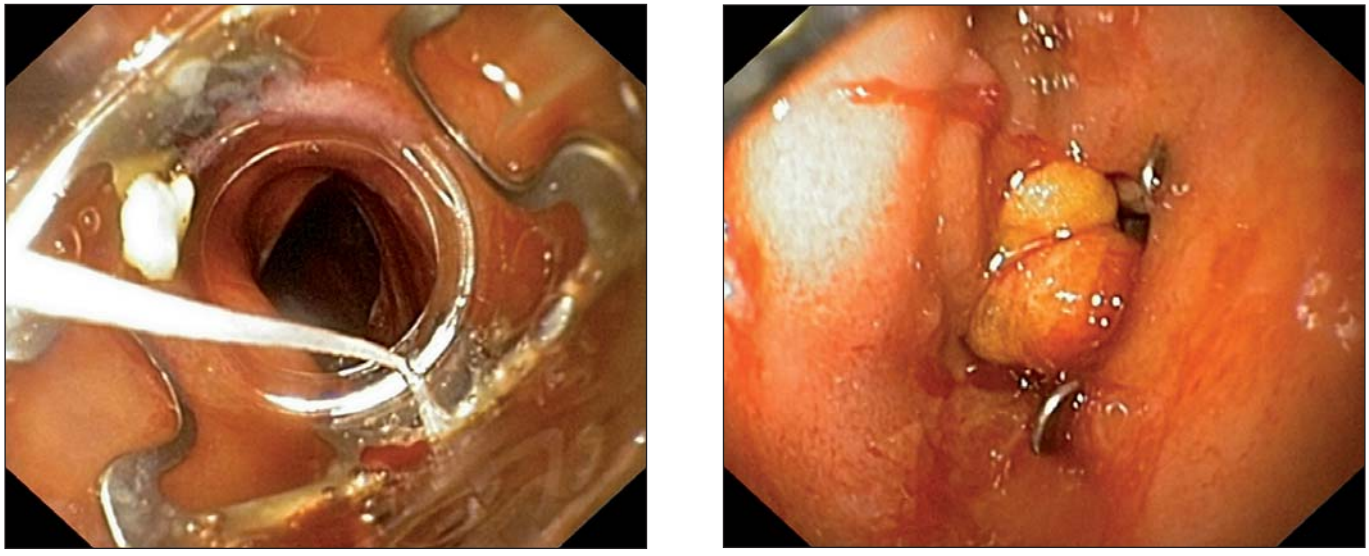

Fig. 1. Duodenal perforation during biliary drainage guided by EUS (A). Endoscopic closure using an over-the-scope clip, OTSC (B).

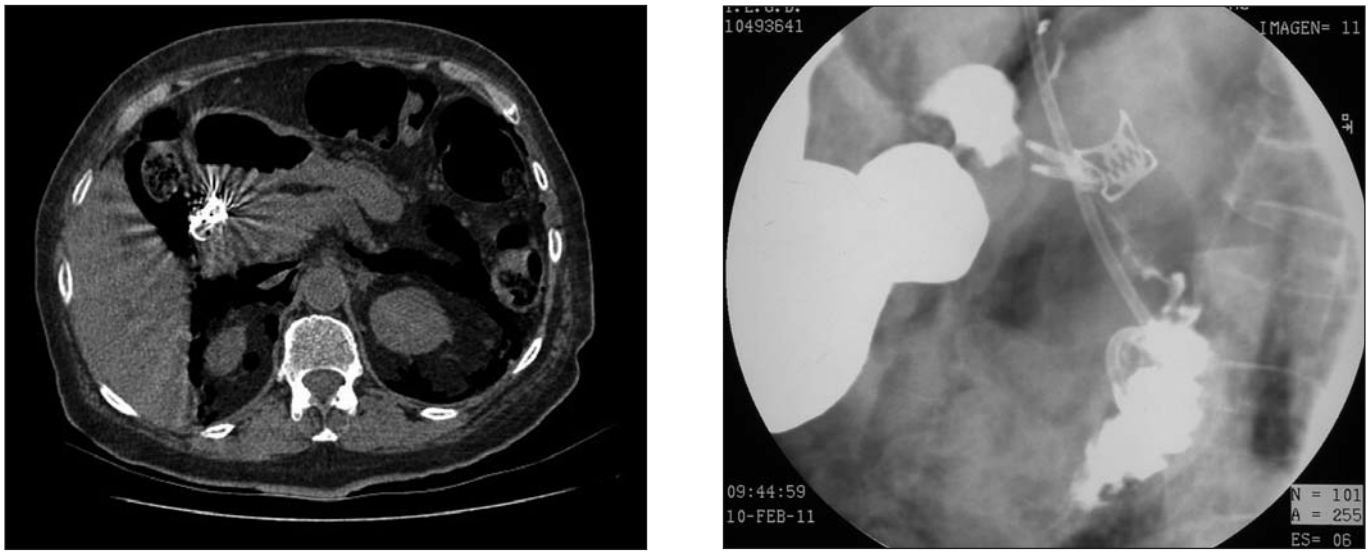

Fig. 2. CT scan shows the OTSC in place, air in retroperitoneum, and no free intraperitoneal fluid (A). Gastrointestinal transit reveals complete sealing of duodenal perforation (B).

doscope. An OTSC atraumatic clip (9.5-11 mm) was deployed with successful closure of the perforation (Fig. 1B). Two endoclips were applied in a margin to ensure complete sealing.

An immediate abdominal CT reported air in retroperitoneum without free fluid (Fig. 2A). The patient was maintained on absolute diet and received antibiotics. Gastrointestinal transit at 5 days showed no extraluminal leakage (Fig. 2 B). Oral feeding was restarted on day 6 and biliary drainage was performed by PTC.

DISCUSSION

The risk of duodenal perforation may be increased in cases of tumor infiltration and passage of an echoendoscope. The use of these OTSC clips is limited in duodenum; however, there are reports in animal models (2) and clinical case series (3-5) supporting its efficacy. We believe that OTSC clips are useful in the closure of duodenal perforations caused by interventional endoscopy.

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TITLE:

Double endosonography-guided transgastric and transduodenal drainage of infected pancreatic-fluid collections using metallic stents

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Short running title: Double EUS-guided drainage using SEMS

Keywords: endoscopic ultrasonography; pancreatobiliary; pseudocyst; therapeutics; transmural drainage.

Abbreviations:

EUS: endoscopic ultrasound; PFC: pancreatic fluid collections; SEMSs self-expanding metallic stents; WOPN: walled-off pancreatic necrosis

Conflicts of interest

Authors declare no Conflict of Interests for this article.

INTRODUCTION

The use of self-expanding metallic stents (SEMSs) in draining PFC has been reported in small case series [1,2]. The practice of more than one transluminal drainage is rarely described [3,4].

CASE REPORT

A 34-year-old male was referred to our hospital for drainage of symptomatic pancreatic fluid collections (PFCs) secondary to an acute pancreatitis. He was affected by gastro-duodenal and biliary obstruction. CT scan images revealed 1 perigastric pseudocyst (well-defined wall, without necrosis content, 70x120mm) and 1 periduodenal walled-off

pancreatic necrosis (WOPN) (thickened wall, partially liquefied collection containing solid content, 80x90mm).

Both PFC were accessed under EUS-guidance with a 6 Fr-cystotom and dilation tract using a 10-mm balloon (Fig.1). First, the pseudocyst was drained transgastrically with a fully covered SEMS with bilateral anchor flanges (AXIOS™, 10x15mm; Xlumena, MountainView, CA) and 800mL of turbid fluid was aspirated (Fig.2). Five days later, a WOPN was drained under EUS-guidance via transduodenal and a 10x40mm fully covered SEMS (WallFlex biliary Rx, Boston Scientific, Natick, MA) plus a coaxial 10Fr.x 5cm, double-pigtail stent to prevent migration were delivered and a purulent fluid was drained. At day 6, abdominal pain and duodenal obstruction were persistent and a CT scan showed total resolution of the perigastric PFC and a decrease in size of the WOPN by <30% with presence of necrotic contents (Fig.3a,3b). A necrosectomy was performed delivering a new specific SEMS (Yo-Yo stent, 10x10mm, Niti-S; TaewoongMedical, Seoul, Korea) to keep open the duodenostomy (Fig.4a,4b). Patient symptoms improved, with a significant resolution of the WOPN in a CT scan 15 days later. At 3 weeks follow-up, complete lesion resolution was revealed in CT scan images and all stents were removed.

DISCUSSION

The practice of more than one transmural drainage with SEMSs is effective for the treatment of infected PFC**.** The use of diabolo-shaped SEMSs improved the overall management.

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Legends:

Fig. 1: EUS image of the walled-off pancreatic necrosis located in the head of the pancreas.
Fig. 2: Endoscopy view through the AXIOS stent showing a significant resolution of the lesion after the spontaneous drainage of 800 mL of turbid fluid.
Fig. 3: CT scan coronal-sagittal oblique view (3a) and 3-dimensional reconstruction (3b) at 6 days after the second drainage including both SEMSs in the same plane: a cystogastrostomy (with a diabolo-shaped SEMS) and a cystoduodenostomy (with a FCSEMS plus a coaxial plastic pigtail stent).
Fig. 4: Endoscopic necrosectomy of an infected walled-off pancreatic necrosis performed 6 days after a single transmural drainage (4a). This maneuver allowed the extraction of non-adherent solid components of the infected cavity (4b), improving patient symptoms.

Fig.1

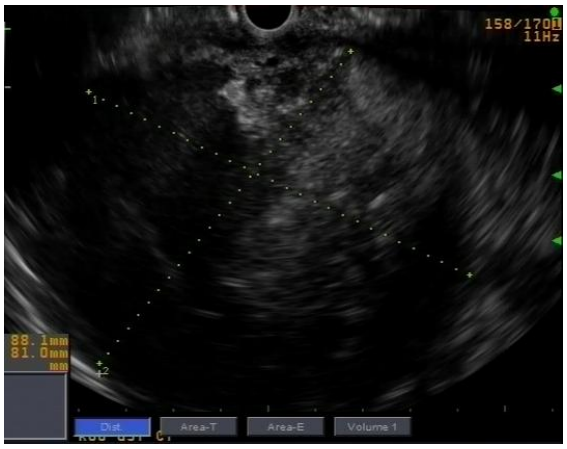

Fig.2

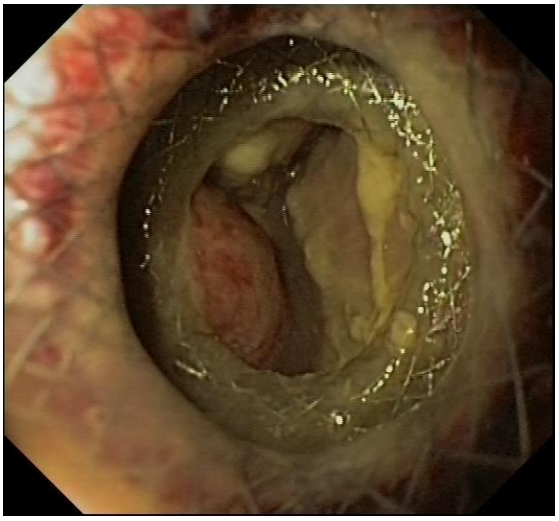

Fig. 4a

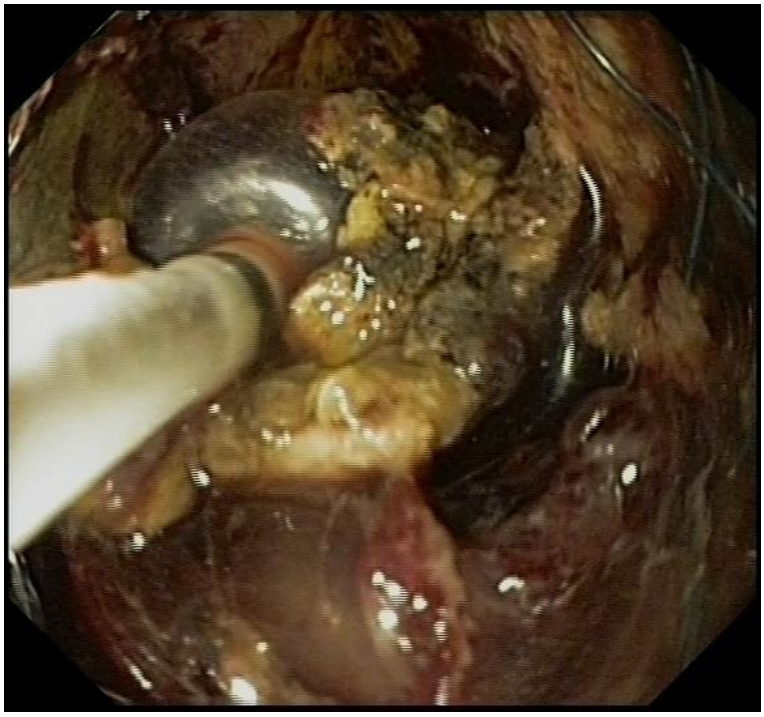

Fig. 4b