Eventos adversos relacionados con las prótesis de aposición luminal en el drenaje de la vesícula biliar y los procedimientos de retirada

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ABREVIATURAS Y ACRÓNIMOS

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BGYR: Bypass gástrico en Y de Roux

CDS: Coledocoduodenostomía

CPE: Colecciones pancreáticas encapsuladas

CPRE: Colangiopanreatografía retrógrada endoscópica

CPRE-AL: Colangiopanreatografía retrógrada endoscópica asistida por laparoscopia

DET: Drenaje endoscópico transmural

DETP: Drenaje endoscópico transpapilar

DPT: Drenaje percutáneo

EA: Evento adverso

EAB-CPRE: CPRE con enteroscopia asistida por balón o espiral

EDGE: *Endoscopic ultrasound directed transgastric ERCP*

EUS-DVB: Drenaje vesícula biliar guiado por ecoendoscopia

EUS-GE: Gastroenteroanastomosis guiada por ultrasonido endoscópico

GY: Gastroyeyunostomía quirúrgica

OVG: Obstrucción al vaciamiento gástrico

PAL: Prótesis de aposición luminal

PMA: Prótesis metálicas autoexpandibles

PP: Prótesis plásticas

USE: Ultrasonografía endoscópica

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RESUMEN

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La presente tesis doctoral expone el trabajo y las conclusiones de la investigación realizada sobre las prótesis de aposición luminal (PAL) en ecoendoscopia terapéutica a través de dos visiones diferentes: el drenaje de la vesícula biliar y la retirada de las prótesis en diferentes indicaciones.

En el transcurso de los años de duración del proyecto doctoral, el doctorando ha adquirido y complementado su formación con otras muchas competencias formativas en el ámbito de la investigación y la innovación.

Ambos estudios se enmarcan en un proyecto prospectivo multicéntrico: el registro nacional de incidencias de PAL sobre el que se basa esta tesis doctoral. Este proyecto fue iniciado en enero del 2019, incluyendo todos los procedimientos en los que se colocaron prótesis de aposición luminal transmurales durante 12 meses en más de 30 centros nacionales con unidades de endoscopia avanzada. Se ejecutó un seguimiento telefónico centralizado suplementario al seguimiento normal de cada centro. Los dos artículos que componen esta tesis analizan parte de los objetivos de este proyecto.

El primero artículo ha evaluado el uso de las PAL en el drenaje de la vesícula biliar. Ha sido publicado en una revista de segundo cuartil (*Journal of Gastroenterology and Hepatology* JCR 2022: 4,1). Se trata de una de las series prospectivas más largas publicadas sobre este tema. El riesgo de eventos adversos dejando la prótesis in situ durante un año es similar a los datos publicados retirando las prótesis. El riesgo acumulado de nuevos eventos biliares al año es inferior al 10%, y se centra fundamentalmente en pacientes que también presentan patología neoplásica pancreatobiliar.

El segundo artículo versa sobre los procedimientos de retirada de este tipo de *stents*. Ha sido publicado en una revista de primer cuartil (*Endoscopy* JCR 2022: 9,3), figurando en la primera página del número de la revista y siendo objeto de una editorial (1). Se

trata de un tema novedoso, ya que existen muy pocos datos al respecto. Los resultados y las conclusiones obtenidas permiten afirmar que la retirada de este tipo de prótesis suelen ser procedimientos sencillos mayoritariamente, asequibles en salas de endoscopia convencional. Identifica factores de riesgo para identificar el pequeño porcentaje de pacientes que podrían requerir técnicas de endoscopia avanzada para la retirada de la PAL.

En conclusión, esta tesis pretende aportar evidencia sobre el uso de las prótesis de aposición luminal tipo Axios en el drenaje vesicular y sobre sus procedimientos de retirada.

ABSTRACT

ABSTRACT

This doctoral thesis presents the work and conclusions of the research about luminal apposing metal stents (LAMS) in therapeutic endoscopy ultrasound through two different visions: the gallbladder drainage and the removal of LAMS in different indications.

Over the years of the doctoral project, the doctoral student has acquired and complemented his training with many other training skills in research and innovation.

Both studies are part of a multicentre prospective project: the national registry of lumen-apposing metal stents incidences, on which this doctoral thesis is based. This project started in January 2019, and included all procedures in which transmural LAMS were placed for 12 months in more than 30 national centres. In addition to the regular follow-up of each centre, centralized telephone follow-up was also scheduled. The two articles that make up this thesis analyse part of the objectives of this project.

The first manuscript evaluated the use of this LAMS for the gallbladder drainage. It was published in a second-quartile journal (Journal of Gastroenterology and Hepatology JCR 2022: 4.1). It is one of the larger prospective series published on this topic. The risk of adverse events leaving the prosthesis in situ for one year is similar to published data when removing the prostheses. The cumulative risk of new biliary events per year is less than 10% and it is mainly focused on patients who also present pancreaticobiliary cancer.

The second manuscript focused on the removal procedures of LAMS. It was published in a first-quartile journal (Endoscopy JCR 2022: 9.3), appearing on the first page of the journal issue and highlighted by an editorial (1). This is a new topic since there is very little data on it. The results and conclusions affirm that removing this type of prosthesis is generally a simple procedure, usually affordable in conventional endoscopy rooms. We identified risk factors associated to the small percentage of patients who may require advanced endoscopy techniques for LAMS removal.

In conclusion, this thesis aims to provide evidence on using LAMS Axios type in gallbladder drainage and their removal procedures.

INTRODUCCIÓN

1. INTRODUCCIÓN

1.1. PRÓTESIS DE APOSICIÓN LUMINAL

1.1.1. Antecedentes

La aposición luminal se define como la unión de dos lúmenes o cavidades cercanas entre sí. La realización de anastomosis quirúrgicas ha sido el método tradicional para establecer la continuidad entre distintos segmentos del tubo digestivo o entre éste y el sistema biliopancreático después de cirugías resectivas o en derivaciones paliativas en neoplasias irresecables. El primer caso descrito de anastomosis quirúrgica mediante un dispositivo metálico, el botón de Murphy, conectando la vesícula biliar con el duodeno, data de 1892 (2). Este dispositivo permitía hacer anastomosis sin suturar los órganos entre sí, sino colocando una pieza metálica en cada uno de los extremos a unir y posteriormente encajando las dos piezas. Tras este primer caso, se comunicaron tres más en los que este dispositivo fue utilizado satisfactoriamente convirtiéndose en un método de uso común para las anastomosis intestinales, siendo el procedimiento de elección para este tipo de operaciones en la Clínica Mayo y en otros lugares de los Estados Unidos hasta mediados de la década de 1930 (2). La técnica fue posteriormente desestimada.

El botón de Murphy demostró que las anastomosis también pueden llevarse a cabo sin suturar entre si los dos cabos a unir. Con el desarrollo de la endoscopia y especialmente de la ecoendosocopia terapéutica empezaron a surgir los primeros intentos de crear anastomosis mediante la inserción transluminal de prótesis en el interior de colecciones pancreáticas (3) o a la vía biliar (4,5).

Estos primeros casos fueron realizados mediante prótesis plásticas (PP) transluminales. Desgraciadamente, se observó que el riesgo de eventos adversos (EA) (migraciones, fugas…) era alto (16-35%) (6). Para paliar esta situación se empezó a emplear prótesis metálicas autoexpandibles (PMA) cubiertas, utilizadas habitualmente para patologías

esofágicas o biliares. Éstas sellan de forma más eficaz el trayecto transluminal, disminuyendo las complicaciones observadas previamente (7,8). Además, en las colecciones pancreáticas necróticas, el mayor calibre del *stent* facilita la evacuación pasiva de contenido sólido y el acceso endoscópico a colecciones complejas, para realizar sesiones de necrosectomía (9).

Sin embargo, las PMA tubulares cubiertas asocian un riesgo de migración relevante, ya que en los drenajes transluminales no existe una estenosis que fije la prótesis, pudiendo ser causa de consecuencias graves. Para prevenirla, se pueden emplear clips o prótesis plásticas de doble *pigtail* coaxiales. Así y todo, estas estrategias no son infalibles y su uso incrementa la complejidad del procedimiento. Además, los extremos de las PMA no suelen ser completamente romos, por lo que pueden provocar lesiones por decúbito en los órganos anastomosados (10).

A la luz de estas limitaciones surgieron las prótesis de aposición luminal (PAL). Éstas pueden considerarse una evolución de las PMA tradicionales para disminuir el riesgo de migración u obstrucción. El primer caso descrito empleando este tipo de prótesis *in vivo* data del 2011, una colecistogastrostomía en un modelo porcino (10).

1.1.2. Partes y tipos de prótesis de aposición luminal

Todas las PAL actualmente comercializadas comparten una estructura similar. Están compuestas por una parte central tubular, con una longitud mucho menor que las PMA tubulares, y una solapa antimigración en cada extremo; son estructuras con forma de diábolo. Están recubiertas de una malla para minimizar la infiltración tisular y la fuga de contenido intestinal o biliar al peritoneo. El sistema de liberación es ligeramente diferente entre los modelos disponibles. La mayoría disponen de catéteres introductores similares a los de las PMA convencionales, aunque algunas, más novedosas, disponen de liberación directa mediante electrocauterio.

Actualmente se han comercializado 5 tipos de PAL (Tabla 1). La más conocida y utilizada es la PAL tipo Axios (Boston Scientific; Boston, Massachusetts), que se describirá con detalle en el siguiente apartado. En segundo lugar, está la prótesis Spaxus (Taewoong; Seúl, Corea del Sur). Su diseño difiere respecto a la prótesis Axios principalmente en la morfología de las solapas antimigración. Sus dos versiones "HOT-Spaxus" y "Niti-S-Spaxus", han sido utilizadas en un importante número de pacientes para el drenaje de colecciones pancreáticas, con buenos resultados tanto técnicos como clínicos (11-13), y también en gastroenteroanastomosis (14). NAGI-stent (Taewoong; Seúl, Corea del Sur), también ha demostrado su eficacia en el drenaje de colecciones pancreáticas (15), gastroenteroanastomosis (16) y varios casos de drenaje vesicular (17,18), la mayoría en pacientes no candidatos a tratamiento quirúrgico. Por último, solo existe una serie de 12 pacientes con colecciones pancreáticas drenadas con Hanarostent Plumber (M.I Tech; Seúl, Corea del Sur) (19).

	Axios (Boston Scientific; Natick, MA, Estados Unidos)	**Spaxus** (Taewoong Medical; Gimposi, Corea del Sur)	**Nagi** (Taewoong Medical; Gimposi, Corea del Sur)	**Aixstent** (Leufen Medical; Berlín, Alemania)	**Hanarostent Plumber** (M.I Tech; Pyeongtaek-si, Corea del Sur)
Stent					
Material	Nitinol Cobertura silicona	Nitinol Cobertura silicona	Nitinol Cobertura silicona	Nitinol Cobertura silicona	Nitinol Cobertura silicona
Tamaños solapas (mm)	21, 24, 29	23, 25, 31	20	25	22-28
Longitud (mm)	10	20	10, 20, 30	30	10, 30
Diámetro lumen (mm)	6, 8, 10, 15, 20	8, 10, 16	10, 12, 14, 16	10, 15	10, 12, 14, 16
Diámetro catéter liberación (“French” Fr)	10,8	10	9, 10	10	10,5
Electrocauterio	Disponible	Disponible	No	No	No
Liberación a través del endoscopio	Sí	Sí	Sí	Sí	Sí

Tabla 1: Tipos y características principales de las diferentes prótesis de aposición luminal (todas las imágenes y la información están disponibles en el sitio web del fabricante).

1.1.3. Prótesis de aposición luminal tipo Axios

La primera PAL comercializada fue el tipo Axios, comunicándose su primer uso en 2011 (10). Es actualmente la más utilizada. En el momento de redactar este texto tiene marca CE *(Conformité Européenne)* para drenaje biliar y pancreático, y también está aprobada en estas indicaciones por la FDA *(Food and Drug Administration)*. Además, se han propuesto varias indicaciones adicionales en los últimos años. Dispone de un sistema de liberación montado sobre un introductor específicamente adaptado a la inserción y liberación mediante ultrasonografía endoscópica (USE). Además, en los últimos años y

como evolución del propio sistema tradicional (“Cold-Axios”), se ha incorporado un introductor con diatermia que permite la inserción del *stent* en un solo paso, evitando los múltiples recambios instrumentales que se deben realizar durante el procedimiento de colocación del modelo original. Como resumen, sus rasgos diferenciales son:

- Fijación al canal de trabajo del ecoendoscopio de una forma similar a la de las agujas de punción-aspirativa con aguja fina (PAAF).
- Liberación independiente de las solapas distal y la proximal. Esto permite liberar la solapa distal bajo control ecográfico en la diana y posteriormente liberar la solapa proximal bajo control ecográfico o endoscópico.
- Mecanismos de freno que permiten la liberación con una sola mano, con el objetivo de minimizar el riesgo de eventos adversos como migración o malposición.

1.2. PRÓTESIS DE APOSICIÓN LUMINAL Y ECOENDOSCOPIA

La ultrasonografía endoscópica se introdujo a principios de la década de los 90 como una técnica de diagnóstico por imagen. Posteriormente se desarrolló la posibilidad de realizar PAAF de masas del tracto gastrointestinal, aunque su capacidad diagnóstica, tanto en cuanto a posibles dianas como en cuanto a los métodos de adquisición de tejido, se ha ido ampliando progresivamente. Además, en los últimos años ha adquirido una gran importancia en la terapéutica endoscópica, siendo considerada la primera técnica endoscópica intervencionista transmural (20-22).

La ultrasonografía endoscópica intervencionista transmural incluye una gran variedad de técnicas como el drenaje de colecciones adyacentes al tubo digestivo, la creación de enteroanastomosis, drenajes biliares en casos de colangiopancreatografía retrógrada endoscópica (CPRE) fallida, etc (23).

Todos estos avances se han producido principalmente por la mejora de la imagen endosonográfica y las agujas de punción (tanto terapéuticas como diagnósticas) junto a la adaptación de una gran cantidad de instrumental de CPRE o de otros procedimientos terapéuticos endoscópicos.

1.2.1. Indicaciones de utilización de las prótesis de aposición luminal

1.2.1.1. Drenaje de colecciones pancreáticas encapsuladas (CPE)

El drenaje de colecciones pancreáticas está indicado en colecciones sintomáticas. Históricamente, el drenaje quirúrgico fue la terapia de elección, pero presenta complicaciones y recurrencias en aproximadamente un 30% de los pacientes (24-26). Con el desarrollo de las técnicas endoscópicas, menos invasivas, se fue produciendo un cambio progresivo en su manejo.

El primer drenaje endoscópico transmural (DET) de colecciones pancreáticas fue publicado en 1989 (27). Este proceso, anterior a la introducción de la ecoendoscopia, requería identificar la colección endoscópicamente, como una compresión externa. Una vez localizada, se realizaba una punción mediante un dispositivo de electrocauterio, posteriormente se dilataba el tracto creado y se colocaba un *stent*, normalmente plástico (PP), para asegurar el drenaje. Si bien esta técnica es segura y eficaz, estaba muy limitada porque la colección sólo era identificable en el 40-50% de los pacientes (28).

Existen diversos trabajos comparando el drenaje quirúrgico con el DET; en todos ellos se observó que los abordajes mínimamente invasivos presentaban un menor porcentaje de complicaciones con respecto a los quirúrgicos (29-31). De igual forma los abordajes endoscópicos y percutáneos han sido comparados, observando más reintervenciones y mayores complicaciones en el grupo de percutáneo que en el grupo endoscópico (32).

El desarrollo de la ecoendoscopia terapéutica permitió drenar las colecciones pancreáticas identificando aquéllas que no ejercen efecto masa, evaluar el grosor de la

pared gástrica, identificar la existencia de vasos interpuestos y escoger el punto óptimo de acceso (33). Este hecho provocó la publicación de diversos estudios comparando ambas técnicas, concluyendo la mayoría de ellos que el drenaje guiado por ecoendoscopia presentaba unos mayores porcentajes de éxito técnico y clínico, así como en identificar colecciones significativamente más pequeñas (34-36).

El diámetro de las prótesis plásticas está limitado a, como mucho, 10Fr y su colocación puede llegar a ser muy dificultosa, influyendo en el éxito técnico (37). Por este motivo, las PMA totalmente cubiertas se hicieron cada vez más populares. La eficacia de dichas prótesis resultó ser muy elevada (85-95%) (38-40), sin embargo, los casos comunicados observaron múltiples eventos adversos debido a que su diseño está pensado para ser colocadas en estructuras tubulares (esófago, colon), lo que hace que el riesgo de fuga y de migración sean elevados (37,41), promoviendo el desarrollo y uso de las PAL para el drenaje de CPE.

Diversos estudios han comparado PAL, PP y PMA. Una serie de casos retrospectiva multicéntrica con 313 pacientes no observó diferencias en el éxito técnico (99,1% *vs* 100% *vs* 97,7%, p= 0,37). Se describió un mayor número de eventos adversos precoces con las PAL (1,6%, 15,1% y 12.3%, p=0,02). A los 6 meses de seguimiento, la resolución completa de las lesiones fue menor con las PP (81% *vs* 95% *vs* 90%; p=0,001) (42).

Un ensayo clínico aleatorizado publicado por Bang *et al* comparó PAL (31 pacientes) *vs* PP (29 pacientes), sin identificar diferencias en el éxito clínico (93,5% *vs* 96,6%, p=1). La proporción de eventos adversos relacionados con el *stent* fue mayor en el grupo PAL (32,3% *vs* 6,9%, p=0,01), ocurriendo sobretodo pasadas 3 semanas desde su colocación, lo que provocó una modificación del protocolo, que consistió en la obtención de un TC abdominal 3 semanas después de la colocación de la PAL, procediendo a su retirada si la CPE se había resuelto (43). Otro ensayo clínico incluyó 42 pacientes, 22 PP *vs* 20 PAL, concluyendo que para CPE grandes las PAL no son superiores a las PP.

Tampoco observó diferencias entre los días de hospitalización (PP 43 [40-67] *vs* PAL 58 [40-86],, p= 0,71) ni en los eventos adversos (PP=4 *vs* PAL=1, p=0,35) (44).

A pesar de que estos estudios no muestran una clara ventaja de la PAL respecto a otras prótesis metálicas, un estudio prospectivo sobre drenaje de CPE analizó y comparó los 3 tipos de prótesis (PP 12, PMA 19 y PAL 27) en 58 pacientes. No se observaron diferencias significativas (96,3% PAL *vs* 81,8% PP *vs* 77,8% PMA, respectivamente; p=0,14) en el éxito clínico (resolución completa o disminución de ≥50% del tamaño de la colección en ausencia de síntomas y sin necesidad de reintervención). Sin embargo, las PAL obtuvieron un mayor éxito para el tratamiento de las necrosis encapsuladas, en comparación con PMA (95,7% *vs* 66,7%, respectivamente; p=0,04) (45).

En una serie de casos retrospectiva multicéntrica sobre eventos adversos asociados a PAL en un total de 328 pacientes con CPE, Fugazza *et al* obtuvieron un éxito clínico del 89,5% (272/304), aunque con 74 (24,3%) de eventos adversos, siendo 54 (68,4%) moderados; proporciones discretamente mayores a las anteriormente publicadas (46).

1.2.1.2. Drenajes biliares y pancreáticos

El drenaje biliar y pancreático guiado por USE ha surgido como alternativa a la cirugía o al DPT (47) en aquellos pacientes en los que la CPRE convencional no es exitosa o factible, por presentar anomalías papilares (invasión por neoplasias pancreáticas o ampulares), una anatomía quirúrgicamente alterada o una canulación fallida a pesar de repetidos intentos (48).

El primer drenaje biliar guiado por ecoendoscopia fue publicado en 2011 (5). Desde entonces se han publicado múltiples estudios comparando dicha técnica con el DPT. Globalmente los resultados son similares en lo que respecta al éxito técnico. Sin embargo, el drenaje guiado por ecoendoscopia ha demostrado un menor riesgo de complicaciones, menor número de reintervenciones y una mayor calidad de vida del

paciente (49-57). Una revisión sistemática reciente (58) con nueve estudios, tres ensayos clínicos aleatorizados (49,53,57) y seis estudios retrospectivos (50-52,54-56) no observó diferencias en el éxito técnico (OR: 1,78; IC 95%: 0,69-4,59; I2=22%). Sin embargo, el drenaje guiado por ecoendoscopia presentó mayor éxito clínico (OR: 0,45; IC95%: 0,23-0,89; I2=0%), menos eventos adversos postprocedimiento (OR: 0,23; IC95%: 0,12-047; I2=57%) y menores reintervenciones (OR: 0,13; IC95%: 0,07-0,24; I2=0%).

Existen dos alternativas según el punto de acceso: intrahepático (hepático-gastrostomía) o extrahepático (coledocoduodenostomía [CDS]) (Figuras 1a y 1b).

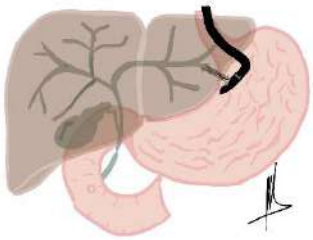

Figura 1a: Hepaticogastrostomía con prótesis metálica

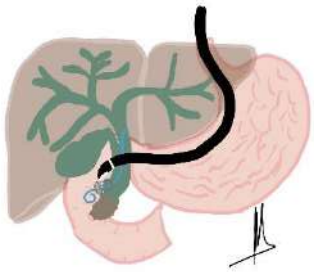

Figura 1b: Coledocoduodenostomía con PAL

En el abordaje intrahepático la elección del *stent* depende de la indicación (maligna o benigna), el grado de dilatación ductal, la longitud de la fístula creada y si el paciente es candidato a tratamiento quirúrgico (59). En los primeros casos comunicados se emplearon *stents* de plástico, pero ante la elevada frecuencia de fuga biliar se empezaron a utilizar PMA (60). Las PAL no suelen ser utilizadas para el drenaje biliar intrahepático, debido a que los radicales intrahepáticos no se encuentran lo suficientemente cerca de la luz del tracto digestivo.

La vía biliar extrahepática, al contrario, suele estar muy cercana al tracto digestivo a nivel del colédoco. Dado que los *stents* de aposición luminal aparentemente minimizan el riesgo de fuga en otras indicaciones, se planteó utilizar las PAL (61). Se ha planteado

que una vía biliar dilatada y una distancia <10 mm a la diana son condiciones indispensables para su utilización (61). Tsuchiya *et al* evaluaron prospectivamente el resultado de CDS con PAL en 19 pacientes, con un éxito técnico del 100% y una mejoría de la ictericia en el 95% (18/19). No registraron incidencias durante el procedimiento, pero el porcentaje de eventos adversos al completar el seguimiento fue del 15,8% (62). Otra serie de casos retrospectiva, con 46 pacientes alcanzó un éxito técnico y clínico del 93,5% y 97,7%, respectivamente; observaron un 11,6% de eventos adversos (63).

Recientemente han sido publicados dos estudios multicéntricos aleatorizados en los que se compara la utilización como primera línea de la CDS *vs* la CPRE en pacientes con obstrucción biliar maligna. El primero incluyó 73 CDS y 71 CPRE. No observaron diferencias significativas con respecto al éxito técnico (90,4% CDS *vs* 83,1% CPRE, p=0,87) ni en el clínico (84,9% *vs* 85,9%, p=0,77). Los eventos adversos tempranos (< 14 días, 9 [12,3%] *vs* 9 [12,7%], p=0,95) y los tardíos (11 [15,1%] *vs* 12 [16,9%], p=0,76) acaecieron también en proporciones equiparables (64). Teoh *et al* incluyeron 155 pacientes (79 CDS y 76 CPRE). El objetivo primario fue evaluar la permeabilidad del *stent* a un año, sin encontrar diferencias significativas entre ambas técnicas (CDS 91,1% frente a CPRE 88,1%, p=0,52). El grupo CDS tuvo éxito técnico significativamente mayor (CDS 96,2% frente a CPRE 76,3%, p<0,001), mientras que el éxito clínico fue similar (CDS 93,7% frente a CPRE 90,8%, p=0,56). La duración del procedimiento fue significativamente más corta en el grupo de CDS (10 [5,75-18] min *vs* CPRE 25 [14-40] min, p<0,001). Los eventos adversos observados a 30 días (13 [16,5%] *vs* 13 [17,1%], p=1) y la mortalidad (4 [5,1%] *vs* 6 [7,9%], p=0,53) fueron equiparables (65). Ambos estudios concluyen que los dos procedimientos pueden ser alternativas para el drenaje biliar primario en pacientes con patología maligna irresecable. La CDS podría plantearse como primera línea si se prevén CPRE complejas.

El drenaje pancreático dispone de muy escasos datos con PAL. Las guías, basadas únicamente en recomendaciones de expertos, sugieren emplear prótesis plásticas para

realizar el drenaje transmural, (66,67). Existen algunos casos descritos de drenaje pancreático transmural realizado con PAL, con buenos resultados. Se requiere que el conducto pancreático principal este considerablemente dilatado (68).

1.2.1.3. Gastroenteroanastomosis

La obstrucción al vaciamiento gástrico (OVG) es la principal indicación de realización de gastroenteroanastomosis. Este síndrome causado por una obstrucción del estómago distal o duodeno proximal impidiendo el tránsito del contenido gástrico al intestino delgado, puede conducir a una desnutrición grave. En la mayoría de los casos es de etiología maligna. A consecuencia de las importantes diferencias de pronóstico y evolución, describiremos de manera separada su uso en patología maligna y benigna.

A) Gastroentroanastomosis en patología maligna

El primer tratamiento paliativo disponible para la OVG fue la gastroyeyunostomía quirúrgica (GY) (69). Desafortunadamente, la mayoría de los pacientes con OVG maligna no son candidatos óptimos para cirugía, ya que presentan un alto riesgo quirúrgico y una esperanza de vida reducida. Los *stents* duodenales se desarrollaron gracias a la experiencia adquirida en el uso de prótesis metálicas autoexpandibles en las estenosis del tracto digestivo (70).

Diversos estudios han mostrado un éxito técnico (definido como el despliegue exitoso del *stent* a través de la estenosis) superior al 90% y un éxito clínico (definido como el alivio de los síntomas obstructivos y la mejoría en la ingesta oral) de las prótesis enterales en OVG que puede oscilar entre el 63% y el 97% (71). Una revisión sistemática reciente con 19 estudios prospectivos de 2009 a 2016 y más de 1200 pacientes con OVG tratados con PMA documentó un éxito técnico global del 97,3% y un éxito clínico del 85,7% (72). La proporción de eventos adversos osciló entre el 0 y el 30% (73-75), siendo los más frecuentes las náuseas, vómitos, dolor abdominal y la colangitis. Este

último es frecuente en aquellos pacientes con neoplasias pancreatobiliares avanzadas que cursan con OVG. El progreso reciente de la EUS intervencionista y la posibilidad de realizar CDS desde el estómago o duodeno ha ampliado las opciones de abordaje de los pacientes con OVG y obstrucción biliar concomitante (76).

Se ha comparado la GY con los *stents* duodenales, observando unas tasas de éxito técnico y clínico similares, con una mejoría de la ingesta más rápida en el grupo *stent* duodenal, pero asociando una menor permeabilidad con el paso del tiempo (77,78). Estos datos harían pensar que la gastroenteroanastomosis quirúrgica sería la mejor opción para este tipo de pacientes. Sin embargo, el pronóstico vital reducido y la ausencia de un postoperatorio que afecte a la calidad de vida hacen que la prótesis enteral sea el tratamiento más frecuente actualmente.

La gastroenteroanastomosis guiada por ultrasonido endoscópico (EUS-GE) mediante PAL permite en teoría combinar las ventajas de las técnicas previamente descritas (79,80) (Figura 2).

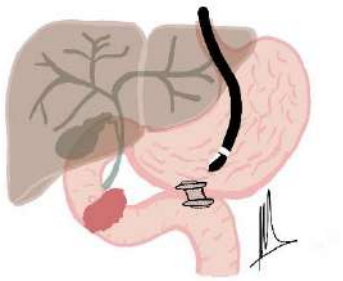

Figura 2: Gastroenteroanastomosis con PAL en paciente con proceso maligno

Desde la introducción de la técnica varios estudios retrospectivos han comunicado unos porcentajes de éxito técnico y clínico del 87-96% y 81-92% respectivamente (81). En 2015 fue publicada por Kashab *et al* la primera serie de EUS-GE tanto en obstrucción maligna (3 pacientes) como en benigna (7 pacientes), con un éxito técnico del 90% y un éxito clínico del 100%, sin observar ningún evento adverso y sin evidencia de recurrencia tras un periodo medio de seguimiento de 150 días (79). Itoi *et al*, informaron

de unos resultados similares en una serie prospectiva en 20 pacientes, con un éxito técnico del 90% con una mejoría significativa del GOOS (Puntuación GOOS pre 0 *vs* puntuación GOOS post 3, p< 0,001), con un 10% de eventos adversos (82). La EUS-GE ha sido comparada con los *stents* enterales en algunos estudios retrospectivos (83-85). El éxito técnico, la duración de la hospitalización y la seguridad fueron similares, mientras que en el estudio de Ge *et al* se encontró un mayor éxito clínico inicial en el grupo EUS-GE (95,8% *vs* 76,3%, p=0,042) (84). La disfunción del *stent* requirió una reintervención significativamente menor en el grupo EUS-GE en ambos estudios. Un reciente estudio retrospectivo publicado a nivel nacional comparando también ambos tipos de técnicas ha observado unos resultados similares; el grupo de EUS-GE presentó una permeabilidad mayor en comparación con el grupo de prótesis duodenal a los 3 meses (HR ajustado 0,37, p=0,033) (85). En lo que respecta a la opción quirúrgica, un estudio retrospectivo multicéntrico comparó EUS-GE (30 pacientes) y GY quirúrgica (63 pacientes); a pesar de que la GY quirúrgica mostró un mayor éxito técnico (100% frente a 87%, p=0,01), el éxito clínico (90% *vs* 87%, p=0,18; OR 1,7, 95%IC: 0,44-7,07) y la recurrencia de los síntomas fueron similares (86). Otro estudio también multicéntrico y retrospectivo, comparando también EUS-GE (25 pacientes) y GY (22 pacientes), observó un éxito técnico similar con una mayor proporción de eventos adversos en el grupo de GY (12% *vs* 41%, p=0,0438) (87).

El tratamiento para la OVG puede ser un desafío y a menudo se necesita un equipo multidisciplinar para evaluar la mejor estrategia terapéutica. Los *stents* enterales proporcionan un alivio rápido de los síntomas obstructivos y una estancia hospitalaria breve en comparación con la GY. Por otro lado, tienen una mayor proporción de fallo técnico y disfunción a largo plazo y, por esta razón, son la estrategia de primera línea en pacientes con una expectativa de vida corta (<3 meses). La EUS-GE tiene la ambición de proporcionar un procedimiento endoscópico mínimamente invasivo, con la consiguiente seguridad y rapidez de acción y, al mismo tiempo, con las ventajas

duraderas de GY, ya que el *stent* metálico se coloca lejos de la estenosis neoplásica y, por lo tanto, está virtualmente libre de riesgo de crecimiento interno. A pesar de estas interesantes novedades, la EUS-GE sigue siendo una técnica difícil y poco estandarizada, y actualmente está limitada a centros con alta experiencia en USE terapéutica (88).

B) Gastroentroanastomosis en patología benigna

La OVG benigna es poco frecuente; entre sus causas podemos encontrar la enfermedad ulcerosa péptica, la pancreatitis aguda o crónica, las lesiones por cáusticos o la enfermedad de Crohn (89). En términos de manejo, la dilatación endoscópica con balón ha reemplazado en gran medida a la cirugía como tratamiento de primera línea (89). Aunque el éxito clínico es alto en las estenosis de origen péptico, con frecuencia se requieren múltiples sesiones y la respuesta a largo plazo es del 70-80% (90). Además, la dilatación puede ser menos exitosa en estenosis secundarias a cáusticos o a pancreatitis debido a cambios fibroestenóticos (91). Otras modalidades de tratamiento, como podrían ser la colocación de *stents* enterales o la cirugía, presentan los inconvenientes descritos en la OVT debido a patología maligna.

La EUS-GE surge como alternativa, ya que además puede actuar como terapia puente para evitar la cirugía en aquellas causas que sean parcialmente reversibles (92). En el 2018 se publica la primera serie de casos retrospectiva multicéntrica con EUS-GE en OVG benigna (26 pacientes), siendo la pancreatitis crónica la más frecuente (11 pacientes). Se observó un éxito técnico del 96,2% y un éxito clínico del 84% (definido como correcta tolerancia oral sin la presencia de vómitos). Sólo se observaron dos EA, solucionados endoscópicamente. Un paciente (4,8%) requirió una reintervención. En 2 pacientes se realizó una retirada selectiva de la PAL, presentando buena evolución posterior (93). Otra serie retrospectiva con 22 pacientes observó unos resultados similares. Se retiró la PAL de forma electiva una vez solucionada la causa de la OVG en

18 de los 21 pacientes (85,7%). Tras ésto, solo 3 pacientes (16%) requirieron conversión a gastroyeyunostomía quirúrgica por OVG recurrente (94).

Una indicación particular de enteroanastomosis en patología benigna es el acceso a la vía biliar en pacientes con anatomía modificada, fundamentalmente portadores de bypass gástrico en Y de Roux (BGYR). Esta cirugía es uno de los principales y más exitosos tratamientos para la obesidad y sus comorbilidades médicas (95-97). Estos pacientes presentan un aumento de incidencia de patología biliar litiásica (98,99), pero el acceso endoscópico al árbol biliar es muy complejo, requiriendo una CPRE con enteroscopia (EAB-CPRE) o asistida por laparoscopia (CPRE-AL). La EAB-CPRE está limitada por unos valores de éxito técnico que oscilan entre el 50% y el 70% (100,101). CPRE-AL presenta valores notables de éxito técnico y clínico, pero se asoció con una duración más prolongada del procedimiento, de la estancia hospitalaria, mayor coste y mayores EA (102-104).

La CPRE transgástrica guiada por ecoendoscopia (*endoscopic ultrasound directed transgastric ERCP* [EDGE]) consiste en la creación de una fístula transgástrica temporal mediante una PAL que conecta el remanente gástrico o el yeyuno proximal con el estómago excluido de pacientes con una cirugía metabólica derivativa (Figura 3). Esta fístula permite acceder a la vía biliar a través del píloro excluido.

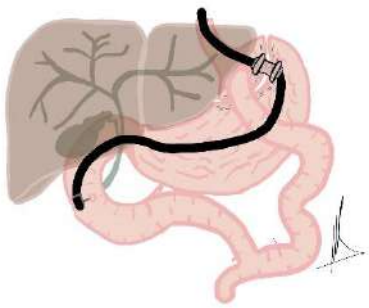

Figura 3: EDGE en paciente con Y de Roux

El primer caso fue en 2015, descrito por Kedia *et al* (105), y posteriormente los mismos autores publicaron 5 casos con un éxito técnico del 100% utilizando una PAL de 15 mm. La CPRE se realizó con éxito en el mismo procedimiento de la creación de la anastomosis en 3 de los 5 pacientes (60%), pero en 2 (40%) se realizó de forma diferida, debido a la dificultad para pasar el duodenoscopio a través del *stent*. No se observaron eventos adversos graves, solo dos desalojos que se solucionaron endoscópicamente. Una vez realizada la CPRE se retiró la PAL y se cerró la fístula mediante sutura endoscópica en 2 de 5 pacientes. No se observó incremento del peso de los pacientes durante el seguimiento (106).

Uno de los primeros estudios multicéntricos prospectivos sobre la seguridad y eficacia del EDGE fue publicado por Ngamruengphong *et al* (107). Alcanzaron el éxito técnico y clínico en los 13 pacientes incluidos. Entre la colocación de la PAL de 15 mm y la CPRE hubo una demora mediana de 11 días (RIC 3-21). Otra pequeña serie de 16 pacientes también alcanzó resultados similares, empleando clips Ovesco, sutura endoscópica y la coagulación con argón plasma para el cierre del trayecto fistuloso, sin asociar incrementos en el peso (108,109). Un estudio con 166 pacientes, restrospectivo y multicéntrico (12 centros) observó un éxito técnico del 98%. La CPRE se realizó en un sólo acto tras la creación de la fístula en un 51%. La PAL fue retirada en todos los casos, realizándose el cierre de la fístula en el 73% de los pacientes tras un tiempo medio de seguimiento de 35 días (RIC 22-54). Se observaron un 17% (28/166) de complicaciones (110).

Se han realizado algunos estudios comparativos entre el EDGE y el abordaje por enteroscopia o laparoscopia. Bukhari *et al* compararon resultados y eventos adversos entre EDGE y EAB-CPRE (30 pacientes por grupo). El éxito técnico fue mayor en el grupo de EDGE (100% *vs* 60%, p<0,001). El tiempo total de procedimiento y la hospitalización fueron significativamente más cortos en el grupo de EDGE (49,9 min *vs* 90,7 min, p<0,001; y 1 *vs* 10,5 días, p=0,02). Sin embargo, los porcentajes de eventos

adversos fueron similares en ambos grupos (6,7% frente a 10,0%, p=1). No hubo cambios en el peso de los pacientes en el grupo de EDGE tras un seguimiento medio de 209 días (111).

Con respecto a la CPRE-AL, en 2018 fue publicado un estudio retrospectivo multicéntrico comparando esta técnica con EDGE. Incluyeron 29 pacientes manejados con EDGE y 43 con CPRE-AL, observando un éxito técnico (96,5% *vs* 100%, p=0,40) y clínico (96,5% *vs* 97,7%, p=1) similares. No hubo diferencias significativas en los eventos adversos (24% *vs* 19%, p=0,57). El tiempo de procedimiento y la duración de la estancia hospitalaria fueron menores en el grupo de EDGE (73 [24-230] min *vs* 184 [55-393] min, p<0,001; y 0,8 [0-5] días *vs* 2,65 [1-12] días, p<0,001) (103).

1.2.1.4. Drenaje de vesícula biliar

La colecistectomía es el tratamiento de referencia en la colecistitis aguda. En pacientes con múltiples comorbilidades y/o en los que el riego quirúrgico se considera inaceptablemente alto existen alternativas que pueden ser efectivas para controlar el cuadro agudo y/o disminuir el riesgo de reingreso biliar. El DPT y el drenaje endoscópico transpapilar (DETP) alcanzan buenos porcentajes de éxito técnico y clínico, pero presentan limitaciones específicas a cada técnica.

El éxito técnico del DPT oscila entre el 95-100% (112). Las complicaciones pueden ser de hasta de un 12%, incluyendo la hemorragia, el neumotórax, la peritonitis biliar, el dolor y la infección de la zona de inserción del drenaje (113,114). Este procedimiento puede estar contraindicado en algunos pacientes como los que presentan una ascitis importante o con coagulopatía (115). En la mayoría se trata de una medida temporal y es necesario la retirada del catéter antes de la colecistectomía o del alta hospitalaria si se desestima la colecistectomía diferida (116). En los pacientes no colecistectomizados, la colecistitis recurrente es frecuente (117). El DETP tiene una eficacia comparable con el DPT, pero con unos períodos de hospitalización discretamente más cortos (118). Por

desgracia, se trata de un procedimiento que puede llegar a ser técnicamente complejo con fracasos técnicos en el 10-20% de los pacientes, ya que es común que el conducto cístico se halle obstruido por inflamación o por un cálculo (119).

Baron *et al* describieron en 2007 el primer caso exitoso de drenaje de la vesícula biliar guiado por ecoendoscopia (EUS-DVB) (120). Esta técnica puede ser utilizada como terapia puente hasta la colecistectomía, conversión de DPT a EUS-DVB, como alternativa al DPT o DETP, o como procedimiento de rescate tras éstos (121). Los primeros drenajes realizados con prótesis plásticas se asociaron con diversas complicaciones como migraciones, fugas biliares, etc (122). Las PMA disminuyeron las complicaciones, permitiendo una permeabilidad prolongada del *stent* (123), aunque con un riesgo elevado de migración (124). Los primeros casos de drenaje vesicular con PAL fueron publicados en 2012 por Itoi *et al* (125) (Figura 4).

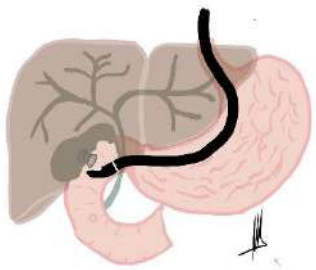

Figura 4: Colecistoduodenostomía con PAL

Ante los buenos resultados obtenidos se realizaron las primeras series descriptivas como la de de la Serna *et al* que incluyó 13 pacientes, alcanzando un éxito técnico del 84,61% (11/13), un éxito clínico del 100% (definido como mejoría inmediata de los síntomas con normalización progresiva de las pruebas de función hepática y de los reactantes de fase aguda) y únicamente 2 eventos adversos que no necesitaron tratamiento intervencionista (126). Una de las mayores series de casos publicada es un estudio retrospectivo con 379 pacientes de 13 centros. Todos los EUS-DVB se realizaron con PAL, la mayoría tipo Axios (285; 75,2%). Se logró un éxito técnico y clínico

del 95,3% y 90,8% respectivamente. La proporción de EA a los 30 días fue del 15,3% y la de mortalidad del 9,2%. El fracaso clínico (RR 8,69; 95%IC [1,56-48,47]) y una experiencia del endoscopista <25 casos de este tipo de procedimientos (RR 4,68, 95%IC [1,79-12,26]) fueron predictores significativos de EA a los 30 días. Únicamente la presencia de eventos adversos a los 30 días fue un predictor significativo de mortalidad (RR 103, 95%IC [11,24-944,04]) (127).

Tras estos primeros procedimientos, se empezaron a realizar algunos estudios comparativos entre EUS-DVB, DPT y DETP. Uno de los primeros publicados fue una serie retrospectiva multicéntrica con 45 EUS-DVB y 45 DPT que no mostró diferencias con respecto al éxito técnico, clínico ni los eventos adversos entre las dos técnicas. Sí observó que la puntuación media en la escala de dolor (definido como puntuación de dolor más alta (1-10) observada el día después de la intervención) fue menor en el grupo EUS-DVB que en el de DPT (2,5 *vs* 6,5, p<0,01), así como la estancia hospitalaria (3 días *vs* 9 días, p<0,05) y el número de reintervenciones (11 *vs* 12, p< 0,01) (128).

Sólo existe un estudio que compare los 3 tipos de técnicas de drenaje, una serie retrospectiva multicéntrica de 372 pacientes (146 DPT, 124 DETP y 102 EUS-DVB). El éxito técnico (98% *vs* 88% *vs* 94%, p=0,004) y clínico (97% *vs* 90% *vs* 80%, p<0,001) fueron significativamente mayores en DPT y EUS-DVB que con DETP. El grupo DPT tuvo un número significativamente mayor de complicaciones en comparación con los grupos EUS-DVB y DETP (20% *vs* 2% *vs* 5%, p=0,01). La estancia hospitalaria media en la EUS-DVB fue significativamente menor (16 *vs* 18 *vs* 19 días, p=0,01), mientras que la necesidad de reintervención adicional fue significativamente mayor en el grupo DPT (49% *vs* 4% *vs* 11%, p<0,001) (129).

Disponemos de un único ensayo clínico aleatorizado entre EUS-DVB y DPT que incluyó 40 EUS-DVB y 40 DPT en pacientes con colecistitis aguda no candidatos a tratamiento quirúrgico. Los resultados de éxito técnico (97,4% *vs* 100%, p=0,49), clínico (92,3% *vs* 92,5 %, p=1), y mortalidad a los 30 días (7,7% *vs* 10%, p=1) fueron estadísticamente

similares, aunque el estudio no tenía potencia para identificar diferencias clínicamente relevantes. EUS-DVB mostró porcentajes significativamente más bajos de reintervenciones a los 30 días (2,6% *vs* 30%, p=0,001), de reingresos no planificados (15,4% *vs* 50%, p=0,002), de colecistitis recurrente (2,6% *vs* 20%, p=0,03) y eventos adversos a los 30 días (12,8% *vs* 47,5%), si bien los eventos adversos del grupo DPT eran mayoritariamente leves (130).

Todos estos resultados sugieren que EUS-DVB es una alternativa o incluso tratamiento de primera elección en casos de colecistitis no candidatos a cirugía.

1.2.1.5. Colecciones postquirúrgicas y abscesos

Las colecciones postquirúrgicas son una de las responsables de una parte relevante de la morbimortalidad en pacientes postquirúrgicos (131,132). Históricamente el tratamiento de elección era la reintervención, que también asocia una morbilidad significativa (132,133). Para intentar reducirla, el DPT guiado por radiología surgió como una alternativa segura y eficaz con un éxito de entre el 60 y el 84% (131,132,134,135). Sin embargo, dependiendo de la ubicación de la lesión, el DPT no siempre es factible, planteándose el uso de la ecoendoscopia como alternativa. Varias series de casos de drenajes guiados por ecoendoscopia mediante prótesis plásticas o metálicas totalmente cubiertas comunicaron porcentajes de éxito técnico y clínico del 96-100% y 80-100% (136-140). El primer estudio publicado sobre el drenaje de colecciones postquirúrgicas mediante PAL data del 2018; incluyó 47 pacientes alcanzando una proporción de éxito clínico del 89,3%, un éxito técnico del 89,3% y una proporción de eventos adversos del 6,4% (132). Otra serie retrospectiva multicéntrica internacional con 62 pacientes con colecciones postquirúrgicas torácicas, abdominales o pélvicas drenadas mediante PAL, comunicó un éxito técnico en el 96,8% y clínico en el 91,9%. La PAL fue retirada en todos los pacientes tras 46,8±26,2 días. Se observaron 8 eventos adversos, sólo 2 de ellos graves (141). Otra serie más heterogénea, con 75 pacientes (sólo 38 drenados

mediante PAL), incluyó colecciones postquirúrgicas precoces (diagnosticadas a <30 días tras la cirugía; 42 pacientes) o tardías (>30 días; 33 pacientes). No observaron diferencias significativas entre las colecciones precoces *vs* las tardías, en lo que respecta al éxito clínico (95% *vs* 93%, p=0,99) ni en los eventos adversos (21,4% *vs* 30,3%, p=0,43). Se ha planteado que el drenaje de este tipo de colecciones tras los primeros días después de la cirugía (6-14 días) es un procedimiento seguro y efectivo, a diferencia de las colecciones pancreáticas (142), si bien los datos disponibles son todavía escasos.

1.2.2. Eventos adversos asociados a las PAL

La estandarización de la definición de eventos adversos y de su gravedad es de gran importancia para comparar procedimientos. Diversas guías como el diccionario de la ASGE (143) o la clasificación AGREE (144) se emplean cada vez de manera más generalizada. Sin embargo, aun disponiendo de unas escalas de gravedad comunes, todavía existe una gran heterogeneidad en las diferentes series, principalmente por el uso de diferentes definiciones, pudiendo incluso variar entre trabajos analizando las mismas indicaciones. Por otra parte, al no existir tampoco seguimientos reglados y tratarse con frecuencia de pacientes con neoplasias en tratamiento paliativo, existe una gran variabilidad en las exploraciones realizadas para alcanzar un diagnóstico. Esto dificulta la comparación entre técnicas y entre centros.

1.2.2.1. Hemorragia

La hemorragia se puede definir como la presencia de signos y síntomas de sangrado digestivo (hematemesis, hematoquecia, melena, rectorragia manifiesta) con disminución de los valores de hemoglobina respecto a los valores previos a la colocación de la PAL. La ASGE establece el umbral de hemorragia clínicamente significativa ante un descenso de hemoglobina >2g/dL (143,145). Sin embargo, no existe un claro consenso en la

literatura; algunos autores no aportan una definición clara (45,143,144) mientras otros si emplean estas definiciones (42,145).

La hemorragia es el efecto adverso más temido, ya que es mayoritariamente agudo y puede resultar fatal. Los porcentajes de hemorragia publicados oscilan del 1-12% en CPE, 0-8,3% en EUS-CDS, 3,8% en EUS-GE y 1,3-8,3% en EUS-DVB (141). Resulta llamativo que el valor en los casos graves es muy superior en las CPE que en el resto de las indicaciones. Se ha hipotetizado que el colapso de la cavidad provocado por las PAL podría aumentar del riesgo de contacto entre vasos retroperitoneales de calibre significativo y las solapas intracavitarias del *stent* (154). El contacto prolongado y los movimientos da la prótesis podrían erosionar dichos vasos, causando el sangrado (46).

En la siguiente tabla se muestran los porcentajes de hemorragia secundaria a las PAL:

Estudio	Año	Diseño	Nº centros	n	Indicación	Hemorragia
Siddiqui *et al* (147)	2016	Retrospectivo, multicéntrico	4	82	CPE	6 (7,3%) (0 graves)
Sharaiha *et al* (148)	2016	Retrospectivo, multicéntrico	17	124	CPE	2 (1,6%) (2 graves)
Yang *et al* (149)	2018	Retrospectivo, multicéntrico	7	122	CPE	1 (1,6%) (1 grave)
Bang JY *et al* (150)	2019	Ensayo clínico aleatorizado, unicéntrico	1	60	CPE	3 (5%) (3 graves)
Fugazza *et al* (46)	2019	Retrospectivo, multicéntrico	15	333	CPE	22 (6,6%) (10% graves)
El Chafic *et al* (151)	2019	Retrospectivo, multicéntrico	6	67	EUS-CDS	1 (1,5%) (100% graves)
Jacques *et al* (152)	2020	Retrospectivo, multicéntrico	7	70	EUS-CDS	1 (1,4%) (0% graves)
Tyberg *et al* (153)	2016	Retrospectivo, multicéntrico	4	26	EUS-GE	1 (3,8%) (0% graves)
Perez-Miranda *et al* (87)	2017	Retrospectivo, multicéntrico	4	25	EUS-GE	2 (8%) (0% graves)
Teoh *et al* (127)	2019	Retrospectivo, multicéntrico	13	379	EUS-DVB	3 (0,8%) (0% graves)
Teoh *et al* (130)	2020	Ensayo clínico aleatorizado	7	40	EUS-DVB	0

Tabla 2: Principales estudios revisando la hemorragia como EA secundaria a la colocación de una PAL.

1.2.2.2. Perforación

La perforación secundaria a la colocación de una PAL se define como la presencia de síntomas y la documentación radiológica, endoscópica o quirúrgica de aire o contenido intraluminal dentro de la cavidad abdominal tras el procedimiento, fuera del tracto gastrointestinal. Se trata de un evento adverso poco frecuente, pero potencialmente grave. La definición de este evento adverso es muy heterogénea en la literatura. Algunos autores mencionan solo pneumoperitoneo o peritonitis (125,147), que son dos entidades clínicas incluidas en la definición previamente descrita; en otro sólo mencionan "perforación" (130).

En la mayoría de los casos esta complicación es identificada durante el mismo procedimiento, por lo que se puede realizar un tratamiento endoscópico, aunque en ocasiones es necesaria la cirugía (155,156).

En la siguiente tabla se muestran los porcentajes de perforación secundaria a las PAL en los estudios más relevantes publicados:

Estudio	Año	Diseño	Nº centros	n	Diana	Perforación
Siddiqui *et al* (147)	2016	Retrospectivo, multicéntrico	4	82	CPE	1 (1,2%) (100% graves)
Fugazza *et al* (46)	2019	Retrospectivo, multicéntrico	15	333	CPE	0
El Chafic *et al*(151)	2019	Retrospectivo, multicéntrico	6	67	EUS-CDS	1 (1,5%) (0% graves)
Tyberg *et al* (153)	2016	Retrospectivo, multicéntrico	4	26	EUS-GE	1 (3,9%) (0% graves)
Perez-Miranda *et al* (87)	2017	Retrospectivo, multicéntrico	4	25	EUS-GE	1 (4%) (100% graves)
Teoh *et al* (127)	2019	Retrospectivo, multicéntrico	13	379	EUS-DVB	2 (0,5%) (0% graves)
Teoh *et al* (130)	2020	Ensayo clínico aleatorizado	7	40	EUS-DVB	1 (2,5%) (0 % graves)

Tabla 3: Principales estudios revisando la perforación como EA secundaria a la colocación de una PAL.

Los valores descritos para este evento adverso son de 0-5% en CPE, 0-3,1% en EUS-CDS, 7-10% en EUS-GE y del 1,2% en EUS-DVB (145). Esta complicación es más frecuente en los procedimientos que implican una anastomosis visceral y/o ductal que en el manejo de colecciones. En las anastomosis viscerales, el acceso y la diana son estructuras móviles, mientras que en las colecciones, éstas suelen estar adheridas a estructuras adyacentes (157,158).

1.2.2.3. Disfunción / infección

La disfunción e infección se definen ante la presencia de síntomas y signos sistémicos (fiebre, elevación de PCR, leucocitosis), síntomas locales (dolor localizado, signos/síntomas específicos) y pruebas de imagen compatibles, en pacientes portadores de una PAL. Dependiendo de la indicación, en drenajes vesiculares incluye la presencia de patología litiásica aguda (colecistitis, pancreatitis, colangitis), en los drenajes biliares incluye datos de obstrucción biliar (ictericia, alteración del perfil hepático, colangitis) y en los drenajes de colecciones pancreáticas, el aumento de volumen de éstas (145).

La relevancia clínica de este EA no está clara, ya que a menudo no es grave, pudiendo manejarse con tratamiento antibiótico o endoscópico sencillo. En CPE su identificación en estudios retrospectivos es compleja, lo que condiciona la gran variabilidad en las publicaciones disponibles (145). En las CPE, puede requerir la realización de necrosectomía endoscópica, especialmente en centros donde se realiza a demanda y no de manera programada según un protocolo.

En la siguiente tabla se muestran los porcentajes de disfunción / infección secundaria a las PAL en los estudios más relevantes publicados:

Estudio	Año	Diseño	Nº centros	n	Indicación	Migración
Siddiqui *et al* (147)	2016	Retrospectivo, multicéntrico	4	82	CPE	5 (6,1%) (0% graves)
Sharaiha *et al* (148)	2016	Retrospectivo, multicéntrico	17	124	CPE	7 (5,6%) (0% graves)
Yang *et al* (149)	2018	Retrospectivo, multicentrico	7	122	CPE	4 (3,3%) (0% graves)
Bang JY *et al* (150)	2019	Ensayo clínico aleatorizado, unicéntrico	1	60	CPE	5 (8,3%) (0% graves)
Fugazza *et al* (46)	2019	Retrospectivo, multicéntrico	15	333	CPE	19 (24,1%) (11% graves)
El Chafic *et al* (151)	2019	Retrospectivo, multicéntrico	6	67	EUS-CDS	7 (10,4%) (0% graves)
Jacques *et al* (152)	2020	Retrospectivo, multicéntrico	7	70	EUS-CDS	7 (10%) (0% graves)
Perez-Miranda *et al* (87)	2017	Retrospectivo, multicéntrico	4	25	EUS-GE	1 (4%) (0% graves)
Teoh *et al* (127)	2019	Retrospectivo, multicéntrico	13	379	EUS-DVB	9 (2,3%) (0% graves)
Teoh *et al* (130)	2020	Ensayo clínico aleatorizado	7	40	EUS-DVB	2 (5%) (0% graves)

Tabla 4: Principales estudios revisando la infección como EA secundaria a la colocación de una PAL.

1.2.2.4. Migración

La migración se define ante la ausencia espontánea del *stent* confirmada mediante técnicas radiológicas u endoscópicas. Puede o no estar relacionada con procedimientos realizados a través de la prótesis. Esta migración puede cursar de forma asintomática o conllevar signos y síntomas (obstrucción intestinal, recidiva sintomática), requiriendo de nuevas intervenciones.

Aún diseñadas para limitar el riesgo de migración, éste sigue siendo no desdeñable, sobre todo en las CPE, donde pueden suponer un 20,9% de los casos (159). Por el contrario, en el uso de las PAL para la creación de anastomosis las migraciones son mucho menos frecuentes, a pesar de presentar tiempos de permanencia mayores. En EUS-GE existen varias series sin migraciones tras períodos de seguimiento largos (79,87,160). En el resto de indicaciones los valores descritos son de 2,7% para EUS-CDS y del 0-2,7% para EUS-DVB (130,145,161-164). Se cree que hay dos motivos principales para estas diferencias: la disminución progresiva de la cavidad diana en las CPE (159,165) y el hecho de que las intervenciones endoscópicas a través de la PAL, como sería el caso de las necrosectomías, sean mucho más habituales en CPE. En cualquier caso, no existen datos experimentales que confirmen estas hipótesis.

En la siguiente tabla se muestran los porcentajes de migración secundaria a las PAL en los estudios más relevantes publicados:

Estudio	Año	Diseño	Nº centros	n	Indicación	Migración
Sharaiha *et al* (148)	2016	Retrospectivo, multicéntrico	17	124	CPE	7 (5,6%) (0% graves)
Yang *et al* (149)	2018	Retrospectivo, multicentrico	7	122	CPE	7 (5,9%) (0% graves)
Bang JY *et al* (150)	2019	Ensayo clínico aleatorizado, unicéntrico	1	60	CPE	2 (3,3%) (0% graves)
Fugazza *et al* (46)	2019	Retrospectivo, multicéntrico	15	333	CPE	20 (25,3%) (0% graves)
Jacques *et al* (152)	2020	Retrospectivo, multicéntrico	7	70	EUS-CDS	1 (1,4%) (0% graves)
Teoh *et al* (127)	2019	Retrospectivo, multicéntrico	13	379	EUS-DVB	3 (0,8%) (0% graves)

Tabla 5: Principales estudios revisando la migración como EA secundaria a la colocación de una PAL.

1.2.3. Retirada de las PAL y sus complicaciones

Algunas indicaciones de la utilización de las prótesis de aposición luminal, como el drenaje de colecciones pancreáticas o el EDGE, suelen requerir la retirada del *stent* al final del tratamiento. En la mayoría de los casos la retirada es una técnica sencilla, pero una pequeña proporción puede llegar a ser técnicamente exigente, requiriendo técnicas de endoscopia avanzada. Si bien existen múltiples artículos evaluando los efectos adversos relacionados con las PAL, los datos sobre la seguridad de su retirada son muy escasos y principalmente retrospectivos. Un estudio retrospectivo unicéntrico con 104 retiradas documentó un porcentaje de eventos adversos del 8,7%, todos moderados o leves (166), Otro trabajo multicéntrico retrospectivo que involucró 93 retiradas observó un 5,4% de eventos adversos, con 2 casos graves, una hemorragia tratada mediante embolización y una perforación que requirió tratamiento quirúrgico(167).

El seguimiento tras la colocación de las PAL puede llegar a ser complejo. Aunque se implantan en unidades de endoscopia avanzada en centros de referencia, el seguimiento a menudo se realiza en sus centros de referencia. Esto implica dos situaciones complejas: en primer lugar, la extracción puede intentarse en instituciones donde no se dispone de procedimientos endoscópicos avanzados, que podrían ser necesarios. En segundo lugar, técnicas de seguimiento, como la necrosectomía o, lo que es más importante, la retirada del *stent*, pueden retrasarse, ya que con frecuencia faltan vías de comunicación convencionales entre los médicos responsables del paciente y los endoscopistas en los centros de referencia. Estas dos situaciones comportan tiempos de permanencia más prolongados, que se han asociado a un incremento de eventos adversos como la hemorragia tardía, el enterramiento o complicaciones en la retirada del *stent* (168,169).

Uno de los factores que puede provocar un procedimiento de retirada compleja es el enterramiento (169-171). Se desconoce la prevalencia real de este fenómeno. Algunos estudios retrospectivos informan de bajos porcentajes; Chandran *et al* identificó un 6%

entre 54 CPE (172). Dos estudios multicéntricos retrospectivos observaron valores de enterramiento llamativamente bajas, 0,9% (1/116 pacientes) en CPE con una mediana de tiempo de permanencia de 7 semanas y 1,1% (1/93) en una serie de casos que incluyó diferentes procedimientos con una mediana de permanencia de 8,3 semanas. (167,173).

JUSTIFICACIÓN DE LOS ESTUDIOS

2. JUSTIFICACIÓN DE LOS ESTUDIOS

El desarrollo de la ecoendoscopia y de las prótesis de aposición luminal ha permitido un incremento casi exponencial de los procedimientos endoscópicos terapéuticos. Lamentablemente, muchos de los trabajos disponibles son unicéntricos y la mayoría retrospectivos. Prácticamente todos se centran únicamente en el análisis del éxito técnico y clínico tras la colocación. Finalmente, gran parte de la literatura disponible versa sobre el drenaje de colecciones peripancreáticas pasando por alto el resto de las indicaciones, una de ellas el drenaje vesicular, sobre el que está centrado el primer artículo de la tesis. El uso de este tipo de prótesis para esta indicación está aumentando significativamente en aquellos pacientes no candidatos a cirugía, dado los buenos resultados en las series de casos publicadas y la relativa sencillez del procedimiento. Sin embargo y dado que tradicionalmente el tratamiento de la patología derivada de este órgano no se había podido realizar por endoscopia, la implantación de esta técnica puede llegar a ser dificultosa pese a los buenos resultados cosechados en los diferentes artículos publicados, muchos de ellos de carácter retrospectivo. Por este hecho consideramos relevante un estudio prospectivo con un seguimiento estandarizado y con un tamaño muestral suficiente, centrado en este caso en el drenaje de la vesícula biliar, para ofrecer una estimación lo más real posible de los eventos adversos asociados a estas prótesis en esta indicación.

Por otro lado, la retirada de las PAL es obligada en algunas indicaciones debido a la resolución de la patología por lo que han sido colocadas o recomendada en otras como el EUS-DVB. Apenas existen datos analizando pormenorizadamente esta retirada, sus posibles complicaciones y sus factores de riesgo. Dada la focalización de la ecoendoscopia terapéutica en centros de referencia, disponer de estos datos puede facilitar el manejo práctico de un grupo creciente de pacientes.

HIPÓTESIS

3. HIPÓTESIS

En base a los comentarios expuestos en la introducción y justificación de la presente tesis doctoral, las hipótesis de trabajo planteadas fueron las siguientes:

- El uso de las prótesis de aposición luminal para el drenaje de la vesícula biliar en pacientes no candidatos a tratamiento quirúrgico presenta altas tasas de éxito técnico y clínico.

- La permanencia de las PAL en el drenaje vesicular, tras un período de seguimiento largo, no aumenta el riesgo de eventos adversos tardíos.

- Las retiradas de las PAL son procedimientos seguros, que en su mayoría requieren técnicas endoscópicas básicas.

- Existen factores de riesgo que permiten identificar las retiradas potencialmente más complejas.

OBJETIVOS

4. OBJETIVOS

El objetivo principal de la tesis fue:

> Evaluar la seguridad de las prótesis de aposición luminal en el drenaje vesicular y describir los procedimientos de retirada de dichas prótesis en los diferentes tipos de indicaciones.

Los objetivos secundarios fueron:

1. Describir los efectos adversos observados, tanto inmediatos como tras un seguimiento durante un año, del drenaje vesicular guiado por ecoendoscopia con prótesis de aposición luminal en aquellos pacientes no candidatos a tratamiento quirúrgico.

2. Describir la proporción de retiradas complejas e intentar identificar los factores de riesgo asociados.

3. Identificar el porcentaje de *stents* enterrados y los factores de riesgo asociados a este fenómeno.

4. Describir los eventos adversos asociados a los procedimientos de retirada de las prótesis de aposición luminal.

COMPENDIO DE PUBLICACIONES

5. COMPENDIO DE PUBLICACIONES

Las hipótesis planteadas fueron evaluadas con la planificación de un estudio prospectivo observacional multicéntrico (RNPAL) que ha dado lugar a dos publicaciones principales:

5.1. PUBLICACIÓN 1

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EUS-guided gallbladder drainage with long-term lumen-apposing metal stent indwell: 1-year-results from a prospective nationwide observational study.

Sergio Bazaga, Francisco Javier García-Alonso, Jose Ramon Aparicio Tormo, Belen Martinez Moreno, Vicente Sanchiz, Joan B Gornals, Carme Loras, Álvaro Terán, Enrique Vazquez-Sequeiros, Rafael Pedraza Sanz, José Carlos Súbtil, Antonio Pérez-Millan, Francisco Uceda Porta, Juan J Vila, Carlos de la Serna-Higuera, Ignacio Couto-Worner, Carlos Guarner-Argente, and Manuel Perez-Miranda; RNPAL (Registro nacional de prótesis de aposición luminal [national lumen-apposing metal stent registry]) study group.

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ORIGINAL ARTICLE - ENDOSCOPY

Endoscopic ultrasound-guided gallbladder drainage with long-term lumen-apposing metal stent indwell: 1-year results from a prospective nationwide observational study

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Key words
endoscopic ultrasound, EUS-guided gallbladder drainage (EUS-GBD), lumen-apposing metal stent (LAMS), prospective nationwide observational study.

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Ethical approval: The registry was approved by the institutional review board at each participating institution and was registered in Clinicaltrials.gov (NCT04059926).
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Abstract

Background and Aim: This study aimed to determine safety and risk factors for adverse events (AEs) of endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) with long-term indwell of lumen-apposing metal stents (LAMS).
Methods: This study is a multicenter prospective observational study on consecutive high surgical-risk patients requiring gallbladder drainage who underwent EUS-GBD with LAMS over 12 months. Centralized telephone follow-up interviews were conducted every 3 months for 1 year. Patients were censored at LAMS removal, cholecystectomy, or death. AE-free survival was determined using log–rank tests. Cumulative risks were estimated using life-table analysis.
Results: Eighty-two patients were included (53.7% male, median [interquartile range] age of 84.6 [76.5–89.8] years, and 85.4% with acute cholecystitis). Technical success was achieved in 79 (96.3%), and clinical success in 73 (89%). No patient was lost to follow-up; 45 patients (54.9%) completed 1-year follow-up with *in situ* LAMS. Median (interquartile range) LAMS indwell time was 364 (47–367) days. Overall, 12 (14.6%) patients presented 14 AEs, including 5 (6.1%) recurrent biliary events (3 acute cholangitis, 1 mild acute pancreatitis, and 1 acute cholecystitis). Patients with pancreatobiliary malignancy had an increased risk of recurrent biliary events (33% *vs* 1.5%, $P = 0.001$). The overall 1-year cumulative risk of recurrent biliary events was 9.7% (4.1–21.8%). The 1-year risk of AEs and of severe AEs was 18.8% (11–31.2%) and 7.9% (3.3–18.2%), respectively. Pancreatobiliary malignancy was the single risk factor for recurrent biliary events; LAMS misdeployment was the strongest risk factor for AEs.
Conclusions: Long-term LAMS indwell does not increase the risk of delayed AEs following EUS-GBD.

Introduction

Laparoscopic cholecystectomy is the gold standard treatment of acute cholecystitis and related gallstone disease. Cholecystectomy effectively prevents biliary event recurrences.[1–3] However, surgery is frequently deferred or avoided in patients with severe comorbidities, poor performance status, or advanced age. Less invasive approaches are commonly favored by both patients and clinicians in these patient subsets.[4]

Percutaneous cholecystostomy (PC) is safe and effective in acute cholecystitis. However, PC does not reduce the risk of biliary event recurrence.[4] Transpapillary endoscopic drainage also shows relatively high clinical success rates but is limited by technical complexity.[5,6] Internal gallbladder drainage by endoscopic ultrasound (EUS-GBD) using lumen-apposing metal stents (LAMS) is increasingly being used. Compared with PC, EUS-GBD seems effective and safe and might additionally reduce the risk of recurrences.[7] Randomized trials comparing EUS-GBD with PC have found equivalent clinical success rates, with reduced post-procedure abdominal pain and fewer reinterventions.[8,9]

Endoscopic ultrasound-guided gallbladder drainage is currently thought to involve elective LAMS removal at a follow-up endoscopic procedure. Current European guidelines suggest LAMS removal with transluminal endoscopic gallstone clearance.[10] Concerns over the potential for LAMS-related adverse events (AEs) associated with long-term stent indwell led to the recommendation of LAMS removal, with possible exchange for double-pigtail plastic stents.[10] However, it is frequently declined, as EUS-GBD is largely performed in frail, elderly patients, where a repeat endoscopic procedure is often inconvenient. Anecdotal and retrospective evidence suggests the possibility of long-term LAMS indwell following EUS-GBD, without apparently increasing the incidence of AEs.[11,12]

Thus, we aimed to further determine the incidence and severity of long-term AEs following EUS-GBD with LAMS.

Methods

The national prospective registry of EUS-guided transmural LAMS (RNPAL) is a multicenter, prospective observational study of consecutive patients receiving an EUS-guided transmural LAMS during a 1-year period at 30 Spanish centers. All centers registered with the Spanish Endoscopy Society (SEED) EUS Interest Group were contacted. All but three (10%) agreed to participate. The registry was approved by the institutional review board at each participating institution and was registered in Clinicaltrials.gov (NCT04059926). All study participants provided written informed consent prior to inclusion.

Study population. All attempted LAMS placements for EUS-GBD performed between January 2019 and January 2020 were considered eligible for this analysis. An attempt was defined as at least the initial puncture of the gastrointestinal (GI) wall. Patients enrolled in randomized clinical trials and those declining to participate were excluded.

Endoscopic ultrasound-guided gallbladder drainage technique. All procedures were performed with an electrocautery-enhanced LAMS (EC-AXIOS System, Boston Scientific Corp, Massachusetts) by fully trained endoscopists with a therapeutic echoendoscope in an endoscopy suite with fluoroscopy equipment. The puncture location was chosen based on patient anatomy and endoscopist preference. Endoscopists were defined as experienced when they had > 25 previous LAMS placements[13]; centers were considered high volume when they performed > 30 procedures per year. Endoscopists used either the multi-device technique involving needle puncture and over-the-wire exchange or the freehand technique for LAMS placement, based on personal preference. With the freehand technique, the enhanced-cautery delivery system was directly inserted through the GI wall into the gallbladder using pure-cut settings. The LAMS was then immediately deployed. The second flange was deployed either under endoscopic monitoring or using the intra-channel stent release technique. The LAMS size was chosen at endoscopist discretion, as was the performance of additional maneuvers during the index EUS-GBD procedure. These included balloon dilation, placement of double-pigtail plastic stents, gallstone removal, or, in case of stent misdeployment (SMD), placement of fully covered metal stents through the LAMS to bridge the gap.

Outcomes. The primary endpoint was the incidence, cumulative risk, and severity of LAMS-related AEs across different practice settings. These included overall and specific AE risk analysis.

Secondary aims included technical and clinical success rates and LAMS-related and overall mortality rates.

Definitions.

- Recurrent biliary events were defined as any new episode of cholecystitis, cholangitis, or acute pancreatitis diagnosed according to current guidelines.[2,14,15]
- Gastrointestinal bleeding was defined as the presence of signs and symptoms of digestive bleeding with a drop in hemoglobin > 1 g/dL compared with baseline values.
- Perforation was defined as abdominal pain accompanied by newly developed inflammatory signs such as fever, elevated white blood count, or elevated C-reactive protein with radiological identification of free air or intraluminal content in the peritoneal cavity or endoscopic/surgical confirmation, thus also including bile leaks and newly developed intraabdominal abscesses.
- Stent migration was defined as the dislodgement of the stent regardless of the presence of symptoms; that is, asymptomatic migrations were also recorded.

Possible AEs outside these definitions were assessed on a one-by-one basis. All AEs were assessed by a commission of five researchers. Causal relationship with the LAMS was categorized as definitive, probable, possible, unlikely, or unrelated.[16] All events catalogued with at least a possible causal relationship were included. Severity was graded following the American Society for Gastrointestinal Endoscopy recommendations.[17]

Technical success was defined as the successful placement of LAMS into the gallbladder through the GI wall. Clinical success was defined as improvement in clinical symptoms and laboratory

tests without further endoscopic, radiological, or surgical procedures. Index admission, 1-month, and 1-year mortality rates were calculated.

Follow-up. Follow-up was performed according to local protocols, with no mandatory imaging or endoscopic procedures. In addition, a centralized follow-up via telephone calls employing standardized questionnaires at 14 days and at 3, 6, 9, and 12 months after stent placement or until LAMS removal, cholecystectomy, or death was performed. The questionnaires (Annex S1) were designed as a high-sensitivity/low-specificity screening tool. In case of an affirmative or missing response to at least one item, a report was requested from local investigators.

Data. Baseline demographic data (age, sex, active malignancy, including disease extension and primary site, anticoagulant and antiplatelet treatment, and procedure indication) were retrieved at inclusion. Data on previous biliary interventions were also retrieved.

Data were collected and managed using the Research Electronic Data Capture (REDCap) tool, a secure, web-based application created to support data capture.[18]

Statistical analysis. Categorical variables were reported as percentages. Normally distributed variables were reported with means and standard deviations, while non-normally distributed variables were reported as median and interquartile range. Pearson's χ^2 test and Fisher's exact test were used to analyze categorical variables. A P-value < 0.05 was considered as statistically significant. Kaplan–Meier curves were used to present overall times to AEs. Cumulative risks were estimated according to the life-table method. Multivariable Cox proportional hazards regression was used to assess possible risk factors of AEs and recurrent biliary events; results were reported using hazard ratios. Possible risk factors were chosen based on previously reported observational data or expert opinions.[10] Those with a significance level ≤ 0.10 were included in a multivariable model using bidirectional elimination. Statistical analysis was performed using the Stata package (StataCorp, 2013, College Station, Texas).

Results

A total of 438 EUS-guided transmural LAMS placement attempts were performed between January 2019 and January 2020. Twelve (2.7%) patients were not eligible to participate because of their inability to provide consent and temporary unavailability of the local investigators or patients undergoing follow-up outside the network of participant centers; 15 (3.4%) declined to participate, and 4 (0.9%) were enrolled in clinical trials. Thus, we included 407 LAMS attempts, mainly pancreatic fluid collection drainages (35.4%) and EUS-guided enteroanastomoses (25.1%). Eighty-two (20.1%) procedures were EUS-GBDs, performed in 12 centers by 14 endoscopists.

Median age was 84.6 years (interquartile range: 76.5–89.8), and 53.7% were male (Table 1). Experienced endoscopists performed most procedures (96.3%), mainly in high-volume centers (87.8%). The most frequent indication for EUS-GBD was acute cholecystitis (85.4%). Nineteen (23.2%) cases had malignant disease, predominantly (n = 12, 14.6%) pancreatobiliary lesions. In two of these (2.5%), the main indication for EUS-GBD was biliary drainage. Among the remaining 10 patients with pancreatobiliary malignancy, 2 did not have obstructive jaundice and 8 had both obstructive jaundice and acute cholecystitis: 4 underwent same-session transpapillary stenting via endoscopic retrograde cholangiopancreatography (ERCP) during EUS-GBD and 4 underwent EUS-GBD to treat both cholecystitis and malignant biliary obstruction (3 patients with occluded prior transpapillary stents and 1 patient in whom same-session ERCP stenting failed). Most (90.2%) EUS-GBD were intended for permanent LAMS indwell.

Table 1 Patients' baseline conditions

	Gallbladder drainage (n = 82)
Age, median (IQR)	84.6 (76.5–89.8)
Male sex, n (%)	44 (53.7%)
Procedure indication, n (%)	
Acute cholecystitis	70 (85.4%)
Mild	–5 (6.1%)
Moderate	–52 (63.4%)
Severe	–13 (15.9%)
Symptomatic cholelithiasis	10 (12.2%)
Access to biliary tree in post-surgical anatomy	2 (2.5%)
Malignant disease, n (%)	
Localized	4 (4.9%)
Metastatic	15 (18.3%)
Pancreatobiliary malignant disease, n (%)	12 (14.6%)
Antiplatelet treatment, n (%)	18 (22%)
Anticoagulant treatment, n (%)	16 (19.5%)

IQR, interquartile range.

Procedure technique. Most endoscopists chose the free-hand technique (91.5%). Transduodenal and transgastric access was chosen in 56.1% and 43.9% of cases, respectively. The 10 × 10-mm LAMS was employed in 52 (63.4%) cases, and the 15 × 10-mm LAMS in 23 (28.1%). A detailed description is shown in Table 2. Overall, 96.3% were technically successful, with three technical failures. Two of these involved distal flange misdeployment; in one case, the LAMS did not reach the gallbladder (Type I SMD), and in another case, the gallbladder wall was punctured (Type II SMD).[19] The patient with Type I SMD recovered after over-the-scope clip (OTSC Clip, Ovesco Endoscopy AG) closure of the gastric access point and then underwent elective cholecystectomy. The patient with Type II SMD underwent urgent cholecystectomy. Another misdeployment occurred in a 62-year-old man where the distal flange was inadvertently deployed into the cystic duct (target misidentification, or Type IV SMD). Two additional SMD instances were successfully bridged using the LAMS-in-LAMS rescue technique and, therefore, not considered technical failures.

Short-term outcomes. Clinical success was reached in 73 (89%) patients. The nine clinical failures included four deaths due to ongoing biliary sepsis, four patients undergoing

Table 2 Procedure description

	Gallbladder drainage (*n* = 82)
Technical success, *n* (%)	79 (96.3%)
Malposition, *n* (%)	4 (4.9%)
Point of access, *n* (%)	
Transgastric	36 (43.9%)
Transduodenal	46 (56.1%)
Freehand technique, *n* (%)	75 (91.5%)
Stent size (mm), *n* (%)	
15 × 10	23 (28.1%)
10 × 10	52 (63.4%)
8 × 8	7 (8.5%)
Balloon dilation after stent placement, *n* (%)	44 (53.7%)
Coexial double-pigtail plastic stent, *n* (%)	45 (54.9%)
Endoscopic removal of gallstones, *n* (%)	7 (8.5%)

cholecystectomy, and one patient requiring an ERCP. Another four patients died during the index admission, two due to disease progression of baseline malignancy, one nosocomial respiratory infection, and one uninvestigated acute respiratory distress, thus resulting in eight deaths (9.8%) during the index admission.

Follow-up. Follow-up was available in all patients, with a median of 364 days (47–367). Forty-five (54.9%) patients completed a 1-year follow-up with the LAMS *in situ*. In 10 (12.2%) patients, the stent was removed after a median indwell time of 21 days (9–87): in 4 due to AEs, in another 4 patients opting for elective cholecystectomy after initially declining surgery, and in 2 of the previously described technical failures. Among the 27 (32.9%) patients who died with the LAMS *in situ*, the median survival was 47 days (12–227). Nineteen (23.2%) patients died after hospital discharge: 10 (12.2%) due to baseline malignancy, 3 (3.7%) due to chronic heart disease, 2 (2.4%) due to AEs, and 4 (4.9%) due to other causes. The 1-month and 1-year mortality rates were 13.4% and 32.9%, respectively.

Adverse events. Twelve (14.6%) patients presented a total of 14 AEs: 6 (7.3%) were mild, 3 (3.7%) moderate, 3 (3.7%) severe, and 2 (2.4%) fatal (Table 3). Four events occurred within 2 weeks

Table 3 Type and severity of adverse events

Overall	12 (14.6%) patients (14 events)
Mild/moderate/severe/fatal	6/3/3/2
Recurrent biliary events	5 (6.1%)
Mild/moderate/severe/fatal	1/2/1/1
Perforation	3 (3.7%)
Mild/moderate/severe/fatal	1/0/2/0
Bleeding	0
Mild/moderate/severe/fatal	
Migration	1 (1.2%)
Asymptomatic/mild/moderate/severe/fatal	0/1/0/0/0
Other	5 (6.1%)
Mild/moderate/severe/fatal	3/1/0/1

of EUS-GBD. Recurrent biliary events were the most frequent AEs, presenting in five (6.1%) patients. The 1-year cumulative risk of AEs and of severe/fatal AEs was 18.8% (95% confidence interval: 11–31.2%) and 7.9% (95% confidence interval: 3.3–18.2%), respectively, as shown in Table 4 and Figure 1.

Three (3.7%) perforations occurred: in two of the technical failures and in another patient with intraabdominal abscess diagnosed 9 days after EUS-GBD. The cause of the abscess remains unclear; cholecystectomy was performed showing the LAMS adequately placed, with no obvious gallbladder perforation. We identified one asymptomatic migration (1.2%) in a cholecystogastrostomy 88 days after LAMS placement. No hemorrhages were noted intraprocedurally or during follow-up. Five patients presented other AEs: acute abdominal pain suggesting a biliary colic in three (mild severity AEs). None required a hospital admission. A patient scheduled for cholecystectomy developed a moderately severe acute cholecystitis 5 days after LAMS removal. Finally, a 74-year-old man with pancreatic cancer who presented with neutropenic fever 38 days after EUS-GBD experienced a swift fatal outcome precluding a complete diagnostic work-up.

Recurrent biliary events. As previously stated, five (6.1%) recurrent pancreatobiliary events (three acute cholangitis, one acute cholecystitis, and one mild biliary acute pancreatitis) were identified after a median of 7 months (range 1–12) from EUS-GBD. A moderately severe acute cholecystitis was due to LAMS obstruction with stones and debris, requiring endoscopic treatment. A severe cholangitis also required endoscopic treatment. The mild acute pancreatitis and a moderately severe acute cholangitis in an 89-year-old woman were managed conservatively. A fatal acute cholangitis occurred in an 89-year-old man with a metastatic pancreatic adenocarcinoma 7 months after stent placement. The 3-month, 6-month, and 1-year cumulative risks of recurrent biliary events were 1.6% (0.2–10.7%), 3.4% (0.9–12.8%), and 9.7% (4.1–21.8%), respectively (Fig. 2).

Risk factors of adverse events and recurrent biliary events. An exploratory analysis is presented in Table 5. The recurrent biliary events analysis included patients with at least 1 day with the LAMS *in situ*. Thus, two technical failures were excluded. Four recurrent biliary events occurred in patients with pancreatobiliary malignancy (4/12). Two events developed in patients without any other biliary drainage and another two in patients with non-functioning transpapillary stents. The only AE among the 68 patients without pancreatobiliary malignancy (1.5%) was one episode of acute pancreatitis. The presence of pancreatobiliary malignancy was the only risk factor for recurrent

Table 4 Cumulative risks after endoscopic ultrasound-guided gallbladder drainage

	Adverse event	Severe/fatal adverse event	Recurrent biliary event
14 days	5% (1.9–12.7%)	2.5% (0.6–9.7%)	0
3 months	9.4% (4.6–18.9%)	4.1% (1.3–12.1%)	1.6% (0.2–10.7%)
6 months	11.1% (5.7–21.1%)	5.8% (2.2–14.9%)	3.4% (0.9–12.8%)
12 months	18.8% (11–31.2%)	7.9% (3.3–18.2%)	9.7% (4.1–21.8%)

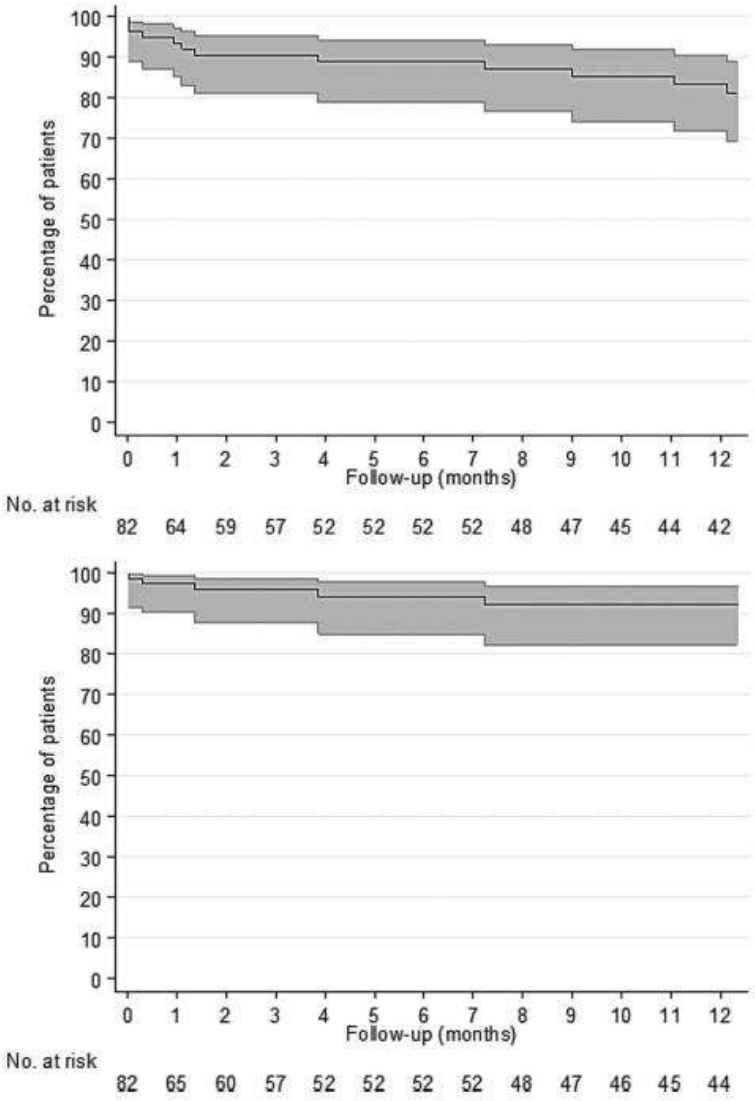

Figure 1 Stent-related adverse event-free survival: (a) overall stent-related adverse event-free survival with 95% confidence intervals and (b) severe/fatal stent-related adverse event-free survival with 95% confidence intervals. Survival curves were built using the Kaplan–Meier method.

biliary events, while the initial SMD, despite being salvaged for technical success, was the strongest risk factor for AEs.

Stone clearance (14.3% *vs* 14.7%, $P = 0.73$), balloon dilation (11.4% *vs* 18.4%, $P = 0.28$), and duodenal access (15.2 *vs* 13.9%, $P = 0.56$) did not reduce the risk of AEs. Coaxial double-pigtail plastic stents significantly reduced the risk of AEs (6.7% *vs* 24.3%, $P = 0.03$), although this did not achieve statistical significance in the multivariable analysis.

Discussion

The current study is the largest prospective observational study on EUS-GBD using LAMS. In keeping with previous reports,[8,20] high technical (96.3%) and clinical success (89%) rates were found for EUS-GBD. The 1-year cumulative risks of AEs and recurrent biliary events were 18.8% (11–31.2%) and 9.7% (4.1–21.8%), respectively. Previous prospective studies with smaller sample sizes reported slightly higher rates, 25.6%[8] and

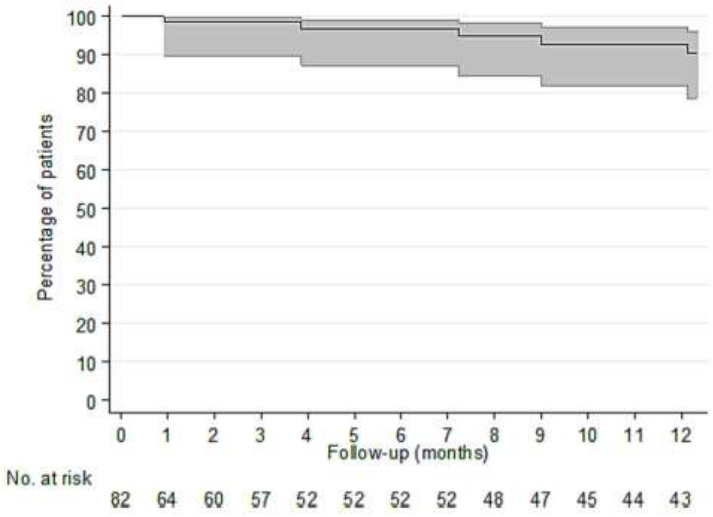

Figure 2 Recurrent biliary event-free survival with 95% confidence intervals. Survival curves were built using the Kaplan–Meier method.

Table 5 Univariable and multivariable analysis of risk factors of adverse events and recurrent biliary events

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*-value	Hazard ratio	*P*-value
Overall adverse events				
Stent misdeployment	18.2 (3.7–90.8)	< 0.001	29.58 (5.9–168.69)	< 0.001
Pancreatobiliary malignancy	4.64 (1.13–18.95)	0.03	6.95 (1.54–31.35)	0.01
Coaxial double-pigtail plastic stent	0.31 (0.08–1.19)	0.09	—	—
Malignant disease	2.97 (0.73–12.1)	0.13	—	—
Experienced operator	0.23 (0.03–1.91)	0.17	—	—
Antiplatelet treatment	0.36 (0.08–1.7)	0.20	—	—
Recurrent biliary events				
Pancreatobiliary malignancy	23.47 (3.6–153.13)	0.001	23.47 (3.6–153.13)	0.001
Malignant disease	6.67 (1.06–41.98)	0.02	—	—
Stent misdeployment	14.74 (1.52–143.03)	0.02	—	—
Experienced operator	0.05 (0.00–0.62)	0.02	—	—
High-volume centers	0.18 (0.03–1.12)	0.07	—	—
Male sex	0.22 (0.02–1.93)	0.17	—	—

Variables included in univariable analysis (results shown if $P \leq 0.20$): age, sex, baseline malignant disease (present *vs* absent), baseline pancreatobiliary malignant disease (present *vs* absent), point of access (gastric cavity *vs* duodenum), stent dimensions, deployment technique (freehand *vs* over-the-wire), coaxial double-pigtail plastic stents, balloon dilation, endoscopic gallstone removal, operator experience, high-volume center, treatment with proton pump inhibitors, antiplatelet agents, or anticoagulants. The recurrent biliary events analysis includes only the 80 patients with ≥ 1 day with the LAMS *in situ*.

30%[21]; available retrospective studies reported AE rates ranging between 10.2% and 17.9%.[6,22–24]

Recurrent biliary events are the most frequent group of AEs following EUS-GBD. We noted a 9.7% risk at 1 year following EUS-GBD, very similar to the 10.3% reported in the DRAC 1 trial.[8] Retrospective case series have reported lower rates of recurrent acute cholecystitis (2.4–7%)[6,8,23,25] and recurrent biliary events (0–10.3%).[6,8,9,12] Compared with other non-surgical alternatives to cholecystectomy, PC does not reduce the risk of recurrent biliary events,[26–28] whereas transpapillary endoscopic drainage reduces reintervention rates to 9–11%,[20,29] especially if the drain is kept *in situ*.[30] In contrast to EUS-GBD, which has consistently shown technical success rates over 95%,[6,8,9,22,23,31] transpapillary endoscopic drainage by ERCP is not technically feasible in 12–21% of cases.[6,20,30] A recent network meta-analysis confirmed these differences in terms of technical and clinical success, need

for reintervention, and recurrent cholecystitis.[32] Hence, EUS-GBD might be preferable, as its excellent short-term outcomes are comparable with those of PC and its long-term outcomes are in the range of those reported for transpapillary endoscopic drainage.

Pancreatobiliary malignancy was the strongest risk factor for recurrent biliary events; one third of patients with pancreatobiliary malignancy developed recurrent biliary events. This rate is even higher than the rate of recurrent biliary events reported after EUS-guided choledochoduodenostomy or hepatogastrostomy.[33,34] Previous reports on EUS-GBD do not clarify the relationship between underlying pancreatobiliary malignancy and the risk or long-term AEs[6,31] or recurrent biliary events.[22] Patients with underlying malignancy typically have previous endoscopic drainage procedures, involving the presence of indwelling transpapillary drains or stents, which may predispose to recurrent biliary events. Regarding access site, no study to date has shown any superiority of transduodenal access over transgastric access.[6,23,35] We consider a stable echoendoscope position and an optimal apposition should perhaps be the guiding parameters to choose the access site.

Our findings may help guide long-term management of patients after EUS-GBD. Delayed bleeding associated with long-term LAMS indwell is still a lingering concern due to previous experience in pancreatic fluid collections,[36,37] leading to the recommendation of limiting indwell time to < 4 weeks.[38] Extrapolation of these well-known risks in pancreatic fluid collections has shaped current recommendations for EUS-GBD with LAMS.[10] However, available retrospective case series with long indwell times and our current prospective data have not identified any delayed bleeds.[6,12,23,39] Leaving the stent *in situ* did not affect the risk of recurrence. In the DRAC 1 trial, cholecystoscopy and LAMS removal was scheduled at 1 month after EUS-GBD, even if only 70% of included patients complied with this follow-up procedure; the 1-year AE rate was 25.6% (10/39), including 4 (10.3%) biliary events.[16] Another prospective study including 30 subjects with 19 stent removals found a 10% (3/30) acute cholecystitis recurrence rate after removal,[21] which suggests that the drawbacks of LAMS removal might outweigh the benefits of permanent indwell. Retrospective studies with scheduled LAMS removal are not available, reflecting the common clinical scenario where a second procedure is often declined. Studies with 25–50% of patients undergoing LAMS removal did not observe differences in long-term outcomes[11,35]; yet, these studies were not adequately powered to detect such differences. Even if scheduled LAMS removal after EUS-GBD has a rationale, the need for a subsequent invasive procedure and the lack of evidence for any improvement in short-term or long-term outcomes question this approach. Our data support leaving the LAMS *in situ* after EUS-GBD for at least 1 year after placement.

Our study has several strengths. It is the largest prospective EUS-GBD study published to date. A pre-established definition of all outcomes was used, and a complementary centralized follow-up was undertaken. The study design allowed estimating cumulative risks; crude rates in conditions with a high proportion of censored subjects underestimate true risks. On the other hand, it presents some drawbacks. Follow-up was limited to 1 year, so the consequences of leaving the LAMS *in situ* beyond this timeframe remain unknown. A relevant number of patients presented with malignant disease undergoing palliative treatment; thus, some events were not thoroughly investigated. The small number of recurrent biliary events and the lack of a specific comorbidity assessment hinder the regression analysis. Finally, technique variations in the procedure, were performed at the discretion of the endoscopist.

In summary, EUS-GBD was safe and effective in a large prospective and multicenter cohort. Moreover, no delayed bleeding episodes were observed despite a long-term stent indwell.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Annex S1 Checklist.

Table S1. Cumulative risks after endoscopic ultrasound guided gallbladder drainage.

5.2. PUBLICACIÓN 2

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Endoscopic removal of lumen-apposing metal stents - risk factors for stent embedment, complex removals, and adverse events: analysis from a multicenter prospective case series.

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Endoscopic removal of lumen-apposing metal stents – risk factors for stent embedment, complex removals, and adverse events: analysis from a multicenter prospective case series

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ABSTRACT

Background Removing lumen-apposing metal stents (LAMSs) may be difficult and even harmful, but these features have seldom been analyzed. We aimed to generate a comprehensive assessment of the feasibility and safety of LAMS retrieval procedures.

Methods A prospective multicenter case series including all technically successfully deployed LAMSs between January 2019 and January 2020 that underwent endoscopic stent removal. All retrieval-related data were prospectively recorded using standardized telephone questionnaires as part of centralized follow-up that ended after stent removal

had been performed. Multivariable logistic regression models assessed the potential risk factors for complex removal.
Results For the 407 LAMSs included, removal was attempted in 158 (38.8%) after an indwell time of 46.5 days (interquartile range [IQR] 31–70). The median (IQR) removal time was 2 (1–4) minutes. Removal was labelled as complex in 13 procedures (8.2%), although advanced endoscopic maneuvers were required in only two (1.3%). Complex removal risk factors were stent embedment (relative risk [RR] 5.84, 95%CI 2.14–15.89; $P=0.001$), over-the-wire deployment (RR 4.66, 95%CI 1.60–13.56; $P=0.01$), and longer indwell times (RR 1.14, 95%CI 1.03–1.27; $P=0.01$). Partial and complete embedment were observed in 14 (8.9%) and five cases (3.2%), respectively. The embedment rate during the first 6 weeks was 3.1% (2/65), reaching 15.9% (10/63) during the following 6 weeks ($P=0.02$). The adverse event rate was 5.1%, including seven gastrointestinal bleeds (5 mild, 2 moderate).
Conclusions LAMS removal is a safe procedure, mostly requiring basic endoscopic techniques attainable in conventional endoscopy rooms. Referral to advanced endoscopy units should be considered for stents with known embedment or long indwell times, which may require more technically demanding procedures.

Introduction

Lumen-apposing metal stents (LAMSs) are being increasingly used to treat pancreatic fluid collections (PFCs) [1–3]. LAMSs are also temporarily deployed to drain other intra-abdominal fluid collections [4] or to create temporary access to the duodenum and the biliary tree after Roux-en-Y gastric bypass surgery [5]. All these indications, along with others, usually require the removal of the stent at the end of the treatment.

While there are many published papers assessing LAMS-related adverse events (AEs) [6–9], data regarding the safety of their removal are scarce and mainly retrospective. A retrospective single center study including 104 stent retrievals reported an 8.7% AE rate, all of which were moderate or mild events [10]; another retrospective multicenter study involving 93 stent retrievals reported a 5.4% retrieval-related AE rate, with two severe AEs (SAEs): a hemorrhage treated by embolization and a perforation that required surgical treatment [11].

Follow-up after LAMS placement is not always easy. They are usually deployed in advanced endoscopy units but follow-up is often performed at the referring institutions. This entails two complex situations. First, removal might be attempted at institutions where advanced endoscopic procedures, which might be required, are not available. Second, follow-up techniques, such as necrosectomy, secondary procedures or, more importantly, stent removal itself might be delayed, as conventional care pathways between attending physicians and out-of-center endoscopists are frequently lacking. In this situation severe delayed bleeding, embedment, or other complications may occur, as these have been associated with longer indwell times [12]. These situations might also complicate removal of the stent.

We therefore aimed specifically to assess the safety and feasibility of LAMS removal. Additionally, we evaluated the risk factors for complex removal, which could be of use in identifying those patients who should be referred to advanced endoscopy units.

Methods

The multicenter, nationwide prospective registry (RNPAL) was established in 2019 and aimed to include all patients who received a transmural LAMS in the 30 participating centers. All outcomes and definitions included in this manuscript were aims stated in the project's original design. The study was approved by the institutional review board of all participating centers and reported following the STROBE Initiative Statement (**Table 1s**, see online-only Supplementary material). All participants signed the informed consent form prior to inclusion in the study.

Study population

The RNPAL registry considered all attempted LAMS deployments between January 2019 and January 2020 to be eligible. Patients participating in randomized clinical trials and those who declined to participate were excluded. All LAMSs that were technically successfully placed that were later endoscopically removed, regardless of the clinical outcome, were included in this subanalysis.

Endoscopic procedures

All stent retrievals were performed under endoscopist- or anesthesiologist-directed sedation with propofol (with or without midazolam), as per each center's protocol. All procedures were performed with conventional or therapeutic gastroscopes. Most LAMSs were located under direct view. Fluoroscopy was employed to locate completely embedded stents. Removal procedures included:

a) proximal flange traction using forceps to pull the luminal flange of the stent
b) flange traction using a snare to pull the luminal flange of the stent
c) distal flange traction using forceps to pull from the distal flange of the stent
d) other methods, all of which were thoroughly described in the case report form.

Definitions and outcomes

Stent removal was defined as the complete extraction of the stent. Stent embedment was endoscopically assessed at stent removal. It was categorized as: "absent" if the whole proximal flange was free; "partial" embedment if the proximal flange was at least partially covered but the metal mesh could be identified; and "total" if the mesh could not be seen with conventional endoscopy (buried stents).

The time needed to remove the stent was prospectively recorded. It was measured from the insertion of the first instrument employed through the endoscope working channel until the LAMS was outside the patient's body. Endoscopists also subjectively rated the task difficulty using a 5-point Likert scale (very easy, easy, intermediate, hard, and very hard). Complex LAMS removals were defined as those procedures specifically described by the endoscopist as "hard" or "very hard," and/or those where removal times were above the 90th percentile of the whole cohort.

The presence of adhered tissue, the integrity of the silicone covering the metal mesh, and the preservation of the stent morphology were assessed after stent removal as dichotomous variables. AEs identified during removal and their severity were defined and graded according to the ASGE recommendations [13].

Study data and follow-up

The study design included scheduled centralized telephone contacts at 14 days, and then 3, 6, 9, and 12 months after stent deployment. Once the stent had been retrieved, centralized follow-up was terminated at the next scheduled contact, unless this contact took place within 2 weeks after stent removal, in which case it was extended until the next scheduled contact. Data were collected and managed using a Research Electronic Data Capture tool (REDCap), a secure web-based application created to support data capture for research studies, providing semiautomatic data quality control [14]. Patient-related and procedural data were included by the local investigators at stent deployment and retrieval.

Statistical analysis

Categorical variables were reported as percentages. Normally distributed continuous variables were reported as the mean and SD, while non-normally distributed variables were reported as the median and interquartile range (IQR); the range was also used in some cases. We used an uncorrected Pearson's chi-squared test or Fisher's exact test, as appropriate, to analyze categorical variables and Student's *t* test or Wilcoxon's rank tests to analyze continuous variables, as appropriate.

To identify the risk factors for complex removals, we used a multivariable logistic regression model. Potential factors for the model were chosen according to the results of previous studies assessing LAMS removal (embedment) [15, 16] and other gastrointestinal stent removals (overall stent indwell time [weeks] and LAMS diameter) [17, 18]. Other variables were included based on experts' opinion (location of transmural access, indication [each one employed as a dichotomous variable], deployment technique [freehand vs. over-the-wire], balloon dilation at deployment, deployment of a double-pigtail plastic stent, proton pump inhibitor or antiplatelet treatment during stent indwell time, and bleeding during follow-up).

Embedment was directly included in the multivariable model. Variables based on experts' opinion and those extrapolated from other procedures underwent a prescreening using univariable logistic regression models. Those reaching a significance threshold of $P<0.20$ in univariable analysis were then evaluated in multivariable logistic regression models. In an iterative process, covariates were removed from the model if they were nonsignificant (establishing a significance threshold of $P<0.10$) and not a confounder. Confounders were maintained if their removal caused a greater than 20 % change in any remaining parameter estimate compared with the full model. The relative risks (RRs) with 95 %CIs were reported. Analyses were performed with Stata (StataCorp. 2013; College Station, Texas, USA).

Results

A total of 407 LAMS were included in the RNPAL study. The present study assessed all endoscopic removal attempts after a technically successful stent placement, which accounted for 158 cases (38.8 %). One technical failure was included, an endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) where the distal flange placed in the cystic duct was removed 10 days after stent placement. Over 80 % of the 249 non-removed stents were EUS-GBDs (31.3 %), EUS-guided gastroenterostomies (EUS-GEs; 34.1 %), and choledochoduodenostomies (EUS-CDSs; 18.9 %), which were placed with the aim of being permanently indwelling.

The outcome of all included stents is shown in **Fig. 1s**. Stents deployed to manage intra-abdominal collections were removed once resolution of the collection had been confirmed. Among the 17 EUS-GEs, nine removals were performed after the patient had undergone endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography (ERCP), six cases presented with benign gastric outlet obstruction, and one was a temporary EUS-GE in a localized periampullary tumor; a 15×10-mm stent replacement for a 20×10-mm stent in a patient with metastatic malignancy was also included.

A detailed description of the patients and their stent insertion procedures is presented in ▶**Table 1**. Most cases were PFCs, including 76 walled-off necroses (WONs; 48.1 %) and 39 pseudocysts (24.7 %). Two patients (1.3 %) had received a coaxial LAMS placed to salvage a proximal flange misplacement: one in a 64-year-old woman undergoing an enteroanastomosis to gain access to the biliary tree in a gastric bypass required a second 15×10-mm LAMS and a 20×100-mm self-expandable metal stent (WallFlex; Boston Scientific); the other an 83-year-old man undergoing an EUS-CDS received a second 8×8-mm LAMS. A double-pigtail plastic stent was placed within the LAMS of 68 patients; at stent removal, 47 (69.1 %) were still in place, eight (11.8 %) had been previously removed, and 13 (19.1 %) had migrated prior to the removal.

▶ **Table1** Baseline characteristics of the 158 patients who had a successfully placed lumen-apposing metal stent later removed endoscopically.

	Pancreatic fluid collection (n=115)	Other procedures (n=43)
Age, median (IQR), years	61.1 (50.6–69.5)	64.5 (52–74)
Sex, male, n (%)	84 (73)	21 (48.8)
Type of procedure, n (%)		
• Walled-off necrosis	76 (66.1)	
• Pseudocyst	39 (33.9)	
• Other fluid collections		19 (44.2)
• Enteroanastomoses		17 (39.5)
• EUS-guided gallbladder drainage		4 (9.3)
• EUS-guided choledo-choduodenostomy		2 (4.7)
• Postsurgical anastomotic dehiscence		1 (2.3)
Puncture site, n (%)		
• Esophagus	1 (0.9)	2 (4.7)
• Gastric fundus	7 (6.1)	2 (4.7)
• Gastric body	96 (83.5)	22 (51.2)
• Gastric antrum	5 (4.3)	6 (14.0)
• First or second part of duodenum	6 (5.2)	3 (7.0)
• Third part of duodenum or jejunum		6 (14.0)
• Colon		2 (4.7)
Stent diameter and length, n (%), mm		
• 20×10	9 (7.8)	9 (20.9)
• 15×10	81 (70.4)	19 (44.2)
• 10×10	25 (21.7)	13 (30.2)
• 8×8		1 (2.3)
• 6×8		1(2.3)
Insertion technique, n (%)		
• Freehand	101 (87.8)	38 (88.4)
• Over the wire	14 (12.2)	5 (11.6)
Balloon dilation after deployment, n (%)	29 (25.2)	23 (53.5)
Coaxial double-pigtail - plastic stent, n (%)	55 (47.8)	13 (30.2)

IQR, interquartile range.

▶ **Table2** Details of the stent removal procedures.

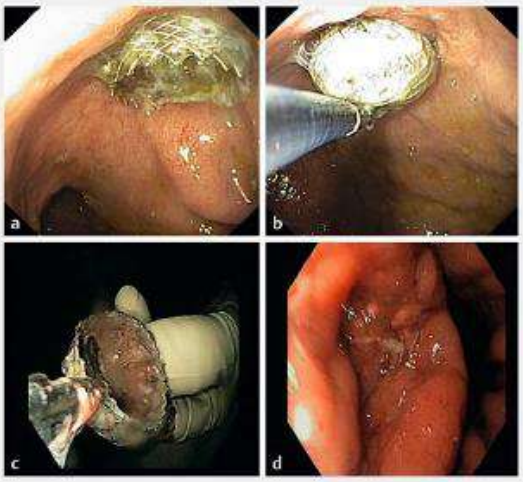
	Pancreatic fluid collection (n=115)	Other procedures (n=43)
Stent indwell time, median (IQR), days	46 (31–65)	52 (28–115)
Removal technique, n (%)		
• Proximal end forceps traction	97 (84.3)	38 (88.4)
• Proximal end snare traction	10 (8.7)	4 (9.3)
• Distal end forceps traction	6 (5.2)	1 (2.3)
• Other	2 (1.7)	
Time taken for removal, median (IQR), minutes	2 (1–5)	1 (1–2)
Endoscopist's subjective assessment, n (%)		
• Very easy	44 (38.3)	23 (53.5)
• Easy	58 (50.4)	15 (34.9)
• Intermediate	8 (7.0)	4 (9.3)
• Difficult	3 (2.6)	1 (2.3)
• Very difficult	2 (1.7)	
Stent embedment, n (%)		
• Absent	99 (86.1)	40 (93.0)
• Partial	11 (9.6)	3 (7.0)
• Complete	5 (4.3)	
Presence of adhered tissue after removal, n (%)	19 (16.5)	6 (14.0)
Intact silicone stent covering, n (%)	105 (91.3)	40 (93.0)

IQR, interquartile range.

Removal description

All the 158 stents were successfully removed. This was possible at the first attempt in 156 (98.7%), while two required a second procedure. Stents were removed after a median indwell time of 46.5 days (IQR 31–70, range 7–303). A detailed description of the retrievals is presented in ▶ **Table 2**.

Most LAMS removals were straightforward procedures (▶ **Fig. 1**), with a median (IQR) removal time of 2 (1–4) minutes. The vast majority (149; 94.3%) were removed by pulling from the proximal flange using conventional foreign body forceps (84.8%) or polypectomy snares (9.5%). Traction from the distal flange was used as a rescue technique for partially embedded stents in 2/14 cases (14.3%), while the remaining stents could be retrieved with proximal flange traction.



▶ **Fig. 1** Step-by-step images of a lumen-apposing metal stent (LAMS) removal procedure showing: **a** the proximal flange of a correctly placed transmural stent; **b** traction being applied to the proximal flange with a forceps to remove the LAMS; **c** the integrity of the stent coating; **d** inspection of the fistula after stent removal.

Fluoroscopy was needed to locate all completely embedded (buried) LAMSs (five cases), three of which could be retrieved with proximal flange traction. Advanced endoscopic maneuvers were needed in two cases, with the indication for the LAMS being drainage of an infected pseudocyst in both cases, and the same removal technique being employed, as follows. The LAMS was located by endosonographic and fluoroscopic vision, and a 19G needle (Expect; Boston Scientific) puncture directed to the stent lumen was performed, followed by the advancement of a 0.035-inch guidewire (Jagwire; Boston Scientific) through the LAMS under fluoroscopic guidance. Serial dilation of the puncture tract was then performed using a 6-Fr cystotome (Cystotome; Endo-Flex) and an 8-mm biliary balloon (Hurricane RX Biliary Balloon Dilatation Catheter; Boston Scientific). Finally, the stent was extracted using rat-toothed forceps.

Complex removal

Overall, 140 LAMS removals (88.6%) were described as easy or very easy by the endoscopist, while only six (3.8%) were defined as difficult or very difficult; 90% of removals were performed in ≤10 minutes. Therefore, we identified 13 complex removals (8.2%), with three (1.9%) defined by the endoscopists, seven (4.4%) because of the prolonged procedure time (median 14 minutes, range 11–60), and three (1.9%) fulfilling both criteria.

Patients with coaxial double-pigtail plastic stents did not have significantly lower rates of embedment (8.6% vs. 13.8%; $P=0.30$) or complex removals (5.9% vs. 10.0%; $P=0.40$).

Multivariable logistic regression analysis identified stent embedment (RR 5.84, 95%CI 2.14–15.89; $P=0.001$) and over-the-wire deployment (RR 4.66, 95%CI 1.60–13.56; $P=0.01$) as independent risk factors for complex removals, and longer indwell times (RR 1.14, 95%CI 1.03–1.27; $P=0.01$) as a confounding factor (▶ **Table 3**).

▶ **Table 3** Univariable and multivariable analysis of risk factors for complex retrieval.

	Relative risk (95%CI)	*P* value
Univariable analysis[1]		
• Stent indwell time, weeks	1.16 (1.05–1.28)	0.003
• Over-the-wire technique	3.25 (1.11–9.57)	0.03
• Bleeding during follow-up	1.76 (1.03–3.01)	0.04
Multivariable analysis		
• Stent embedment[2]	5.84 (2.14–15.89)	0.001
• Over-the-wire technique	4.66 (1.60–13.56)	0.01
• Stent indwell time, weeks	1.14 (1.03–1.27)	0.01

[1] Other variables included in univariable analysis (results shown only if $P \leq 0.20$) were proton pump inhibitor or antiplatelet treatment during stent indwell time, bleeding during follow-up, overall stent indwell time, location of transmural access, indication (each one employed as a dichotomous variable), LAMS diameter, deployment technique (freehand vs. over the wire), balloon dilation, and coaxial double-pigtail plastic stent.
[2] Stent embedment was directly included in the multivariable analysis.

Stent embedment

A partial embedment was observed in 14 cases (8.9%), while a complete embedment was found in five cases (3.2%). A detailed description of patients with and without an embedded stent is shown in ▶ **Table 4**. Among PFCs, embedment was observed in 18% of pseudocysts and 11.8% of walled-off necroses. Cases where the LAMS was partially embedded required a median (IQR) of 4.5 (2–7) minutes for its removal and the five cases presenting with complete embedment required a median (range) of 16 (5–60) minutes, while non-embedded stents required a median (IQR) of only 2 (1–3) minutes. Overall, embedded stents required longer removal times ($P=0.01$).

The risk of embedment was strongly related to the indwell time, as shown in ▶ **Fig. 2**. Embedment was observed in 3.1% (2/65) of LAMSs removed during the first 6 weeks and in 15.9% (10/63) of those removed between the 7th and 12th weeks ($P=0.02$). Furthermore, in the remaining 30 stents removed after the first 12 weeks, the embedment rate was 23.3%.

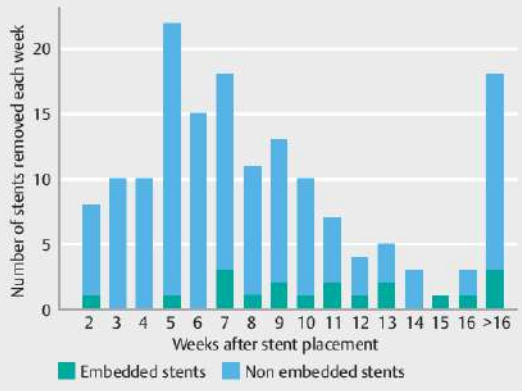
Retrieval-related adverse events

We did not identify any SAEs associated with LAMS removal. A total of seven gastrointestinal bleeds (4.4%) were observed: five mild cases where the patient could be discharged after stent removal and two moderate cases requiring a short hospital admission after endoscopic treatment (adrenaline injection in one case and hemostatic powder in another) for a second-look endoscopy to be performed. Moreover, one patient developed moderate acute cholecystitis 5 days after undergoing scheduled removal of a LAMS placed for gallbladder drainage.

▶ **Table 4** Characteristics of patients with and without an embedded lumen-apposing metal stent (LAMS).

	Embedded LAMS (n = 19)	Non-embedded LAMS (n = 139)	*P* value
Age, median (IQR), years	63.3 (53.3–69.5)	61.3 (50.6–71)	0.90
Sex, male, n (%)	14 (73.7)	91 (65.5)	0.50
Type of procedure, n (%)			0.23
• Pancreatic fluid collections	16 (13.9)	99 (86.1)	
• Other procedures	3 (7.0)	40 (93.0)	
Puncture site, n (%)			0.85
• Gastric fundus	1 (11.1)	8 (88.9)	
• Gastric body	15 (12.7)	103 (87.3)	
• Gastric antrum	2 (18.2)	9 (81.8)	
• Duodenum or jejunum	1 (6.7)	14 (93.3)	
Stent diameter and length, n (%), mm			0.87
• 10 × 10	5 (13.2)	33 (86.8)	
• 15 × 10	13 (13.0)	87 (87.0)	
• 20 × 10	1 (5.6)	17 (94.4)	
Insertion technique, n (%)			> 0.99
• Freehand	17 (89.5)	122 (87.8)	
• Over-the-wire	2 (10.5)	17 (12.2)	
Balloon dilation after deployment, n (%)	3 (15.8)	49 (35.3)	0.09
Coaxial double-pigtail plastic stent, n (%)	6 (31.6)	62 (44.6)	0.28
Stent indwell time, median (IQR), days	73 (46–99)	44 (29–66)	0.01

IQR, interquartile range.



▶ **Fig. 2** Bar graph showing the number of stents removed each week and whether they were embedded or not.

Discussion

Our study, the largest prospective case series specifically assessing LAMS withdrawals, reveals that most stent removals are technically simple and straightforward procedures, with an excellent safety profile. A small proportion may however be more technically demanding and some of these may require advanced endoscopic techniques, mainly if embedment is present.

Our case series, with over 150 procedures, confirms LAMS removal is a simple procedure, with nearly 95 % of removals performed by simple proximal flange traction. Furthermore, we identified a low AE rate (5.1 %) and, more importantly, no SAEs. It is interesting to highlight the multiple case reports that have been published describing different advanced maneuvers to retrieve embedded LAMSs [15, 19, 20]. This large body of literature might lead to a misconception about the relative frequency with which such maneuvers are needed. In fact, 98.7 % of LAMSs in our series were retrieved with a snare or a foreign body forceps.

LAMS embedment was the strongest risk factor for complex removals. The actual prevalence of stent embedment is unknown. Retrospective studies have reported low rates. Chan-

dran et al. identified a 6% rate among 54 PFCs [21], and two other retrospective multicenter studies reported meagre embedment rates: 0.9% (1/116 patients) among PFCs with a median indwell time of 7 weeks; 1.1% (1/93) in a Spanish case series including different procedures with a median indwell time of 8.3 weeks [11,22]. However, a randomized trial comparing LAMSs and plastic stents in WONs reported a significantly higher rate of buried stents (6.5% [2/31]), all of which required complex withdrawal maneuvers [9]. The 12% rate found in our study therefore represents the highest embedment rate published. This is probably related to the prospective design of the study, as partial embedment does not usually make stent removal difficult and consequently it is seldom reported unless it causes an AE or requires advanced techniques. In our study, more than 85% of the partially embedded LAMSs were removed with the standard pull technique. In contrast, the 3.2% complete embedment rate closely resembles data from previous studies.

Longer indwell times have been previously reported as a risk factor for embedment, using a 4-week threshold [12,23]. We identified a slightly longer threshold, with a 3.1% embedment rate in the first 6 weeks and a 15.9% risk in the following 6 weeks.

An interesting and previously unreported finding of our study was the association of over-the-wire stent placement with complex removal of LAMSs. This could be explained by a protective effect caused by the electrocautery used in the free-hand technique. This hypothesis has been previously postulated for other endoscopic techniques. Endoscopic balloon dilation (EBD) is currently the treatment of choice for postsurgical colorectal anastomotic strictures [24,25], but stricture relapse is relatively frequent [26] and has been related to traumatic injury leading to the formation of scar tissue in the deeper muscle layer [27]. In contrast, an electrocautery incision technique has been reported as an alternative treatment for anastomotic colorectal strictures [28–30] with a lower relapse rate, theoretically by avoiding the scar tissue formation. Furthermore, the use of electrocautery reduces the formation of adhesions in surgical colonic anastomoses [31].

Our study presents a series of strengths. It is the largest prospective case series specifically addressing LAMS removals published to date. A pre-established definition of all outcomes was used, and the complementary centralized follow-up diminished the risk of under-reporting AEs. In addition, the large number of participating centers allowed the inclusion of operators with different levels of experience. On the other hand, it also has some drawbacks. The definition of complex withdrawals was based on the subjective assessment of the endoscopist, which can cause interobserver variability and lead to bias, although we tried to diminish this by including an objective variable: stent retrieval time. Additionally, other possible risk factors for complex removal, such as through-the-stent procedures or local infection (infected WONs, cholecystitis) were not registered or included in the multivariable models.

In summary, our study shows that LAMS withdrawal is a safe procedure, requiring basic endoscopic techniques, and is therefore attainable in conventional endoscopy rooms; however, experienced operators are still needed if advanced endoscopic techniques are required and to assess cases where the initial proximal traction maneuvers fail. Therefore, the removal of embedded LAMSs and those with an indwell time over 6 weeks or placed using an over-the-wire technique should be scheduled in advanced endoscopy units.

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Competing Interests

M. Perez-Miranda is a consultant for Boston Scientific, Olympus, Medtronic, and M.I.Tech. The remaining authors declare that they have no conflict of interest.

Clinical trial

Trial Registration: EU Clinical Trials Register (https://www.clinicaltrialsregister.eu) | Registration number (trial ID): NCT04059926 | Type of study: Prospective multicenter study

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RESUMEN GLOBAL DE LOS RESULTADOS

6. RESUMEN GLOBAL DE LOS RESULTADOS

Del registro RNPAL, que incluyó 407 pacientes, se analizaron 82 a los que se les realizó un EUS-DVB con PAL tipo Axios, dando lugar a la primera publicación de esta tesis doctoral. De estos 82 pacientes, el 53,7% fueron varones, con una mediana de edad de 84,6 años (RIC: 76,5-89,8). La indicación más frecuente del drenaje vesicular fue la colecistitis aguda. En el 90,2% de los pacientes la PAL se colocó con intención permanente.

Con respecto a los procedimientos, el 96,3% de los mismos fueron realizados por endoscopistas con experiencia, en centros de alto volumen. Se obtuvo un éxito técnico del 96,3% y un éxito clínico del 89%. El acceso transduodenal o transgástrico fue escogido según preferencias del operador, sin observar diferencias significativas tras el análisis estadístico, siendo el tamaño de la PAL más empleado el de 10x10 mm.

En relación con el seguimiento, 45 pacientes completaron todo el año, a 10 se les retiró la PAL tras una media de 21 días y 27 pacientes fallecieron con la PAL in situ.

En cuanto a los eventos adversos, doce (14,6%) pacientes presentaron un total de 14 eventos adversos; 6 (7,3%) fueron leves, 3 (3,7%) moderados, 3 (3,7%) graves y 2 (2,4%) mortales. Los eventos biliares recurrentes fueron el evento adverso más frecuente (6,1%), siendo la presencia de patología maligna biliopancreática concomitante el único factor de riesgo para dicho evento adverso. La colocación de doble *pigtail* trans-PAL redujo significativamente el riesgo de eventos adversos, aunque en el análisis multivariante no se observaron diferencias significativas.

Del mismo registro anteriormente citado, se intentó la retirada de la PAL en 158 (38,8%) pacientes, dando lugar a la segunda publicación. Las indicaciones en las que se retiraron más prótesis fueron las CPE, seguido de las colecciones no pancreáticas y las gastroenteroanastomosis.

Con respecto a los procedimientos, el tiempo medio de permanencia de las PAL fue de 46,5 días (RIC: 31-70). La duración mediana de la retirada fue de 2 minutos (RIC 1-4) y la técnica más utilizada para estos procedimientos fue la tracción proximal con pinza. Un 88,6% fueron descritos por los endoscopistas como “fáciles” o “muy fáciles”. La extracción fue catalogada como compleja en trece procedimientos (8,2%), aunque solo dos requirieron maniobras endoscópicas avanzadas (1,3%). Se identificaron diversos factores de riesgo de retirada compleja que fueron:

- El enterramiento de la prótesis (riesgo relativo [RR]: 5,84 [2,14-15,89], p=0,001). Se observó enterramiento parcial y completo en 14 (8,9%) y 5 (3,2%) casos respectivamente.
- La colocación del *stent* sobre guía (RR: 4,66 [1,60-13,56], p=0,01).
- Los tiempos de permanencia más largos (RR: 1,14 [1,03-1,27], p=0,01). El porcentaje de enterramiento durante las primeras 6 semanas fue del 3,1% (2/65), alcanzando un 15,9% (10/63) durante las 6 siguientes [p=0,02].

Con respecto a los eventos adversos, se observaron 7 hemorragias: cinco casos leves y dos moderados, además de una colecistitis aguda.

RESUMEN GLOBAL DE LA DISCUSIÓN

7. RESUMEN GLOBAL DE LA DISCUSIÓN

En la presente tesis hemos demostrado que la EUS-DVB presenta elevados porcentajes de éxito técnico y clínico y que la permanencia de PAL a largo plazo aparentemente no aumenta el riesgo de eventos adversos tardíos en esta indicación. Además, hemos observado que la extracción de las PAL en cualquier tipo de indicación es un procedimiento seguro, que en la mayoría de las ocasiones requiere técnicas endoscópicas básicas, pudiéndose realizar en salas de endoscopia convencionales.

En pacientes de edad avanzada o con múltiples comorbilidades, el riesgo de eventos adversos asociados a la colecistectomía y de reingreso puede oscilar entre el 10,2% y el 17,9% (174,175). Esto hace que se desestime la cirugía en muchos de estos pacientes, generando la necesidad de abordajes mínimamente invasivos, como el DPT o el drenaje endoscópico transpapilar (DETP). Una opción más reciente es el EUS-DVB. En nuestra serie, el éxito técnico del EUS-DVB fue del 96,3%, que asemeja los resultados disponibles en la literatura (127,128,130,161,176). El riesgo acumulado de eventos biliares recurrentes fue del 9,7% al año del drenaje, datos muy similares al único ensayo clínico sobre este tema (9) y discretamente mayores que las diferentes series retrospectivas publicadas (130,161,162,176,177). Sin embargo, la mayoría de estos estudios ofrecen porcentajes que, dado el elevado número de pérdidas durante el seguimiento en este tipo de pacientes, probablemente infraestiman el riesgo real. Con el DPT este tipo de eventos son claramente más frecuentes, oscilando entre el 41-46%, (117,178–180), mientras que en el DETP los resultados son muy similares a las observadas en nuestro estudio (9-11%) (129,181). Sin embargo, esta técnica tiene la limitación de que el procedimiento no es técnicamente factible en hasta un 12-21% de los casos (129,176,182). Un metaanálisis recientemente publicado, comparando las 3 técnicas, sugiere que la necesidad de reintervención y eventos biliares recurrentes es mayor con DPT y DETP que con EUS-DVB (183).

Un hallazgo relevante es que el factor de riesgo más importante de recidiva fue la presencia de patología biliopancreática maligna; un tercio de los pacientes con neoplasias a este nivel desarrollaron eventos biliares recurrentes. Este valor observado es incluso mayor que el identificado después de una coledocoduodenostomía o hepaticogastrostomía (184,185). Las series publicadas sobre EUS-DVB no especifican la prevalencia de neoplasias biliopancreáticas o de antecedentes de intervencionismo biliopancreático en sus muestras (127,176,182), mientras que en nuestra serie suponían prácticamente el 15% de los pacientes incluidos. Esta sobrerrepresentación probablemente se deba a la atención en unidades de hospitalización de aparato digestivo y al frecuente manejo endoscópico previo de la obstrucción biliar, puesto que la mayoría de estos pacientes suelen tener drenajes endoscópicos previos. Aunque consideramos que estos procedimientos previos condicionan de manera relevante el riesgo de recidiva biliar, resulta difícil cuantificar de manera precisa su influencia, dada la gran variabilidad en los procedimientos realizados.

Un tema controvertido derivado del uso de este tipo de prótesis y que concierne especialmente al drenaje vesicular, es la necesidad o no de retirada de las PAL. Existe consenso en que deben ser retiradas en aquellas indicaciones como las colecciones pancreáticas y deben mantenerse de forma indefinida en las gastroenteroanastomosis para el tratamiento de la OVG de etiología maligna. En el caso de la EUS-DVB, existe todavía controversia y una llamativa disociación entre las recomendaciones de las sociedades científicas (186) y la práctica clínica real. Las series de casos retrospectivas disponibles con tiempos de permanencia prolongados y nuestros datos prospectivos coinciden en que no se identifican hemorragias tardías (161,176,177,187), que es la principal justificación para la retirada temprana. Es importante destacar que apenas existen series de casos de práctica clínica real en los que se retire la prótesis sistemáticamente. Esto se debe al perfil de pacientes en el que se plantea el EUS-DVB, habitualmente sujetos frágiles, con múltiples comorbilidades y una esperanza de vida

reducida. En estos casos, suele ser el propio paciente quien desestima la realización de nuevos procedimientos invasivos para retirar la PAL. Sí disponemos sin embargo de datos prospectivos con retiradas programadas, el ensayo DRAC 1, en el cual tras el drenaje vesicular realizaban una revisión endoscópica transprostésica para retirar las litiasis (130). Si la vesícula estaba limpia de litiasis o se realizaba la extracción de estas de forma completa por vía endoscópica, se procedía a extraer la PAL y reemplazarse por una prótesis plástica tipo *pigtail*. Por el contrario, si los cálculos no se eliminaban por completo, se repetía la misma exploración en intervalos de tiempo variables hasta la eliminación completa de las litiasis. A pesar de tratarse de un ensayo clínico con un protocolo tan claro, el 31% de los participantes declinaron someterse a nuevas endoscopias para la retirada de la prótesis, con lo cual el número de retiradas realizadas fue de 27. Este número es demasiado pequeño para poder identificar diferencias relevantes en la proporción de eventos adversos comparado con las series en las que las PAL no se retiraron. Sin embargo, podemos confirmar que la hemorragia secundaria, principal limitante para una permanencia prolongada de la PAL, no es un evento adverso frecuente en EUS-DVB. Puesto que someter a ancianos frágiles a un procedimiento invasivo sí puede conllevar eventos adversos, consideramos que la retirada programada debería probar sus beneficios antes de recomendarse sistemáticamente.

En el segundo estudio analizamos más de 150 procedimientos de retirada de PAL en diferentes indicaciones. Más del 90% se realizaron mediante tracción simple de la solapa proximal con una pinza de cuerpo extraño o un asa de polipectomía estándar. Además, se observó un riesgo muy bajo de eventos adversos (5,1%), sin identificar ninguno grave.

Globalmente un 8,2% de las retiradas fueron catalogadas como complejas, ya fuera por la sensación subjetiva del endoscopista o por la duración del procedimiento. El enterramiento de la PAL (14 [8,9%] *stents* con un enterramiento parcial y 5 [3,2%] con un enterramiento completo) y el tiempo de permanencia resultaron factores de riesgo

independientes de retirada compleja. La proporción de *stents* enterrados en nuestra serie es muy superior a los datos publicados. En una serie retrospectiva de 54 CPE se observó un valor del 6% (172). Otros dos estudios multicéntricos retrospectivos presentan proporciones aún menores: 0,9% (1/116) en una serie de CPE con una mediana de permanencia de 7 semanas y 1,1% (1/93) en una serie con diferentes indicaciones con una mediana de tiempo de permanencia de 8,3 semanas (167,188). Por otra parte, un ensayo aleatorizado que comparó PAL y *stents* de plástico en CPE documentó un valor significativamente mayor, 6,5% (2/31), de *stents* enterrados, que además requirieron maniobras de extracción complejas en todos los casos (150). En cualquier caso, el 12,1% de enterramientos documentados en nuestra serie representa el porcentaje de enterramiento más alto publicado. Esto probablemente esté relacionado con el diseño prospectivo del estudio y la recogida del enterramiento, total o parcial, como una variable específica, ya que el enterramiento parcial no suele dificultar la extracción del *stent* y, por lo tanto, rara vez se documenta, a menos que cause un evento adverso o requiera técnicas avanzadas. Más del 85% de los *stents* parcialmente enterrados se retiraron con tracción simple. Por el contrario, el porcentaje de enterramiento completo del 3,2% se asemeja mucho a los datos de estudios descritos previamente.

El tiempo de permanencia es el segundo factor de riesgo de retirada compleja. Su peso como factor de riesgo es más controvertido, dado que puede ser muy variable según la indicación de la PAL y, además, está interrelacionado con el enterramiento, presentando éste una asociación más potente con la retirada compleja. Sin embargo, el enterramiento requiere de una endoscopia para confirmar su presencia, por lo que muchas veces sólo se puede confirmar al tiempo de intentar la retirada. Contrariamente, el tiempo de permanencia es un dato muy sencillo de estimar, por lo que habitualmente va a ser el principal determinante para estimar el riesgo de retirada compleja.

Las recomendaciones acerca del tiempo de permanencia vienen condicionadas por el riesgo de hemorragia en colecciones pancreáticas, recomendándose un tiempo de permanencia del *stent* de menos de 4 semanas (189). Si la recomendación de retirada viniera únicamente por el riesgo de enterramiento y/o retirada compleja, en nuestra serie hemos identificado un umbral ligeramente más largo, con unos porcentajes de enterramiento del 3,1% en las primeras 6 semanas y un riesgo del 15,9% en las siguientes 6 semanas.

Un hallazgo novedoso en nuestros estudios fue que la colocación de la PAL sobre guía y sin diatermia resultó ser un factor de riesgo de retirada compleja. Esto podría explicarse debido a un efecto protector provocado por el electrocauterio. Esta hipótesis ya ha sido postulada previamente para otras técnicas endoscópicas como la dilatación con balón, técnica de elección para el tratamiento de las estenosis benignas. Dicha técnica produce lesiones traumáticas que conducen a la formación de tejido cicatricial en la capa muscular más profunda, provocando que la recaída de este tipo de estenosis sea relativamente frecuente (190-192). Por el contrario, parece que la técnica de incisión con electrocauterio como tratamiento alternativo para las estenosis (193-195) presenta menor riesgo de recaída, evitando teóricamente la formación de tejido cicatricial. Además, planteando una analogía con las intervenciones quirúrgicas, el uso de electrocauterio reduce la formación de adherencias en las anastomosis quirúrgicas (196).

Limitaciones y fortalezas de los estudios

El primer estudio de la tesis analiza una de las mayores series prospectivas publicadas hasta la fecha sobre drenajes vesiculares. Utilizamos una definición preestablecida para todos los eventos adversos, realizándose un seguimiento centralizado de los mismos que facilitó su recogida. Además, consideramos todos los eventos biliares recurrentes (colangitis, pancreatitis, etc.), no únicamente las colecistitis. Por último, el diseño prospectivo del estudio permitió estimar riesgos acumulados, facilitando la toma de decisiones clínicas. Por otro lado, un número relativamente elevado de pacientes presentaba patología maligna no candidata a tratamiento curativo, por lo que probablemente algunos eventos adversos no fueron investigados a fondo. Este hecho nos podría haber conducido a una sobrestimación de los porcentajes de eventos adversos. Así mismo, el pequeño número de eventos biliares recurrentes recogidos, dificultó la realización del análisis de regresión. Finalmente, las variaciones técnicas en la realización de los procedimientos no estaban preestablecidas, sin que fueron escogidas a criterio del endoscopista, provocando mayor heterogeneidad de los procedimientos. Sin embargo, este hecho acerca nuestros resultados a la práctica clínica habitual.

Con respecto al segundo estudio, al igual que el primero, se trata de la mayor serie de casos prospectiva que aborda específicamente los procedimientos de retirada de las PAL. De igual forma, una definición preestablecida de los EA y un seguimiento centralizado permitió disminuir el riesgo de infranotificación de EA. Además, el elevado número de centros participantes permitió la inclusión de operadores con diferentes niveles de experiencia. Las principales limitaciones de este estudio fueron principalmente dos: en primer lugar, la definición de retirada compleja se realizó en base a una valoración subjetiva del endoscopista, dando lugar a sesgos evidentes; tratamos de disminuir este hecho incluyendo el tiempo de retirada, estableciendo el umbral en el percentil 90. En segundo lugar, otros posibles factores de riesgo de retirada compleja,

como por ejemplo la realización de procedimientos a través del *stent* en colecciones pancreáticas o drenajes vesiculares, no fueron registrados o incluidos en el análisis multivariante.

En conclusión, podemos decir que las PAL son seguras y eficaces en el drenaje vesicular, con valores de éxito técnico y clínico elevados en aquellos pacientes no candidatos a cirugía. Además, no se observa un incremento de los eventos adversos a pesar de la permanencia de la prótesis a largo plazo. Los procedimientos de retirada de este tipo de prótesis suelen ser sencillos y rápidos, pudiéndose realizar mediante técnicas de endoscopia básica y por tanto pudiendo ser abordables en una sala de endoscopia convencional. Sin embargo, en un pequeño porcentaje de pacientes pueden requerir algún tipo de procedimiento endoscópico avanzado.

CONCLUSIONES

8. CONCLUSIONES

Los resultados obtenidos en los estudios que componen esta Tesis Doctoral permiten extraer las siguientes conclusiones:

1. El drenaje de la vesícula biliar guiado por ecoendoscopia es un procedimiento efectivo y seguro en aquellos pacientes no candidatos a tratamiento quirúrgico.

2. Mantener la PAL in situ durante un año tras el drenaje de la vesícula biliar presenta unos riesgos acumulados de eventos adversos similares a los publicados en estudios con retiradas programadas. El único factor de riesgo asociado a eventos adversos biliares ha sido la presencia de neoplasias biliopancreáticas.

3. La retirada de las PAL para cualquier indicación es un procedimiento seguro que sólo precisa técnicas endoscópicas básicas en la gran mayoría de pacientes. Es por tanto un procedimiento asequible en salas de endoscopia convencional.

4. Los factores de riesgo de retirada compleja fueron: el enterramiento de la prótesis, la colocación del *stent* sobre guía y unos tiempos de permanencia prolongados.

LÍNEAS FUTURAS DE INVESTIGACIÓN

9. LÍNEAS FUTURAS DE INVESTIGACIÓN

Fruto de la investigación llevada a cabo en la presente tesis, se plantean nuevas líneas de investigación derivadas de la principal, como perspectivas futuras para complementar y seguir haciendo crecer el conocimiento acerca de las prótesis de aposición luminal. En primer lugar, están pendientes de publicar los datos de seguridad y eficacia recogidos en el registro nacional sobre prótesis de aposición luminal tipo Axios en las indicaciones distintas al drenaje vesicular.

Con respecto al drenaje vesicular, sería interesante ampliar el seguimiento de los pacientes incluidos, ya que las conclusiones actualmente disponibles se ciñen obligatoriamente a los primeros 12 meses tras el procedimiento. Otro aspecto a plantear como futura línea y dado los buenos resultados obtenidos en el estudio, sería la realización de un drenaje de la vesícula biliar de forma profiláctica en aquellos pacientes no candidatos a tratamiento quirúrgico que presentan o han presentado algún episodio de patología biliar (colangitis, pancreatitis, etc), con el fin de observar si el drenaje vesicular puede disminuir la recurrencia de eventos biliares en este tipo de pacientes. Por otra parte, también se podría analizar el papel del drenaje vesicular como primera línea de tratamiento, tras CPRE fallida, de la obstrucción biliar neoplásica como alternativa a la hepaticogastrostomía o la coledocoduocenostomía, dada la relativa sencillez de este procedimiento.

En lo que se refiere a las retiradas, planteamos realizar dos estudios observacionales, metodológicamente sencillos, multicéntricos y probablemente internacionales, en los que se evaluasen diferentes aspectos de los resultados y conclusiones obtenidos en la tesis. En el primero de ellos consistiría programar la retirada de todas las PAL en las salas de endoscopia convencional sin tener en cuenta el grado de experiencia del endoscopista que realice dicho procedimiento, identificando el porcentaje de éxito y los eventos adversos. El segundo estudio tendría el objetivo de evaluar el porcentaje de

migraciones y enterramientos observados en la retirada las PAL retiradas antes de las 6 semanas tras su puesta. Tras la colocación del *stent*, se programaría su retirada en un período no superior a las 6 semanas; si la indicación requiriese continuar con algún tipo de *stent* o drenaje se plantearía el recambio por alguna alternativa descrita en la literatura.

Con estas posibles nuevas líneas de investigación, se contribuiría a reforzar los resultados obtenidos en los dos estudios con los cuáles se ha elaborado esta tesis doctoral.

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10. BIBLIOGRAFÍA

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ANEXOS

11. ANEXOS

11.1. CUESTIONARIOS DE MONITORIZACIÓN DE AMBOS ESTUDIOS

VISITA 14 días

	Sí	No
¿Sigue ingresado desde la prueba (endoscopia) del día XX/XX/XXXX en la que le pusieron la prótesis del estudio?		
¿Ha tenido que volver a ingresar en un hospital desde el alta?		
¿Ha sido en el mismo hospital en el que le hicieron el procedimiento? Especifique el centro y fecha:_____		
¿Ha tenido que ir a urgencias desde el alta?		
¿Ha tenido fiebre?		
¿Ha visto heces negras o vomitado sangre?		
¿Ha recibido trasfusiones de sangre?		
¿Le han tenido que hacer alguna endoscopia más desde el alta?		
¿Le han tenido que operar desde el alta?		
¿Le han retirado la prótesis desde el alta?		
¿Cree Vd que ha tenido algún problema de salud derivado de la presencia de la prótesis?		

Si alguna de las respuestas es positiva se deberá contactar con el investigador de referencia del centro.

VISITAS 3, 6, 9,12 meses

	Sí	No
¿Ha tenido que volver a ingresar en un hospital desde la última visita telefónica el día XX/XX/XXXX?		
¿Ha sido en el mismo hospital en el que le hicieron el procedimiento? Especifique el centro y fecha:_____		
¿Ha tenido que ir a urgencias desde la última visita telefónica?		
¿Ha tenido fiebre?		
¿Ha visto heces negras o vomitado sangre?		
¿Le han tenido que hacer alguna endoscopia desde la última visita telefónica?		
¿Le han tenido que operar desde la última vista telefónica?		
¿Le han retirado la prótesis desde la última visita telefónica?		
¿Cree Vd que ha tenido algún problema de salud derivado de la presencia de la prótesis?		

Si alguna de las respuestas es positiva se deberá contactar con el investigador de referencia del centro.

CUADERNO DE RECOGIDA DE DATOS DE EVENTOS

Identificador: _____

Evento	**Gravedad**	**Fecha Diagnóstico**	**Causalidad**	**Manejo**
□ Hemorragia □ Perforación □ Infección (disfunción) □ Obstrucción biliar (disfunción) □ Obstrucción al tránsito (disfunción) □ Migración (asintomática) □ Migración (obst tránsito 2aria) □ Migración (obstrucción biliar 2aria)	□ Leve □ Moderado □ Grave □ Fatal	__ __/__ __/__ __ dd/mm/aa	□ Improbable □ Posible □ Probable □ Definitiva	□ Conservador □ Endoscópico □ Radiológico □ Quirúrgico

□ Migración sintomática (otros) □ Otros (especificar)				

Notas:_____

_____

11.2. RESOLUCIÓN COMITÉ ÉTICO RNPAL TIPO AXIOS

Junta de Castilla y León
Consejería de Sanidad

Sacyl
ÁREA DE SALUD VALLADOLID OESTE

INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Dña. ROSA CONDE VICENTE, Secretario Técnico del Comité de Ética de la Investigación con medicamentos (CEIm) del Área de Salud de Valladolid Oeste

CERTIFICA:

Que este Comité ha evaluado el Proyecto de Investigación con **Ref.: PI118-18**

Título: **"Registro nacional de incidencias de las prótesis de aposición luminal tipo Axios"**

Protocolo: **Versión 1.0**
HIP/CI: **Versión 1.0**

Y considera que:

- Se cumplen los preceptos éticos formulados en la Declaración de Helsinki de la Asociación Médica mundial sobre principios éticos para las investigaciones médicas en seres humanos y en sus posteriores revisiones, así como aquellos exigidos por la normativa aplicable en función de las características del estudio, y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuado el procedimiento para obtener el consentimiento informado.
- La capacidad del investigador y sus colaboradores y las instalaciones y medios disponibles, tal y como ha sido informado, son apropiados para llevar a cabo el estudio.

Este CEIm acepta que dicho estudio sea realizado en el Hospital Universitario Río Hortega por el **Dr. Sergio Bazaga Pérez de Rozas** como Investigador Principal.

CEIC Área de Salud de Valladolid Oeste. Farmacología Clínica. Hospital Universitario Río Hortega. C/ Dulzaina, 2. Valladolid 47012.
Tel.:983420400.Ext. 84400. reonvi@saludcastillayleon.es

Junta de Castilla y León
Consejería de Sanidad

Sacyl
ÁREA DE SALUD VALLADOLID OESTE

Dña. ROSA CONDE VICENTE, Secretario Técnico del Comité de Ética de la Investigación con medicamentos (CEIm) del Área de Salud de Valladolid Oeste

HACE CONSTAR QUE:

En la reunión celebrada el día 07 de Septiembre de 2018, Acta 13/2018, el Comité de Ética de la Investigación con medicamentos (CEIm) decidió emitir **INFORME FAVORABLE** al estudio, cumpliéndose los requisitos establecidos en la Legislación vigente para que la citada decisión sea válida.

El CEIC del Hospital Universitario del Río Hortega, tanto en su composición como en los PNT, cumple con las normas de BPC (CPMP/ICH/135/95) y en la actualidad lo conforman los siguientes miembros:

PRESIDENTE: D. Antonio Dueñas Laita (Médico, Farmacólogo Clínico).

VICEPRESIDENTE: D. Manuel González Sagrado (Médico, Unidad de Apoyo a la Investigación. Representante de la Comisión de Investigación)

SECRETARIO TÉCNICO. Dª Rosa Mª Conde Vicente (Doctora en Investigación en Ciencias de la Salud).

VOCALES:

D. Juan Manuel Alonso Fernández (Diplomado Universitario en Enfermería).
D. Miguel Catalá Pindado (Farmacéutico).
D. Mariano Fuentenebro Virseda (Licenciado en Derecho. Miembro ajeno a profesión sanitaria)
D. Alberto Olalla Ubierna (Miembro ajeno a profesión sanitaria).
D. José Luis Pérez Castrillón (Médico, Medicina Interna).
D. Baltasar Pérez Saborido (Médico, Cirugía General y Aparato Digestivo).
D. José Manuel Rodríguez Valencia (Médico, Medicina Familiar y Comunitaria).
D. Álvaro Sanz Rubiales (Médico, Oncología. Representante del Comité de Ética Asistencial)

Lo que firmo en Valladolid, a 07 de Septiembre de 2018

ROSA MARIA CONDE VICENTE - DNI 09296839D
Fecha: 2018.09.07 14:37:22 +02'00'

Comité de Ética de la Investigación con Medicamentos (CEIm) Área de Salud de Valladolid Oeste

Fdo. Dña. Rosa Mª Conde Vicente
Secretario Técnico CEIm

11.3. OTRAS PUBLICACIONES RELACIONADAS CON LA TESIS

11.3.1. Publicación 1

EUS-guided gastroenterostomy versus duodenal self-expandable metal stent for malignant gastric outlet obstruction: results from a nationwide multicenter retrospective study (with video).

Sánchez-Aldehuelo R, Subtil Iñigo JC, Martínez Moreno B, Gornals JB, Guarner-Argente C, Repiso Ortega A, Peralta Herce S, Aparicio JR, Rodríguez de Santiago E, **Bazaga S**, Juzgado D, González-Panizo F, Albillos A, Vázquez-Sequeiros E.

Gastrointestinal Endoscopy 2022; 96: 1012-20.

ORIGINAL ARTICLE: Clinical Endoscopy

EUS-guided gastroenterostomy versus duodenal self-expandable metal stent for malignant gastric outlet obstruction: results from a nationwide multicenter retrospective study (with video) CME

Rubén Sánchez-Aldehuelo, MD,[1] José Carlos Subtil Iñigo, MD, PhD,[2] Belén Martínez Moreno, MD,[3] Joan Gornals, MD, PhD,[4] Carlos Guarner-Argente, MD, PhD,[5] Alejandro Repiso Ortega, MD,[6] Sandra Peralta Herce, MD,[2] José Ramón Aparicio, MD, PhD,[3] Enrique Rodríguez de Santiago, MD, PhD,[1] Sergio Bazaga, MD,[4] Diego Juzgado, MD,[7] Fernando González-Panizo, MD,[7] Agustín Albillos, MD, PhD,[1] Enrique Vázquez-Sequeiros, MD[1,7]

Madrid, Pamplona, Alicante, Barcelona, Toledo, Spain

Background and Aims: Traditionally, palliative treatment of malignant gastric outlet obstruction (GOO) has been surgical, but surgical treatment carries significant morbidity and mortality rates. Endoscopic placement of a duodenal self-expandable metal stent (D-SEMS) has been proven to be successful for this indication in the short term. However, D-SEMSs are likely to malfunction over time. EUS-guided gastroenterostomy (EUS-GE) may help overcome these limitations. We aimed to evaluate stent failure–free survival at 3 months.

Methods: A nationwide multicenter, observational study of D-SEMS and EUS-GE procedures for patients with malignant GOO was conducted at 7 academic centers from January 2015 to June 2020. Stent failure–free survival at 1, 3, and 6 months; technical and clinical success; adverse events (AEs); and patient survival were evaluated in both groups and compared.

Results: Ninety-seven patients were included in the D-SEMS group and 79 in the EUS-GE group. Pancreatic cancer was the main underlying malignancy in 53.4%. No statistically significant differences regarding technical (92.8% vs 93.7%) or clinical success (83.5% vs 92.4%) were found. AE rates did not differ between groups (10.3% vs 10.1%), although 2 events in the EUS-GE group required surgical management. Patients in the EUS-GE group had improved stent patency when compared with those patients in the D-SEMS group at 3 months (92.23% vs 80.6%; adjusted hazard ratio, .37; $P = .033$).

Conclusions: EUS-GE seems to have improved patency outcomes when compared with D-SEMS placement for palliative treatment of malignant GOO. Prospective trials are needed to fully compare their efficacy and AE profile. (Gastrointest Endosc 2022;96:1012-20.)

(footnotes appear on last page of article)

Palliation of malignant gastric outlet obstruction (GOO) remains a major problem in gastric and pancreatic neoplasms.[1-3] The main goal in patients with GOO who are not candidates for surgical cure is to relieve obstructive symptoms and permit administration of palliative therapy.[4]

Malignant GOO has been classically treated by palliative surgical gastrojejunostomy, with high efficacy but with significant morbidity (15.7%-26.5%) and mortality rates (4.8%-26.5%).[5,6] For this reason, less-invasive approaches have been developed.[7,8] Endoscopic placement of a duodenal self-expandable metal stent (D-SEMS) for palliation of malignant GOO has shown reasonable technical (89.1%-100%) and clinical success (85.7%-94.3%).[9-13] Nevertheless, D-SEMSs have also been shown to have a limited efficacy in the long term, with a significant rate of stent malfunction and recurrence of GOO symptoms (5.4%-42.5%).[10,14]

A more recently introduced technique to bypass malignant GOO is EUS-guided gastroenterostomy (EUS-GE) in which EUS is used to place a lumen-apposing metal stent (LAMS) between the stomach and proximal jejunum. This approach may reduce the risk of stent malfunction because of tumor ingrowth.[15] A small number of studies have shown promising technical (88%-95%) and clinical success (85%-94%) and an acceptable adverse event (AE)

rate for EUS-GE.[4,16-20] However, there is little evidence to date comparing the performance characteristics and long-term efficacy of EUS-GE with D-SEMS placement.[1,21] In this analysis we compared the efficacy of D-SEMS placement versus EUS-GE.

METHODS

Study design

We performed a nationwide multicenter analysis comparing D-SEMS placement and EUS-GE for GOO. All institutions performing both techniques (D-SEMS and EUS-GE) in Spain were invited to participate in the study. Consecutive D-SEMSs implanted because of symptomatic malignant GOO between January 2015 and December 2016 (D-SEMS group) and EUS-GE performed between January 2017 and June 2020 (EUS-GE group) were included in the study. Demographic data and procedural and clinical follow-up information were collected through in-hospital and primary healthcare medical records. The cutoff of January 2017 corresponded to the introduction of the EUS-GE technique in Spain.

Adult patients with symptomatic malignant GOO who were not candidates for curative surgical resection were included in the study. Exclusion criteria were patients with asymptomatic or benign GOO and those with a previous surgical and/or endoscopic treatment. Presence of mild or moderate ascites was not considered a contraindication for EUS-GE. However, severe ascites limiting the ability to identify an intestinal loop contraindicated the procedure.

Procedures were performed after written informed consent was obtained from patients and with patients under deep sedation or general anesthesia and intravenous prophylactic antibiotics according to each institution protocol. Oral intake was progressively initiated within the first 24 to 48 hours, and patients were discharged according to medical criteria.

Institutional review board approval was obtained for this retrospective study (protocol study 173/18).

Main outcome

Stent failure–free survival (adequate stent patency) at 3 months was the main outcome of our study. It was defined as the composite outcome of technical success and absence of stent malfunction (stent migration or obstruction secondary to tumor in- or overgrowth).

Secondary outcomes

Stent failure–free survivals at 1 and 6 months were secondary outcomes. Technical success was defined as the creation of a connection of the stomach with the patent distal small bowel, whereas technical failure occurred when this procedure could not be successfully completed. Clinical success was assessed according to the Gastric Outlet Obstruction Scoring System (0, no oral intake; 1, only liquids; 2, soft solids; 3, almost complete diet; 4, full diet) when improvement in Gastric Outlet Obstruction Scoring System (until $\geq$1) 2 weeks after intervention was achieved. AEs referred to all those stent-related events occurring at the end of the procedure, including bleeding, perforation, aspiration, pain, pancreatitis, cholangitis, and death, according to the American Society for Gastrointestinal Endoscopy lexicon for AEs.[22] Patient follow-up was performed until the last clinical visit, end of study, or death, if this occurred.

D-SEMS technique

The procedure was performed using a therapeutic gastroscope (GIF-1TH190; Olympus, Hamburg, Germany). A .035-inch guidewire (Jagwire; Boston Scientific, Marlborough, Mass, USA) was gently advanced across the stricture under radiographic and endoscopy monitoring, with the help of a Fogarty catheter (4.5F 3-lumen balloon-V; Olympus), and contrast was injected to define the anatomy and length of the stricture and place the most appropriate stent. An uncovered through-the-scope D-SEMS (Wallflex Duodenal 22 × 90/22 × 120 mm; Boston-Scientific) was then deployed under endoscopic or fluoroscopic guidance.

EUS-GE technique

A therapeutic gastroscope (GIF-1TH190; Olympus) was used to allow placement of a .035-inch guidewire (Jagwire; Boston-Scientific) across the stricture until the guidewire reached the proximal jejunum. A nasobiliary catheter (7F nasal-biliary drainage tube-V; Olympus, Tokyo, Japan) was then advanced over the wire until reaching the jejunum, and a coil was formed at that point (Fig. 1). The therapeutic gastroscope was carefully withdrawn, keeping the nasobiliary catheter in the jejunum under radiographic control to prevent dislodgment. The linear echoendoscope (GF-UCT180; Olympus, Hamburg, Germany) was then advanced into the stomach, parallel to the nasobiliary catheter. The intestinal loop was distended by instilling methylene blue–dyed water with the help of a motor pump and 20 mg/mL intravenous scopolamine butylbromide, until the jejunal loop was identified on the EUS image. A free-hand approach was used to access the distended jejunal loop. A commercially available cautery-tipped LAMS (HOT-AXIOS 15 × 10/20 × 10 mm; Boston Scientific) was used in all cases, and an electrosurgical generator used a pure cut current (140 W), without coagulation effect. The LAMS was preloaded with a .035-inch guidewire (Jagwire; Boston Scientific) inserted through the working channel of the echoendoscope, and using the free-hand technique and under no guidewire, the LAMS traversed the gastric and jejunal wall under direct EUS control. The distal flange was deployed in the jejunal lumen, and then a gentle pull of the LAMS was performed until the distal flange acquired a conic shape, and finally the proximal flange was released inside the echoendoscope channel. LAMS deployment was

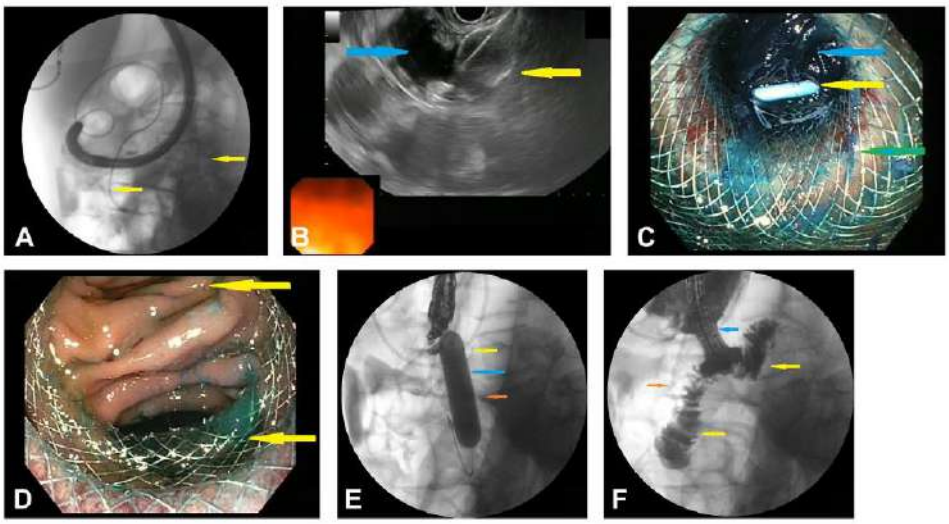

Figure 1. Endoscopic, radiologic, and endosonographic images of steps of EUS-guided gastroenterostomy. **A,** Radiographic view shows a nasocystic tube advanced over a guidewire (*yellow arrows*) into the proximal jejunum for water/methylene blue instillation and distention of jejunal loop. **B**, EUS views showing the distended jejunal loop (*blue arrow*) after instillation and the deployed distal flange of the lumen-apposing metal stent (LAMS; *yellow arrow*). **C**, Endoscopic image after LAMS deployment showing the jejunal loop with methylene blue (*blue arrow*), the nasocystic tube advanced into the jejunum (*yellow arrow*), and the proximal end of the LAMS as seen from the stomach (*green arrow*). **D**, Endoscopic view showing the LAMS and the afferent and efferent loop of the jejunum (*yellow arrows*). **E**, Radiograph showing the LAMS being balloon dilated (*blue arrow*), showing an adequate deployment of the proximal (*yellow arrow*) and distal flange (*orange arrow*). **F**, Iodinated contrast is injected through the working channel of the endoscope while being placed into the LAMS (*blue arrow*), showing adequate refill of afferent and efferent jejunal loops (*yellow arrows*). Note the nasocystic irrigation tube (*orange arrow*) is placed in close vicinity of the created anastomosis.

completed by gently pulling back the echoendoscope while pushing the LAMS catheter. Methylene blue–dyed water was seen at that moment coming out from the jejunum, confirming adequate LAMS placement.

Balloon dilatation of the LAMS to reach an adequate diameter was performed at the discretion of the endoscopist (10-15 mm). Iodinated contrast was injected with the help of a Fogarty balloon (4.5F 3-lumen balloon-V; Olympus, Hamburg, Germany) at the level of the anastomosis to radiographically confirm the EUS-GE had no leak. Video 1 (available online at www.giejournal.org) demonstrates the technique used.

Statistical analysis

Statistical analyses were conducted using the Stata/SE 14.0 statistical software package (StataCorp, College Station, Tex, USA). All analyses were 2-tailed, and $P < .05$ was considered to be statistically significant. Categorical variables are reported as proportions and percentages, with 95% confidence interval (CI), whereas continuous variables are presented as mean and standard deviation or median and interquartile range according to normal or skewed data distribution. The Fisher exact test was used to compare categorical variables and the Student *t* test to compare continuous variables.

Statistical analysis was done according to an intention-to-treat strategy. In the survival analysis, differences between groups were assessed by plotting Kaplan-Meier survival curves and calculating adjusted hazard ratios (HRs) with 95% CIs. Cox models were used to compare the study groups with respect to stent failure–free survival and overall survival. In the multivariate analysis, we adjusted for variables with a plausible physiopathologic impact on the outcome of interest or that were found to be significant in the univariate analysis. Because death is a frequent event in this type of patient and may act as a competing event, a sensitivity competing-risk analysis using a Fine-Gray model was also performed to analyze the risk of stent failure. The proportional hazards assumption was tested using Schoenfeld residuals. Binary logistic regression and adjusted odd ratios were used to compare the rate of AEs. Finally, we performed a sensitivity analysis using logistic regression to assess stent failure–free survival in a binary data framework.

RESULTS

Patient characteristics

During the study period, 176 patients were identified and included: 97 in the D-SEMS group and 79 in the

TABLE 1. Patient baseline characteristics

	Duodenal self-expandable metallic stent	EUS-guided gastroenterostomy	*P* value
Patients	97 (55.1)	79 (44.9)	
Age, y	70.8 ± 11.7	72.4 ± 10.7	.3285
Male sex	58/97 (59.8)	43/79 (54.4)	.47
Location of stenosis			.015
Gastric body	18/97 (18.6)	15/79 (19)	
Antrum/pylorus	34/97 (35.1)	18/79 (22.8)	
Duodenal bulb	20/97 (20.6)	34/79 (43)	
Second portion of duodenum	20/97 (20.6)	8/79 (10.1)	
Third/fourth portion of duodenum	5/97 (5.16)	4/79 (5.1)	
Etiology of malignancy			.308
Pancreas	45/97 (46.4)	49/79 (62)	
Stomach	27/97 (27.8)	15/79 (19)	
Duodenum	6/97 (6.2)	5/79 (6.3)	
Biliary tract and gallbladder	8/97 (8.3)	5/79 (6.3)	
Other	11/97 (11.3)	5/79 (6.3)	
Tumor stage			.621
II	6/97 (6.2)	8/79 (10.1)	
III	20/97 (20.6)	17/79 (21.5)	
IV	70/97 (72.2)	54/79 (68.4)	
Peritoneal carcinomatosis	29/97 (29.9)	34/79 (43)	.083
Eastern Cooperative Oncology Group performance status scale			.025
0	10/97 (10.3)	7/79 (8.9)	
1	27/97 (27.8)	14/79 (17.7)	
2	26/97 (26.8)	36/79 (45.6)	
3	22/97 (22.7)	19/79 (24.1)	
4	5/97 (5.1)	3/79 (3.8)	
Chemotherapy	47/97 (48.5)	36/79 (46.2)	.762

Values are n or n/N (%) or mean ± standard deviation.

EUS-GE group. Patient demographic features were similar, but EUS-GE group patients were more likely to have duodenal bulb stenosis and higher Eastern Cooperative Oncology Group scores (Table 1). The most frequent underlying malignancy was pancreatic cancer (94/176 [53.4%]) followed by gastric cancer (42/176 [23.9%]).

Main outcome: 3-month stent failure–free survival (adequate stent patency)

As shown on Figure 2, patients in the D-SEMS and EUS-GE groups were surveyed for a median time of 87 and 97 days, respectively. In our survival analysis, patients in the EUS-GE group had a significantly longer stent patency when compared with those patients in the D-SEMS group at 3 months (adjusted HR, .37; $P = .033$) (Table 2). A higher overall rate of stent failure was observed in the D-SEMS group (25/97 [25.8%]) when compared with the EUS-GE group (7/79 [8.9%]) (Table 3 and Supplementary Table 1, available online at www.giejournal.org).

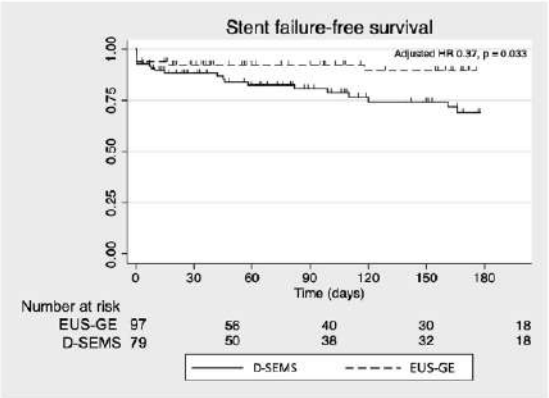

Figure 2. Kaplan-Meier survival curves regarding stent failure–free survival in the 2 groups. *D-SEMS*, Duodenal self-expandable metallic stent; *EUS-GE*, EUS-guided gastroenterostomy; *HR*, hazard ratio.

TABLE 3. Technical and clinical outcomes

	Duodenal self-expandable metallic stent	EUS-guided gastroenterostomy	Univariate analysis	Multivariate analysis	
	n (%, 95% CI)	n (%, 95% CI)	*P* value	Adjusted odds ratio (95% confidence interval)	*P* value
Patients, n (%)	97 (55.1)	79 (44.9)			
Stent failure–free					
1 mo	86/97 (88.7, .81-.94)	73/79 (92.4, .84-.96)	.48	.91 (.27-3.05)	.88
3 mo	81/97 (83.5, .75-.90)	73/79 (92.4, .84-.96)	.11	.50 (.17-1.52)	.22
6 mo	76/97 (78.4, .79-.85)	72/79 (91.1, .83-.96)	.06	.35 (.13-.94)	.04
Last follow-up	72/97 (74.2, .65-.82)	72/79 (91.1, .83-.96)	.004	.28 (.11-.76)	.01
Technical success	90/97 (92.8, .86-.96)	74/79 (93.7, .86-.97)	.82	.64 (.16-2.55)	.54
Clinical success	81/97 (83.5, .75-.9)	73/79 (92.4, .84-.96)	.08	2.16 (.77-6.07)	.14
Adverse events	10/97 (10.3, .06-.18)	8/79 (10.1, .04-.19)	.74	.83 (.23-2.15)	.54
Bleeding	1/97 (1.03)	2/79 (2.5)			
Perforation	3/97 (3.1)	1/79 (1.3)			
Misdeployment	0/97 (0)	3/79 (3.8)			
Pancreatitis and/or cholangitis	4/97 (4.1)	0/79 (0)			
Severe pain	1/97 (1)	1/79 (1.3)			
Bronchoaspiration during procedure	1/97 (1)	1/79 (1.3)			

Values are n/N (%) or n/N (%, 95% confidence interval) unless otherwise defined.

with recurrence of symptoms that were successfully managed by placing a second LAMS (HOT-AXIOS 20 × 10 mm) alongside the initial one.

Technical and clinical success

Technical success was achieved in 90 of 97 patients (92.8%) in the D-SEMS group and in 74 of 79 patients (93.7%) in the EUS-GE group (Table 3). Technical failures in the D-SEMS group were because of an inability to advance the guidewire across the stenosis (6/7 [85.7%]) or incomplete deployment of the stent because of tumor burden (1/7 [14.3%]). In the EUS-GE group, a 15 × 10 mm HOT-AXIOS LAMS was placed in 74.7% of cases and a 20 × 10 mm HOT-AXIOS LAMS in the remaining 25.3%. Technical failure in the EUS-GE group occurred in 5 cases (6.3%). Causes of EUS-GE technical failure were LAMS misdeployment in 3 cases (2 in the peritoneum and 1 in the colon: 2 were endoscopically treated with an over-the-scope clip and 1 required surgery), failure to advance a guidewire across the duodenal stenosis in 1 case, and failure to puncture the intestinal loop with the LAMS in 1 case, requiring a D-SEMS placement. Although univariate analysis showed a trend toward superiority of EUS-GE over D-SEMS placement for clinical success (92.4% vs 83.5%, $P = .076$), multivariate analysis adjusting for relevant variables disclosed no significant differences between groups (Table 3).

Adverse events

The rate of AEs in both groups, 10.3% in the D-SEMS group and 10.1% in the EUS-GE group, did not significantly differ either in the univariate or multivariate analysis (Table 3). It is important to highlight that 40% of the AEs in the D-SEMS group were mild and were a consequence of D-SEMS obstruction of pancreatic or biliary drainage. Three patients in the D-SEMS group (3/97 [3.1%]) presented a delayed duodenal perforation and were offered palliative care. Massive bleeding occurred in 1 patient, requiring blood transfusion and intensive care unit admission with a good clinical outcome. One patient presented with severe pain that was treated with opioids, and 1 patient aspirated during the procedure and died 1 day later.

In the EUS-GE group, stent misdeployment occurred in 3 patients as described. Two patients presented with bleeding. One patient presented with a moderate hemorrhage at the anastomosis that was successfully treated by endoscopy. The second hemorrhage case was at the level of the anastomosis as well and required surgery after failed endoscopic and radiology therapy. One patient presented with a delayed perforation, and palliative care was given because of her poor clinical condition. One patient presented with severe pain that was treated with opioids, and a final patient presented with bronchoaspiration during the procedure and died 3 days later.

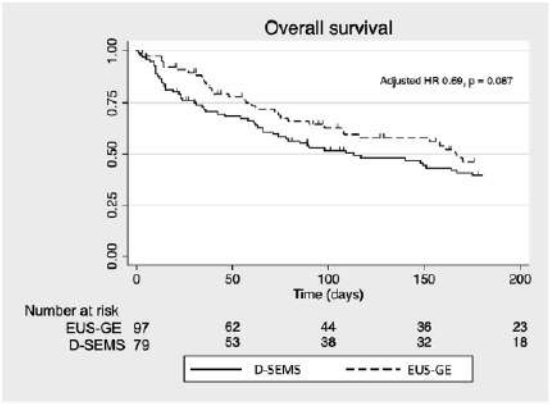

Figure 3. Kaplan-Meier curves showing patient survival in both groups. *D-SEMS*, Duodenal self-expandable metallic stent; *EUS-GE*, EUS-guided gastroenterostomy; *HR*, hazard ratio.

Overall patient survival

Overall survival of the entire cohort (D-SEMS and EUS-GE groups) at days 30 and 90 were 81% (95% CI, 74.3-86.5) and 58.0% (95% CI, 50.0-65.1), respectively. By the end of follow-up, 45 of 176 patients were alive (25.56%) (Fig. 3). Differences between treatment groups were not found to be statistically significant (adjusted HR, .69; 95% CI, .45-1.06; P = .087) (Fig. 3 and Supplementary Table 2, available online at www.giejournal.org).

DISCUSSION

Our results suggest that EUS-GE is not inferior to D-SEMS placement for palliation of malignant GOO in terms of technical and clinical success or safety. Malignant GOO may be treated by surgical or endoscopic means. Placement of a D-SEMS was associated with a faster resumption of oral intake, lower AEs, and shorter hospitalization when compared with surgery.[23-25] Unfortunately, D-SEMS treatment is associated with a significant risk of recurrence of GOO symptoms (risk ratio, 5.08; 95%; CI, .96-26.74), and additional endoscopic reinterventions are likely to be required.[25]

Our study suggests that patency may be greater for EUS-GE in the setting of malignant GOO. The potentially longer patency of EUS-GE with LAMSs, compared with D-SEMS placement, is likely related to avoidance of the tumor tract. A longer stent patency is likely to be associated with a lower need for reintervention, and it may help improve patient quality of life and survival. Results from the present study (25.8% D-SEMS dysfunction) are consistent with prior reports by Ge et al[26] and Adler and Baron[27] at 25.8% and 22%, respectively.

It is important to highlight that most failures in the D-SEMS group were related to late stent dysfunction because of tumor growth, and a minor percentage was because of technical problems at the time of stent placement. On the contrary, in this study most failures in the EUS-GE group occurred at the moment of the implant, and only a few (2.5%) were because of a late stent malfunction. Improvements in stent design or fixation systems for the small-bowel loop are required to facilitate success at LAMS placement during EUS-GE. Furthermore, a number of endoscopic salvage techniques have been described to avoid rescue surgery in cases of LAMS misdeployment (closure of gastric wall defect with an over-the-scope-clip, placing a new coaxial LAMS, and/or telescoping a fully-covered SEMS).[1,28,29]

Overall, the observed rate of D-SEMS failure (25.8%) was significantly higher (P = .004) than the observed rate reported for EUS-GE with a LAMS (8.8%), and these differences remained statistically significant after the multivariate analysis. Although the cost of the LAMS systems exceeds that of duodenal stents, this may be offset by additional procedures needed to manage stent malfunction. Cost-effectiveness trials are needed.

Regarding safety, the rate of AEs related to stent placement in our study did not significantly differ between the 2 groups, being 10.3% in the D-SEMS group and 10.1% in the EUS-GE group. It is remarkable that in the present study, none of the patients who underwent EUS-GE with LAMS placement presented with AEs related to pancreatic or biliary obstruction, whereas 4 patients in the D-SEMS group did. This is consistent with the findings by Ge et al.[26] It is reasonable to believe that if the endoscopic stent is not deployed against the major papilla (eg, EUS-GE), drainage of biliary and pancreatic secretions is more likely to be preserved and pancreatitis and cholangitis may be prevented. Furthermore, if a biliary intervention is required, the presence of a D-SEMS reduces the endoscopic possibilities to treat the biliary obstruction.[26] Two patients in the EUS-GE group required surgery for misdeployment and major hemorrhage, respectively. Therefore, larger studies are needed to evaluate specific major AEs associated with this technique. Supplementary Table 3 (available online at www.giejournal.org) summarizes the outcomes from studies of EUS-GE for malignant GOO.

Our study has additional limitations, including differences in baseline characteristics between groups. Even though the etiology of the malignancy did not differ, the D-SEMS group was more likely to have the obstruction in the stomach and the EUS-GE group in the duodenum. Additionally, the Eastern Cooperative Oncology Group score was slightly higher in the EUS-GE group. However, multivariate analysis, adjusting for these and other potential confounders, was performed, and we did not find significant differences in technical or clinical success and AEs. Although it was not a main outcome of the study and our study was not adequately powered to analyze it, a trend toward significance in survival favoring EUS-GE was identified (P = .087).

Future prospective comparisons directly designed to answer this question are needed. Inclusion of centers with variable degrees of expertise in therapeutic EUS suggests that our results may apply more broadly.

In summary, our results suggest that EUS-GE may improve long-term gastric outlet patency in malignant GOO patients, with a similar safety profile. Prospective comparative trials are needed.

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Abbreviations: AE, adverse event; CI, confidence interval; D-SEMS, duodenal self-expandable metallic stent; EUS-GE, EUS-guided gastroenterostomy; GOO, gastric outlet obstruction; LAMS, lumen-apposing metal stent.

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11.3.2. Publicación 2

Predictors of the need for necrosectomy in patients with walled-off pancreatic necrosis treated with lumen apposition metal stents.

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Predictors of the need for necrosectomy in patients with walled-off pancreatic necrosis treated with lumen apposition metal stents

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Abstract

Background and aims Endoscopic necrosectomy through lumen apposition metal stents (LAMS) is increasingly being used for complicated walled-off pancreatic necrosis (WOPN), but the need for necrosectomy after stent placement is not well understood. The aim of this study was to evaluate clinical, endoscopic, and radiologic predictors of the need for necrosectomy in patients treated with LAMS.

Methods We retrospectively reviewed patients with WOPN treated with LAMS from 2014 to 2017. Necrosectomy was performed only in patients who had recurrent fever or hemodynamic instability during follow-up. Univariate and multivariate analyses were performed.

Results We included 15 patients, 67% men and median age was 75 (54–76) years. Two (13%) presented adverse events, one immediate and one delayed. In the first case, the stent migrated to the gastric cavity during deployment but was relocated in the same procedure. In the second case, the patient presented bleeding on day 36 due to a pseudoaneurysm that was successfully treated with embolization. Clinical success was 100%, but five patients (33%) required endoscopic necrosectomy (4 mechanical and 1 irrigation) and one (7%) required surgical necrosectomy of distant collections. The percentage of necrosis in the collection detected in a previous CT scan (45 [35–66]% vs 10 [5–17]%) was the only factor to predict the need for necrosectomy in the multivariate analysis (OR 1.18 [1.01–1.39]).

Conclusion LAMS is efficient to treat WOPN but more than a third will need necrosectomy. The percentage of necrosis in the collection detected in the CT scan seems to predict the need for necrosectomy.

Keywords Walled-off pancreatic necrosis · Lumen-apposing metal stents · Necrosectomy · Prediction · Risk factors

Abbreviations

LAMS	Lumen-apposing metal stents
WOPN	Walled-off pancreatic necrosis.
ASGE	American society of gastrointestinal endoscopy

Complicated walled-off pancreatic necrosis (WOPN) is a life-threating event after acute pancreatitis. It has classically been managed with surgery, entailing a prolongated and complex clinical evolution. Endoscopic necrosectomy is increasingly being used as a minimally invasive procedure [1]. However, the technique is not standardized and several approaches have been described. In the initial series, double pigtail plastic stents with a nasocystic drain were used [2], occasionally followed by stent removal and tract balloon-dilation for subsequent necrosectomy sessions [3]. In some studies, multiple transgastric drains were used prior to necrosectomy [4], and instead of pigtails, biliary or esophageal metallic stents have also been used [5, 6]. Biliary metallic stents have a diameter no larger than 10 mm and a length of at least 40 mm, characteristics that hinder endoscopic access to the necrotic cavity through the stent. Currently, lumen apposition metal stents (LAMS) are being

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used for the endoscopic management of complicated WOPN [7, 8]. These metal stents have a larger diameter and shorter length, allowing access to the necrotic cavity using either standard or therapeutic gastroscopes [9, 10].

In the series reported to date, complicated WOPN is often managed with only one endoscopic drainage. However, some patients require multiple drainage procedures or even multiple necrosectomy sessions [11, 12]. Some endoscopists perform necrosectomy during the initial drainage or 2 or 3 days after. However, necrosectomy is an aggressive procedure with an elevated risk of complications. The expected clinical evolution after initial LAMS deployment could modify the endoscopist's decision about the initiation of necrosectomy sessions or about the type of drainage to use in each individual patient. Consequently, predicting a complicated course entailing the use of necrosectomy might justify the use of larger LAMS that facilitate access to the necrotic cavity, lavage, and necrosectomy.

The present study retrospectively evaluated clinical, endoscopic, and radiologic predictors of the need for necrosectomy in patients with WOPN treated by endoscopic drainage with LAMS.

Patients and methods

Study design

In this non-commercial, retrospective, observational study, we included all patients with WOPN treated by endoscopic drainage with LAMS from September 2014 to November 2017. We excluded patients with other types of collection (i.e., pseudocyst or postsurgical collection), those who died in the early stages of WOPN for reasons other than drainage, and those with incomplete data that precluded clinical evaluation. Demographic, radiologic, endoscopic, and follow-up data were recorded using a predefined datasheet. Data were reviewed by specialized endoscopists and radiologists.

The local ethics committee approved the study protocol (IIBSP-WOP-2018-85). Consent for the study was waived due to the retrospective nature of the study.

Procedure

All patients signed informed consent for the endoscopic procedure. A linear array echoendoscope was used to evaluate the WOPN from the stomach or duodenum. For most cases, a direct free-hand technique was used to deploy a LAMS with the Hot Axios system (Boston Scientific Corp, Marlborough, Mass, USA). Occasionally, if the drainage access was complex, the collection was punctured with a 19G needle (Boston Scientific Corp, Marlborough, Mass, USA), and a 0.35" guidewire was placed to guide Hot Axios deployment.

Post-procedure management

Patients were hospitalized for at least 48 hours, or as clinically required until intravenous antibiotic treatment was completed. A prophylactic antibiotic (ceftriaxone 1g i.v.) was administered if there was no previous indication for antibiotic treatment.

Necrosectomy was not performed or scheduled in any case immediately after the endoscopic drainage, regardless of collection characteristics. It was only indicated during follow-up when clinically needed, as in the case of complications such as recurrent fever or hemodynamic instability. Once necrosectomy was indicated, it was scheduled every 2–3 days until complete debridement was achieved. The technique was mainly performed extracting debris with snares. To facilitate this process, the LAMS was retrieved and relocated during each necrosectomy session as previously described by our group [13].

A CT scan was scheduled within one month after the drainage, and the stent was retrieved once the collection collapsed and there were no signs of pancreatic duct disruption.

Objectives, outcomes, and definitions

The main objective was to evaluate clinical, endoscopic and radiologic predictors of the need for necrosectomy in patients with WOPN treated by endoscopic drainage with LAMS. We first evaluated the need for necrosectomy, expressed as the percentage of patients who required this. We then analyzed possible predictors of necrosectomy. These included:

- Clinical factors: age, sex, etiology of acute pancreatitis, reason for requiring endoscopic drainage (infection, obstruction, jaundice, or others), time from acute pancreatitis, time from complication requiring treatment, and blood tests prior to the drainage (leucocytes, hemoglobin, platelets, PCR, bilirubin).
- Radiological factors: collection size, location, number of collections, necrosis characteristics (heterogeneous/homogeneous), signs of infection, percentage of necrosis in the collection, and density (Hounsfield Units).
- Endoscopic: collection size, necrosis characteristics (heterogeneous/homogeneous), and size of the stent.

The secondary objectives were to investigate the following:

- The technical success of endoscopic treatment with LAMS: the percentage of patients in whom the stent was correctly placed.
- The clinical success of endoscopic treatment with LAMS: the percentage of patients for whom endoscopic treatment was effective in itself as the patient did not require later surgery.
- Adverse events of endoscopic treatment with LAMS: the diagnosis of bleeding, perforation, infection, stent obstruction, or others was evaluated on the basis of the clinical course and discharge report of each patient. Complications were defined according to the ASGE lexicon [14].
- Need for surgery: the percentage of patients requiring surgery after failed endoscopic treatment.

Statistical analysis

Data are reported as median (interquartile range [IQR]) or proportions. For the primary outcome, univariate analysis of factors associated with the need for necrosectomy was performed using the χ^2 and Fisher exact test for qualitative variables and the non-parametric Mann–Whitney *U* for quantitative parameters. Multivariate logistic regression models were performed to assess the association between the predictors and the need for necrosectomy. For this analysis, the possible predictors selected were the factors that were significant in the univariate analysis or possible confounders. The backwards stepwise method was used to identify key risk factors. Univariate and multivariate adjusted odds ratios (OR) and 95% confidence intervals (95%CI) are reported. Secondary outcomes are reported as proportions.

Statistical analysis was performed at the end of the study period using the SPSS (v 24). All authors had access to the study data and reviewed and approved the final manuscript.

Results

General description

Twenty-three patients were evaluated for the study. Figure 1 provides a flow chart of these patients. Five of the 23 were excluded as the drained collection was postsurgical (3), or because a pseudocyst was drained with plastic pigtails (2). Three patients died early after drainage due to complications of the acute pancreatitis. These complications were not considered to be related to the endoscopic procedure: two of the three patients presented perforation at some distance from the drainage point (one at the terminal ileum and the other at the sigmoid colon) and underwent emergent surgery. The third patient had an exacerbation of the pancreatitis, but no further treatment was initiated due to advanced age and comorbidities. The remaining 15 patients were included in the study.

Table 1 shows the participants' demographic and baseline clinical data, CT scan, and endoscopic characteristics. Two thirds of the patients were male, with a median age of 75 (54–76) years, and the etiology of the pancreatitis was biliary or alcohol in 80% of the cases. The indication for endoscopic drainage was WOPN infection in most cases, but 27% received treatment due to biliary or gastrointestinal obstruction.

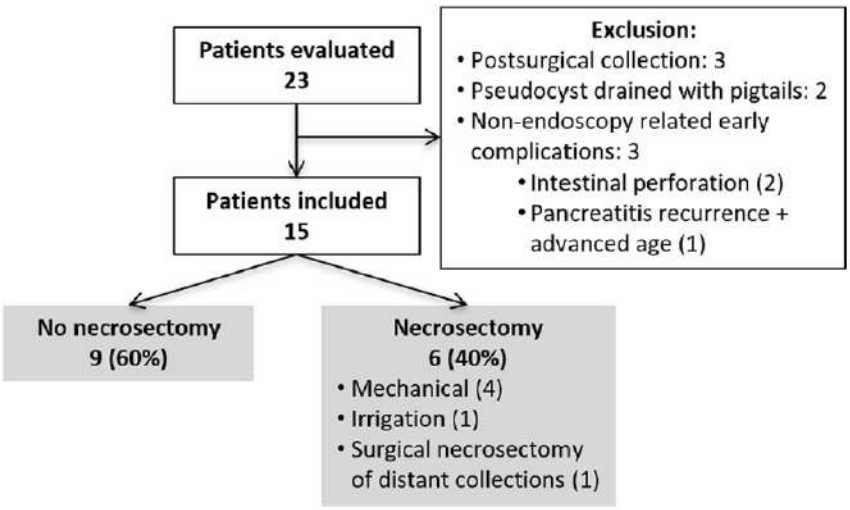

Fig. 1 Study flow chart

Table 1 Participants' demographic and clinical characteristics, and CT scan and endoscopic data

	General $N = 15$
General characteristics	
Sex, *n* (%)	
Male/Female	10 (67%)/5 (33%)
Age, (years)	75 (54-76)
Etiology, *n* (%)	
Biliary	7 (47%)
Alcohol	5 (33%)
Others	3 (20%)
Drainage indication, *n* (%)	
Infection	11 (73%)
Obstruction	4 (27%)
CT scan characteristics	
Collection morphology, *n* (%)	
Uniloculated	8 (53%)
Multiloculated	7 (47%)
Collection density, (Hounsfield units)	7 (4-14)
Signs of infection, *n* (%)	2 (13%)
Distant collections, *n* (%)	7 (47%)
Content appearance, *n* (%)	
Dense	5 (33%)
Liquid	3 (20%)
Mixed	7 (47%)
Collection size, mm	135 (105–140)
Necrotic content, %	20 (5–40)
Endoscopic characteristics	
Stent size, *n* (%)	
15 × 10	12 (80%)
10 × 10	2 (13%)
8 × 8	1 (7%)
Pigtail intrastent, *n* (%)	3 (20%)
Immediate adverse events, *n* (%)	1 (7%)

Endoscopy procedure features and adverse events

EUS-guided drainage was performed 35 days (IQR 15-46) after the onset of acute pancreatitis. The largest collection size in the CT scan had a median of 135 mm (IQR 105-140). Most collections, 11 (73%), were drained with a 15 × 10 LAMS. An additional pigtail was deployed inside the stent in 3 cases (20%). All drainages were performed through a transgastric route.

Complicated WOPN was solved endoscopically in 14 (93.3%). The other patient required surgical necrosectomy from a distant left pararenal collection. Nevertheless, the LAMS was maintained in place despite surgery and the retrogastric collection solved with the endoscopic treatment. Two patients in the necrosectomy group additionally received transparietal drainage with a pigtail of a distant pararenal collection.

Eight unexpected events were recorded in 7 patients (46.7%). One was immediate (7%) as the stent migrated to the gastric cavity during deployment but was relocated during the same procedure. In five patients, the infection relapsed due to stent obstruction. These patients were treated with necrosectomy. One patient requiring necrosectomy presented upper acute bleeding due to the formation of a pseudoaneurysm (7%) on day 36. This occurred two weeks after the necrosectomy sessions were completed so the event was related to the presence of LAMS rather than to the necrosectomy itself. The event was solved with embolization of the gastroepiploic artery. The last patient was the one that required surgery due to infection of distant collections.

Necrosectomy

Six patients (40%) required necrosectomy (five endoscopic and one surgical). The first session was performed due to hemodynamic instability or recurrent fever after a median of 27 days (IQR 12.5-61). Four sessions (IQR 2.5-7.5) were needed to complete treatment. For the endoscopic cases, in four the necrosectomy was performed extracting debris, mainly with snares. The remaining patient required only one session of necrosectomy with irrigation.

Table 2 shows the characteristics of patients requiring and not requiring necrosectomy, and the association of each factor with the need for necrosectomy. The percentage of necrosis in the collection detected in the previous CT scan (45 [35–66]% vs 10 [5–7]%, $p = 0.001$) predicted the need for necrosectomy in the univariate analysis. Additionally, the size of the largest collection (140 [131–148] mm vs 115 [87–140] mm) was close to statistical significance. As it was considered a possible confounder factor, it was included in the multivariate analysis. However, only the percentage of necrosis in the collection predicted the need for necrosectomy in the multivariate analysis (OR 1.18 [CI95% 1.01–1.39]; $p = 0.043$). Five of the 6 patients requiring necrosectomy presented a percentage of necrosis ≥ 40%, but only one in the other group ($p = 0.01$). Patients were discharged after 21 days (IQR 7-56 days).

The median time between stent deployment and retrieval was 115 days (IQR 62-140). We did not observe collection relapse in a follow-up of 51 (IQR 31-62) months.

Discussion

In the present study, the success rate for the endoscopic treatment of WOPN with LAMS was high and the incidence of severe adverse events was low. Additionally, we observed that necrosectomy was needed in 40% of the

Table 2 Characteristics of patients requiring and not requiring necrosectomy, and the association of each factor with the need for necrosectomy

	Necrosectomy $n = 6$	No necrosectomy $n = 9$	Univariate OR (95%CI) p	Multivariate OR (95%CI) p
General characteristics				
Sex, n (%)			1 (0.11–8.95) 1	
Male	4 (67%)	6 (67%)		
Female	2 (33%)	3 (33%)		
Age, years	75 (64–76)	62 (52–83)	1.02 (0.94–1.10) 0.64	
Etiology, n (%)			– – 0.53	
Biliary	2 (33%)	5 (56%)		
Alcohol	2 (33%)	3 (33%)		
Others	2 (33%)	1 (11%)		
Drainage indication, n (%)			1.75 (0.17–17.69) 1	
Infection	4 (67%)	7 (78%)		
Obstruction	2 (33%)	2 (22%)		
CT scan characteristics				
Collection morphology, n (%)			– – 1	
Uniloculated	3 (50%)	5 (56%)		
Multiloculated	3 (50%)	4 (44%)		
Collection density, (Hounsfield Units)	9.5 (3.9–18)	5.7 (4–12.5)	1.06 (0.90–1.26) 0.48	
Largest collection size, (mm)	140 (131–148)	115 (87–140)	1.06 (0.99–1.13) 0.1	0.96 (0.93–1) 0.052
Signs of infection, n (%)	1 (17%)	1 (11%)	– – 1	
Distant collections, n (%)	4 (67%)	3 (33%)	4.0 (0.45–35.8) 0.32	
Content appearance, n (%)			– – 0.24	
Dense	3 (50%)	2 (22%)		
Liquid	0	3 (33%)		
Mixed	3 (50%)	4 (44%)		
Necrotic content, %	45 (35–66)	10 (5–18)	1.13 (1.01–1.27) 0.034	1.18 (1.01–1.39) 0.043
Endoscopic characteristics				
Stent size, n (%)			– – 0.29	
15 × 10	6 (100%)	6 (67%)		
10 × 10	0	2 (22%)		
8 × 8	0	1 (11%)		
Pigtail intrastent, n (%)	1 (17%)	2 (22%)	0.70 (0.05–10.01) 1	
Intraprocedural adverse events, n (%)	1 (17%)	0	– – 0.40	

patients, with the percentage of necrosis in the collection in the previous CT scan being the only factor that could predict the need for necrosectomy.

LAMS are increasingly being used to treat complicated WOPN. Several series have described a high success rate, with over 90% of cases, with this treatment [15, 16]. Our study confirms these results as the treatment was ineffective only in patients with severe early complications from the pancreatitis presenting soon after drainage, and not related to the technique, or those with distant disconnected collections. These patients required surgery. Endoscopic management was successful in all the other patients.

The need for necrosectomy in 40% of patients is similar to the figures in other series. In one large multicenter analysis that included 328 patients, necrosectomy was used in 34.8% of patients [17]. In contrast, regardless of the clinical course, other authors defend the use of necrosectomy during the initial drainage or 2 or 3 days after the initial drainage [18, 19]. However, necrosectomy is an aggressive procedure with an elevated risk of complications. One multicentric Japanese series including 57 patients reported an incidence of 33% of adverse events related to necrosectomy, including death in 11% [20]. Bleeding was the most frequent event (58%). Additionally, a systematic review including 260 patients reported an incidence of procedure-related morbidity of 27% [21]. In consequence, as others previously suggested [22], to diminish the risks associated with necrosectomy we prefer to wait for clinical evolution and delay its use until clinically needed. Nevertheless, this practice might delay patient recovery. Two patients in our study initiated necrosectomy at a very late stage after the initial drainage, one on day 71 and one on day 58. If it had been performed immediately after the initial drainage, the time to recovery would probably have been much shorter.

To avoid the risks related to necrosectomy without delaying recovery, the ability to predict which patients will require necrosectomy could improve clinical practice. We evaluated multiple factors possibly associated with the need for necrosectomy, but only a higher percentage of necrosis in the collection detected in the previous CT scan was predictive (Fig. 2). This factor has also previously been suggested as a predictor [23]. Nevertheless, several types of stents, including plastic or biliary metallic stents were used in that study. Our study confirms this finding in patients treated exclusively with LAMS. While our data is limited and prospective larger studies are needed, collections with a percentage of necrosis > 40% in the CT scan could be considered for direct necrosectomy.

It has been suggested that the use of LAMS might increase the risk of reinfection due to obstruction of the stent [24, 25]. This is attributed to the fact that faster drainage might increase the impact of dense necrosis, eventually obstructing the stent. Nevertheless, with the introduction of larger stents and easier one-step drainage systems, we may be able to treat more complex collections, with a denser component, and decrease the incidence of obstruction. This aspect should be clarified in further comparative clinical trials.

Another concern with LAMS is the possibility of delayed complications such as bleeding or buried LAMS. Two retrospective case series including over 300 PFCs have reported bleeding rates of 3.9–7.2% [17, 24] but rates below 2% have been found in other large retrospective case series [25]. However, this adverse event can be fatal [26]. One study reported an incidence of delayed bleeding of

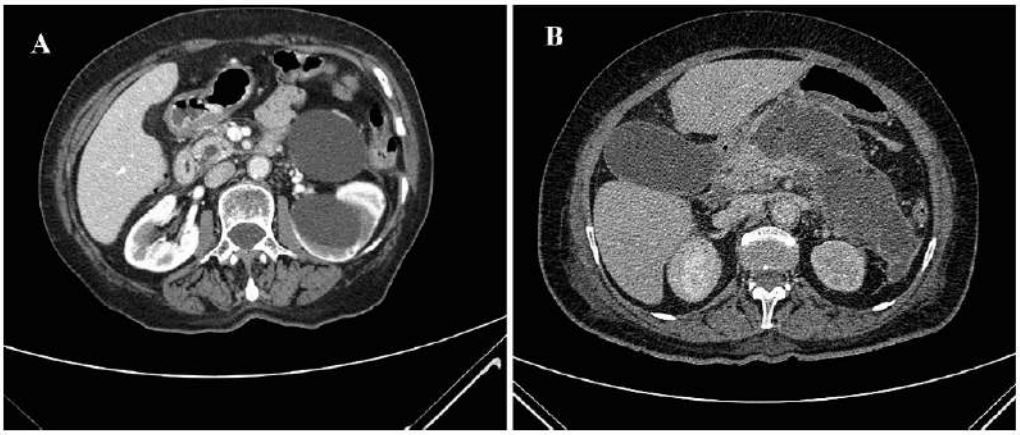

Fig. 2 CT scan images of two patients with walled-off pancreatic necrosis. Image **A** reveals a low content of necrosis, characterized by a collection with regular and well-defined margins and content mainly homogeneous. Image **B** shows a characteristic image of a collection with high volume of necrosis, with irregular shape and content mainly heterogeneous

15.5%, mainly due to the formation of a pseudoaneurysm [27]. Additionally, an interim analysis of a prospective randomized study reported adverse events in 50% of the 12 first patients treated with LAMS, half of them due to pseudoaneurysm bleeds. This finding led to a change in the study protocol, including early CT scan and removal of the stent if collections were solved at 3 weeks. A reduction in the adverse event rate was subsequently observed [28]. We also observed a case of bleeding due to a pseudoaneurysm more than a month after LAMS deployment. In consequence, we routinely carefully assess for the presence of vessels around the cavity, revising the CT scan and the EUS prior to drainage. If large vessels are in contact or close to the drained collection, we evaluate drainage with plastic stents or we perform an early CT scan follow-up to evaluate the relation of the stent to the vessels and discuss its early retrieval.

The main strength of this study is that it evaluated the efficacy of EUS drainage and the factors associated with the need for necrosectomy specifically in patients treated with LAMS. Predicting the need for necrosectomy might have several benefits: first, it might shorten the evolution of the disease and hospital stay. Second, it could avoid necrosectomy and its risks in patients who do not benefit from this aggressive procedure. Third, it might be an indication to use larger stents, such as the recently developed LAMS with diameters as large as 20 mm. Furthermore, it could give clinicians greater confidence to discharge patients with a lower risk of reinfection.

The study also has its limitations. First, the relatively low number of cases may reduce the reliability of the multivariable analysis. Second, the retrospective evaluation of the factors possibly related to the need for necrosectomy could perhaps bias the results. Nevertheless, the radiologist and the endoscopist who evaluated the CT scan and the EUS were blinded to each patient's outcome. And third, the evaluation of EUS static images limits the interpretation of possible factors associated with the ultrasonographic aspect.

In conclusion, one-third of patients with symptomatic WOPN drained with LAMS needed endoscopic necrosectomy and only one required concomitant surgical necrosectomy, which means high efficiency of the procedure. A high percentage of necrosis in the collection detected in the previous CT scan seems to predict the need for necrosectomy, and might be helpful to schedule early necrosectomy or to indicate the use of larger diameter stents.

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Compliance with ethical standards

Disclosures Drs. Laura González-González, Sergio Bazaga, Marianette Murzi, Anna Brujats, Mireia Trias, Beatriz de Riba, Raffaella Romito, Juan Colán-Hernández, Mar Concepción, Jordi Gordillo, Juan Carlos Pernas, Maria Poca, German Soriano, and Carlos Guarner-Argente have no conflicts of interest or financial ties to disclose.

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11.3.3. Publicación 3

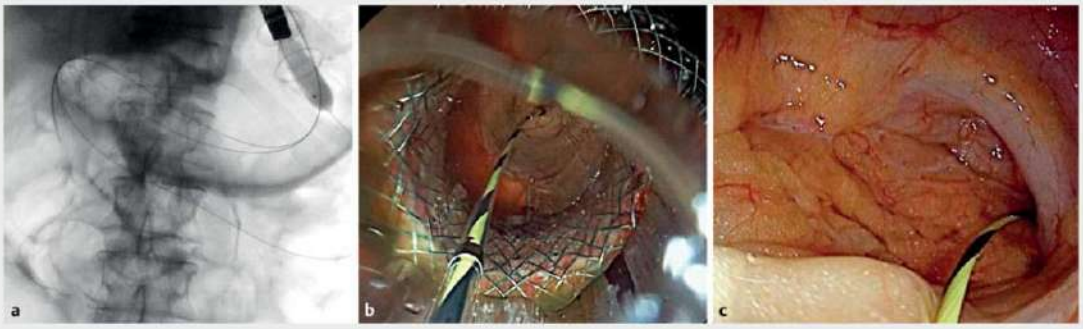
Intraperitoneal endoscopic salvage using an enteral stent for a misdeployed lumen-apposing metal stent during endoscopic ultrasound-guided gastroenterostomy.

Bazaga S, Garcia-Sumalla A, Laquente B, Gornals JB.

Endoscopy 2022; 54: E232-3.

E-Videos Thieme

Intraperitoneal endoscopic salvage using an enteral stent for a misdeployed lumen-apposing metal stent during endoscopic ultrasound-guided gastroenterostomy

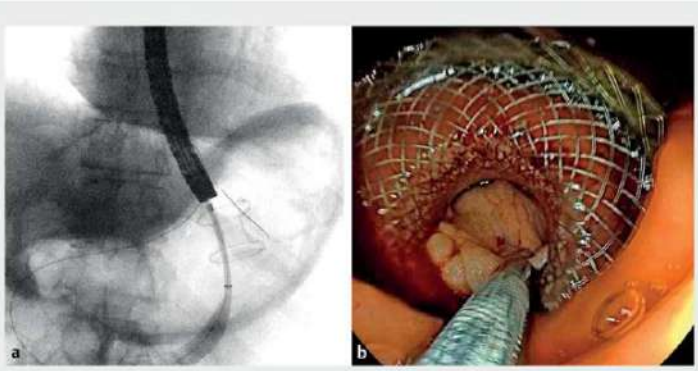


▶ **Fig. 1** Images showing: **a, b** dilation of a misplaced lumen-apposing metal stent (LAMS) to allow the scope to be passed into the peritoneum; **c** peritonoscopy being performed through LAMS with the intention of identifying the point of entry of the guidewire inside the bowel.

A 57-year-old man with duodenal carcinoma and a biliary self-expandable metal stent (SEMS) presented with gastric outlet obstruction and an endoscopic ultrasound (EUS)-guided gastroenterostomy was proposed.

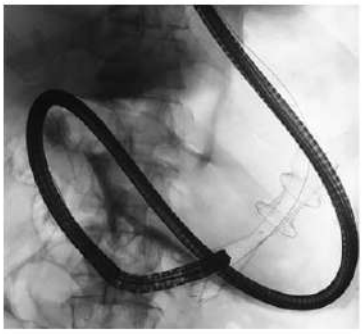
After the bowel had been dilated up to 15 mm to allow the gastroscope to be passed across the duodenum, loops of the small bowel were distended with 1 L of saline mixed with methylene blue, using the water-jet channel. A small-bowel loop was then accessed using the freehand technique with the delivery system of an electrocautery-enhanced lumen-apposing metal stent (LAMS; Hot AXIOS; 20×10 mm). During advancement of the preloaded guidewire, the bowel loop became tented away and the EUS window was lost, so the distal flange was deployed with concerns of possible misplacement. After deployment of the proximal flange, no flow of blue fluid was noted.

The peritoneal cavity was identified endoscopically through the LAMS and the echoendoscope was exchanged for a therapeutic gastroscope. The guidewire tip, located in the duodenum, was stretched to the outside with the purpose of stabilizing the bowel. Balloon expansion of the LAMS up to 15 mm allowed the gastroscope to be passed into the peritoneal cavity using the LAMS as a trocar. Peritonoscopy was performed under fluoroscopy guidance and the entry point of the guidewire into the bowel was identified (▶ **Fig. 1**). Dilation of the enteral wall up to 8 mm facilitated the advancement of a fully covered SEMS (Niti-S EnteralColonic; 20×80 mm; Taewoong Medical) through the LAMS. These technical aspects prevented the risk of tenting away of the bowel loop and loss of the guidewire. Enterography confirmed that the enteral stent was well positioned though the misplaced LAMS, allowing a correct deployment of the rescue stent under fluoroscopy and endoscopy guidance (▶ **Fig. 2**). Lastly, the distal end within the duodenum was checked, and an antimigratory clip was fixed (▶ **Fig. 3**; ▶ **Video 1**).

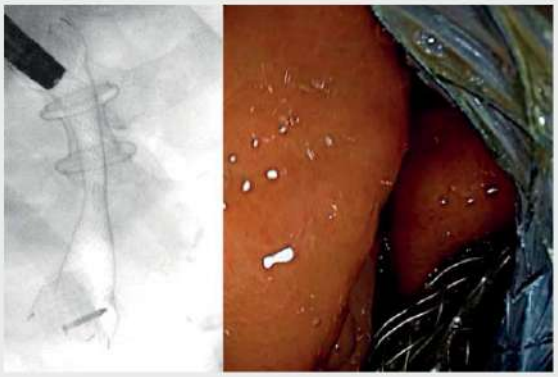


▶ **Fig. 2** Views of the enteral fully covered self-expandable metal stent deployed within the misplaced lumen-apposing stent to create a bridge between the small bowel and the stomach on: **a** fluoroscopy; **b** endoscopy.

Bazaga Sergio et al. Intraperitoneal endoscopic salvage… Endoscopy 2022; 54: E232–E233



▶ **Fig. 3** Fluoroscopic image showing the distal end of the enteral stent being checked from the duodenum.



Video 1 Intraperitoneal endoscopic salvage using an enteral stent for a lumen-apposing metal stent that was misdeployed during the creation of an endoscopic ultrasound-guided gastroenterostomy.

Several rescue options have been previously presented for gastroenterostomy [1–5]. If the wire access to the target loop is not preserved, LAMS misdeployment can require natural orifice transluminal endoscopic surgery (NOTES) or conventional surgery. If the guidewire is secure, a second enteral SEMS can be deployed safely under peritonoscopy and fluoroscopy guidance.

Endoscopy_UCTN_Code_CPL_1AL_2AG

Competing interests

J. B. Gornals is a consultant for Boston Scientific. The remaining authors declare that they have no conflict of interest.

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11.3.4. Publicación 4

EUS-guided biliary rendezvous as an emergent rescue after failed choledochoduodenostomy using a lumen-apposing metal stent.

Garcia-Sumalla A, **Bazaga S**, Gornals JB.

VideoGIE 2021; 6: 263-5.

VIDEO CASE REPORT

EUS-guided biliary rendezvous as an emergent rescue after failed choledochoduodenostomy using a lumen-apposing metal stent

Albert Garcia-Sumalla, MD,[1] Sergio Bazaga, MD,[1] Joan B. Gornals, MD, PhD[1,2]

A 60-year-old man with pancreatic cancer and liver metastases who had been referred previously for biliary drainage was recommended palliative oncologic treatment. After a failed transpapillary attempt via ERCP, same-session EUS-guided biliary drainage was chosen. On EUS examination, a minimally dilated common bile duct (CBD) up to 9 mm was identified from the duodenal bulb. An EUS-guided choledochoduodenostomy (CDS) using a lumen-apposing metal stent with an electrocautery-enhanced delivery system (EC-LAMS) (8 × 8 mm, HotAxios; Boston Scientific, Marlborough, Mass) was performed from a long-scope position using a free-hand plus preloaded guidewire technique.

The cautery-enabled catheter was advanced less than 1 finger's width at too perpendicular an angle, hitting the opposite CBD wall. The guidewire could not be inserted deeply, making a loop at the level of the CBD's access. Deployment of both flanges appeared to be correct, but an EUS image detected a partial malposition of the internal flange. Attempts at advancing the guidewire in an upward/downward direction (failed rendezvous [RV] approach) were unsuccessful, and the LAMS was removed.

Because the CBD was still dilated, a second attempt at EUS-guided CDS using a smaller EC-LAMS (6 × 8 mm, HotAxios) was made. However, this technically failed because of a considerable amount of bile between the CBD and

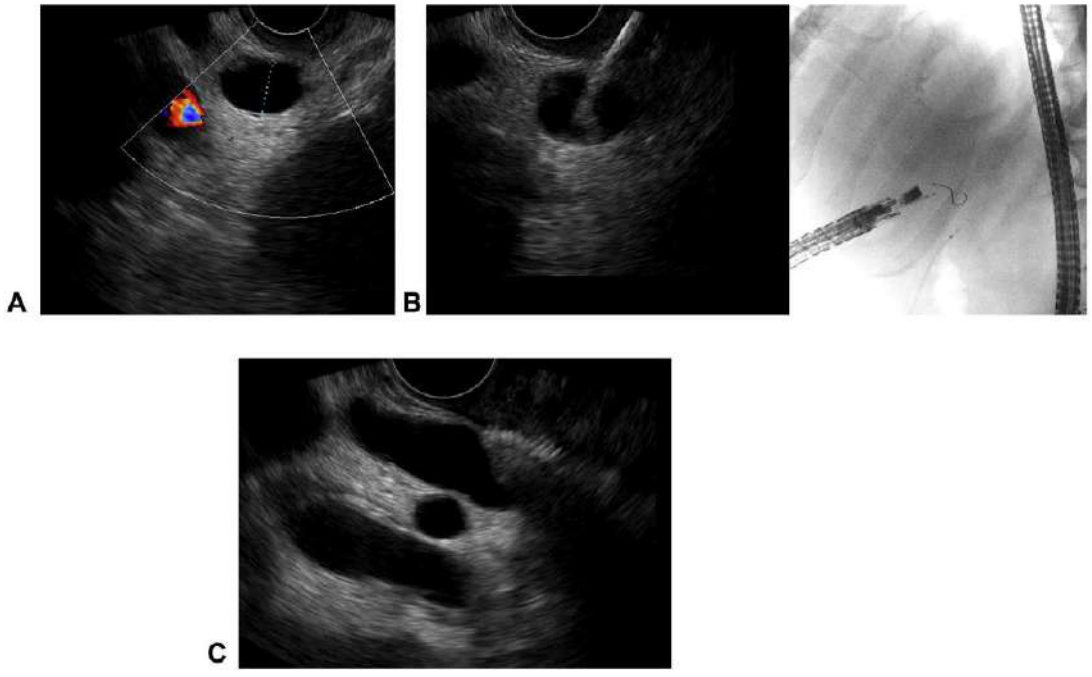

Figure 1. A, Failed EUS-guided choledochoduodenostomy using a lumen-apposing metal stent with an electrocautery-enhanced delivery system (8 × 8 mm, HotAxios) and a free-hand plus preloaded guidewire technique. The common bile duct was barely dilated. **B,** The cautery-enabled catheter was advanced into the common bile duct, but the guidewire could not be inserted deeply. **C,** EUS image detected a partial malposition of the internal flange of the lumen-apposing metal stent.

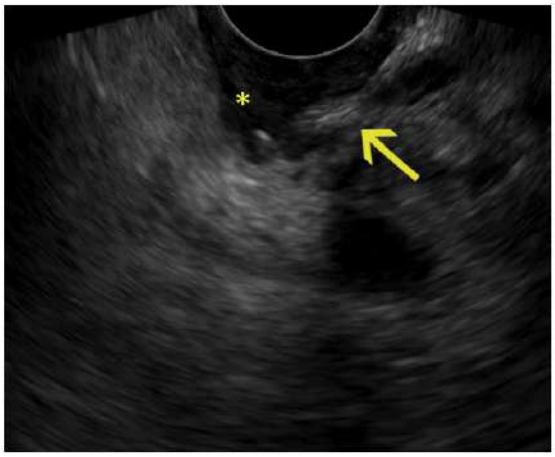

Figure 2. A second attempt at EUS-guided choledochoduodenostomy using a smaller lumen-apposing metal stent with an electrocautery-enhanced delivery system (6 × 8 mm, HotAxios) technically failed because of a considerable amount of bile between the common bile duct and the duodenal wall. Accumulated bile (*asterisk*); dislodged distal flange (*arrow*).

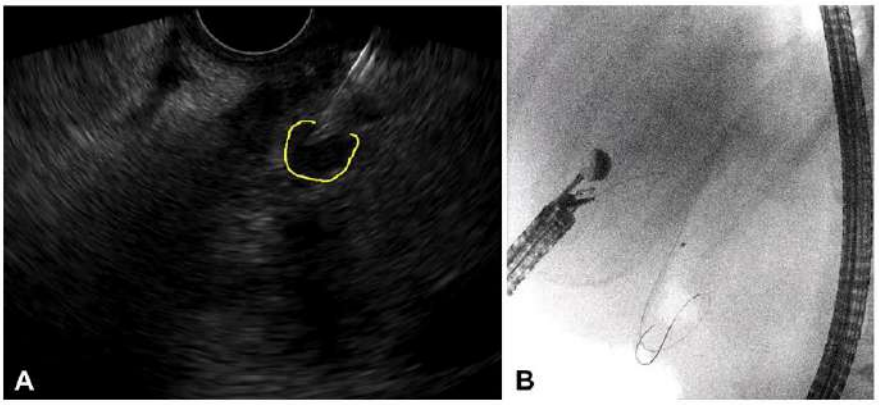

Figure 3. A, EUS-guided rendezvous as an emergent rescue was performed with an EUS-guided puncture of the common bile duct using a 19-gauge, 0.025-inch guidewire. **B,** Successful guidewire insertion across the tumor and papilla.

duodenal wall. An EUS-guided RV as an emergent rescue was performed using a 19-gauge, 0.025-inch guidewire. This maneuver was technically demanding because of the small CBD diameter, but it was possible to advance a guidewire through the papilla until it reached the duodenum. Finally, a fully covered metal stent was inserted, sealing the disruption of the CBD wall (Figs. 1 to 3; Video 1, available online at www.giejournal.org). The patient underwent the procedure well without severe consequences and died 4 months later because of advancement of his illness.

Adverse events after EUS-CDS using EC-LAMS are possible, and a CBD <15 mm has been reported as a risk factor for technical failure.[1-3] Knowledge of endoscopic rescue options (EUS-guided RV, coaxial SEMS) is crucial to resolve potentially serious unplanned events, such as a failed EUS-CDS using a LAMS (Video 1).[4]

DISCLOSURE

Dr Gornals is a consultant and paid speaker for Boston Scientific. All other authors disclosed no financial relationships.

Abbreviations: CBD, common bile duct; CDS, choledochoduodenostomy; EC-LAMS, lumen-apposing metal stent with an electrocautery-enhanced delivery system; RV, rendezvous.

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11.3.5. Publicación 5

Lumen apposing metal stents versus tubular self-expandable metal stents for endoscopic ultrasound-guided choledochoduodenostomy in malignant biliary obstruction.

de Benito Sanz M, Nájera-Muñoz R, de la Serna-Higuera C, Fuentes-Valenzuela E, Fanjul I, Chavarría C, García-Alonso FJ, Sanchez-Ocana R, Carbajo AY, **Bazaga S**, Perez-Miranda M.

Surgical Endoscopy 2021; 35: 6754-62.

Lumen apposing metal stents versus tubular self-expandable metal stents for endoscopic ultrasound-guided choledochoduodenostomy in malignant biliary obstruction

Marina de Benito Sanz[1] · Rodrigo Nájera-Muñoz[1] · Carlos de la Serna-Higuera[1] · Esteban Fuentes-Valenzuela[1] · Ignacio Fanjul[1] · Carlos Chavarría[1] · Francisco Javier García-Alonso[1] · Ramón Sanchez-Ocana[1] · Ana Yaiza Carbajo[1] · Sergio Bazaga[1] · Manuel Perez-Miranda[1]

Received: 8 July 2020 / Accepted: 15 November 2020

Abstract

Background and aims EUS-guided choledochoduodenostomy (EUS-CDS) is an effective option for biliary drainage in malignant biliary obstruction. Lumen apposing metal stents (LAMS) are increasingly been used for EUS-CDS. It is unknown how LAMS compare to tubular self-expandable metal stents (SEMS) for EUS-CDS. Our aim is to compare the clinical outcomes of LAMS versus SEMS for EUS-CDS.

Patients and methods Single-center retrospective cohort study of consecutive patients with unresectable malignant biliary obstruction who underwent EUS-CDS after failed ERCP for initial biliary drainage between 2011 and 2019. Clinical outcomes were compared between patients who had conventional covered SEMS and LAMS placed for EUS-CDS. Outcome measures included unplanned procedural events, technical success, clinical success, adverse events and reinterventions. Survival was analyzed by the Kaplan–Meier method.

Results During the study period 57 patients met inclusion criteria (37 LAMS, 20 SEMS). All EUS-CDS were technically successful (LAMS group 95% CI 90.3–100%, SEMS group 95% CI 83.2–100%). There were no differences between groups in unplanned procedural events (4 LAMS deployment issues, 2 mild bleeding in SEMS group; 10 vs 10.8%), clinical success (37/37 [100%] vs 19/20 [95%]), and short-term adverse events (5/37 [13.5%] vs 4/20 [20%], $p=0.71$). Complete follow-up data were available in 41 patients for a mean of 376 ± 145 days. Endoscopic reintervention was required for duodenal stent placement ($n=9$) or biliary stent dysfunction ($n=4$), with no difference between LAMS and SEMS group (6/37 [16.2%] vs 7/20 [35%]). There were no differences in overall survival between both groups.

Conclusions EUS-guided choledochoduodenostomy after failed ERCP has equally high technical and clinical success rates with either LAMS or SEMS in patients with malignant biliary obstruction. No differences in adverse events, reinterventions and survival were seen with either type of stent. The cost-effectiveness of LAMS vs SEMS for EUS-guided choledochoduodenostomy remains to be proven.

Keywords Lumen apposing metal stent (LAMS) · Biliary drainage (EUS-BD) · EUS-guided choledochoduodenostomy · Malignant biliary obstruction · Self-expandable metal stent (SEMS)

Malignant tumors involving the bile duct typically present with obstructive jaundice. Persistent obstructive jaundice impairs patient quality of life and may potentially lead to serious complications, including liver and renal failure [1].

Although surgical resection is the only curative treatment, a minority of patients with pancreatobiliary malignancies undergo resection, because tumor stage or patient comorbidities often preclude surgery. In most cases of malignant biliary obstruction, palliative biliary drainage is the required treatment approach. Endoscopic retrograde cholangiopancreatography (ERCP) is well established as the preferred non-operative modality for biliary drainage because of a high technical success rate and acceptable adverse event rate [2].

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When ERCP cannulation fails or when retrograde endoscopic biliary access is precluded by duodenal strictures or surgically altered anatomy, percutaneous transhepatic biliary drainage (PTBD) or surgical bypass are the traditional alternative drainage methods. However, PTBD and bypass surgery are both associated with marked adverse event rates. Over the last three decades, the palliative role of surgery and PTBD in malignant biliary obstruction has declined in favor of less invasive endoscopic approaches. In addition to ERCP, endoscopic ultrasound-guided biliary drainage (EUS-BD) has emerged as an effective modality for biliary drainage [3, 4]. EUS-BD has increasingly been performed as an alternative to PTBD in patients with unresectable malignant biliary obstruction and failed ERCP [3]. Technical and clinical success rates over 90% have been reported for EUS-BD [5]. However, the adverse event rate is significant (26%) and there is a small but definite mortality risk (0.4%) [5]. This high adverse event rate is thought to reflect the learning curve of EUS-BD, the heterogeneity of techniques used, and the lack of dedicated accessories. EUS-BD includes several approaches involving intrahepatic or extrahepatic biliary access combined with transmural or transpapillary stent placement [6]. EUS-guided choledochoduodenostomy (EUS-CDS) is among the most commonly taken EUS-BD approaches for distal malignant biliary obstruction.

In the last few years, efforts to facilitate EUS-BD and to decrease the risk of adverse events have led to the development of dedicated accessories. A lumen apposing metal stent (LAMS) specifically designed to create anastomoses to the gastrointestinal tract has become available for EUS-CDS, following its widespread dissemination for EUS-guided drainage of pancreatic collections and the gallbladder. LAMS have largely replaced other stent choices for EUS-guided gallbladder drainage in patients with acute cholecystitis unfit for surgery [7, 8]. Recent reports of EUS-CDS using a dedicated biliary LAMS show promising results [9–14] Single-step (free-hand) or single-exchange (over-the-wire) LAMS insertion is possible using an electrocautery enhanced delivery system, which appears to simplify EUS-CDS [11]. EUS-CDS with traditional tubular self-expandable metal stents (SEMS) however, involves multi-step dilation of the puncture tract. Even if LAMS insertion for EUS-CDS appears to be simpler than traditional SEMS insertion, there remain concerns over the long-term patency of LAMS placed for EUS-CDS. The overall reported adverse event rate of EUS-CDS with LAMS may be as high as 37% in studies with longer follow-up [14]. To date, no comparative study between LAMS and conventional tubular SEMS for EUS-CDS is available. In this study we aimed to compare the safety and efficacy or LAMS versus SEMS for EUS-CDS in unresectable distal malignant biliary obstruction after failed ERCP.

Patients and methods

This is a single-center retrospective cohort study comparing the safety and efficacy of LAMS versus SEMS for EUS-CDS in the management of unresectable distal malignant biliary obstruction. The project was approved by the Institutional Review Board in February 2020. Dual informed consent for ERCP and EUS-BD was routinely obtained from patients with biliary obstruction or their families in our Unit. All authors had access to the study data and have reviewed and approved the final manuscript.

Patients

Patients were identified from a prospectively maintained single-center interventional endoscopy database. Consecutive patients who underwent EUS-CDS between January 2011 and January 2019 were identified. Patients with unresectable distal malignant biliary obstruction who underwent EUS-CDS with a metal stent (SEMS or LAMS) for biliary drainage because of previous failed ERCP were included for analysis. Patients with unresectable distal malignant biliary obstruction who underwent EUS-CDS because of stent dysfunction following prior ERCP with stent placement were excluded from the analysis.

Procedures

All procedures were performed by experienced endoscopists in an endoscopy suite with a therapeutic echoendoscope. All patients were sedated using endoscopist-directed intravenous administration of midazolam and propofol, unless critically ill. No patient received prophylactic antibiotics in our cohort. For the technique of EUS-CDS, the echoendoscope was passed into the duodenum to visualize common bile duct. A 19-gauge needle (Expect; Boston Scientific, Marlborough, Mass) preloaded with water-soluble contrast material was used to puncture the common bile duct and entry was confirmed by contrast material injection. The needle was flushed with saline solution, and a 0.035-inch or 0.025-inch, 450-cm long guidewire was passed into the common bile duct.

Commercially available fully covered SEMS either with (BCS Hanarostent, M.I.Tech, Seoul, Korea) or without (Wallflex, Boston Scientific, Marlborough, Mass, USA) internal antimigration flaps (Fig. 1) or LAMS (Axios and Hot Axios, Boston Scientific, Marlborough, Mass, USA) (Fig. 2) were used. Stents were inserted over-the-guidewire into the common bile duct and deployed transmurally within the duodenum under combined EUS, fluoroscopic and endoscopic visualization, as previously reported. The free-hand

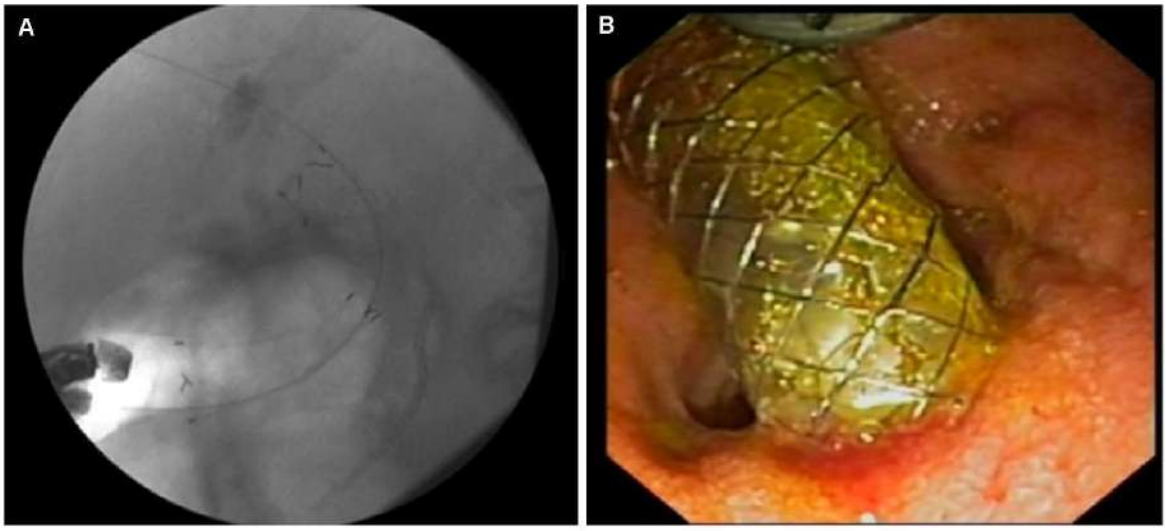

Fig. 1 EUS-guided choledocoduodenostomy using self-expandable metal stent. **A** Fluoroscopic view. **B** Final endoscopic appearance of stent deployed in the duodenal bulb

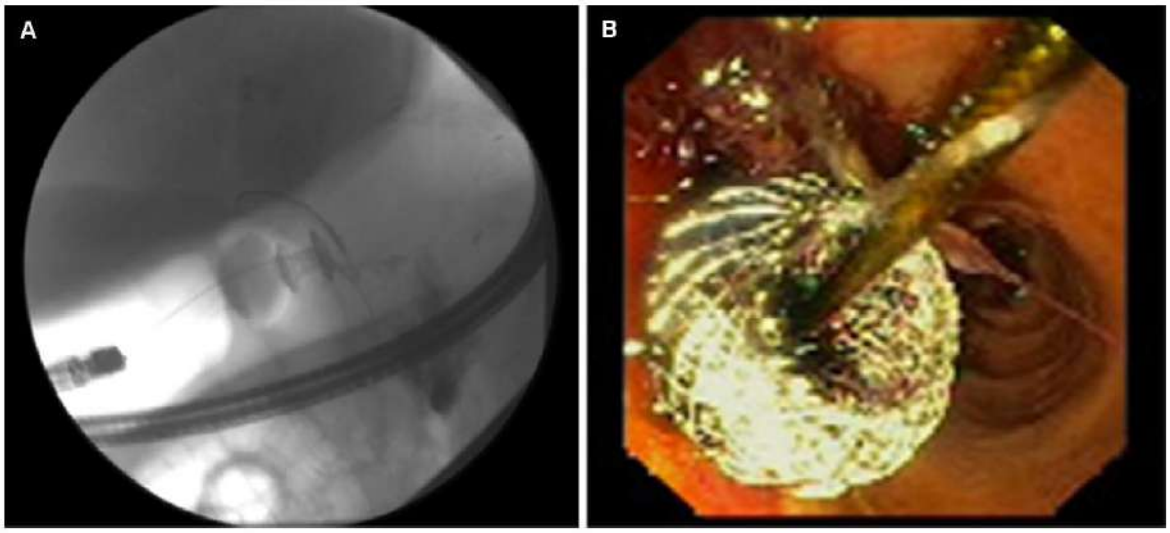

Fig. 2 EUS-guided choledocoduodenostomy using lumen apposing metal stent. **A** Fluoroscopic view. **B** Final endoscopic appearance of lumen apposing metal stent deployed in the duodenum

LAMS insertion technique was not routinely used in this cohort. Coaxial double pigtails stents were placed inside the SEMS or LAMS for additional anchorage at the discretion of the endoscopist. EUS-BD with SEMS was introduced in our center in September 2003 whereas LAMS was first placed for EUS-CDS in March 2012. There was a gradual shift from SEMS towards increased LAMS use, with no strict criteria for one stent type or another. However, technical factors, such a needle puncture within 2-cm of the hepatic duct confluence, or a guidewire taking a downward course, favored the choice of LAMS over SEMS. Conversely, when the common bile duct diameter was less than 12-mm, SEMS were preferred over LAMS for EUS-CDS.

Outcome measures

The main outcome measures were the technical success, clinical success and short-term adverse event rates. Our

secondary outcome measures were reintervention rates and patient survival.

Definitions

Technical success was defined as the correct transduodenal stent placement, with both ends of the stent (internal intraductal and external intraduodenal) properly placed and an adequate bile outflow verified by fluoroscopy and/or endoscopy.

Clinical success was defined as a 50% decrease in bilirubin from the last available pre-procedure value within 1 week (±2 days) following EUS-CDS or a serum bilirubin below 2 mg/dL within one month.

Unplanned procedural event was defined according to Teoh et al. [15] as any deviation in planned procedural steps, including but not limited to guidewire dislodgement and stent misdeployment, regardless of its impact on technical success or post-procedural adverse events.

Short-term adverse event was defined as any adverse event potentially related to the procedure within the first two weeks following EUS-CDS. Adverse events and their severity were defined and graded according to the ASGE lexicon [16].

Reintervention was defined as any therapeutic percutaneous or endoscopic procedure performed because of biliary or gastric outlet obstruction, bleeding, stent migration, regardless of the cause, whether underlying disease-related or stent-related.

Follow-up

Follow-up visits were performed at the discretion of the treating physician, with periodic clinic visits, laboratory analysis and imaging, as necessary.

Those patients who were followed-up until death or who had any clinical follow-up in the 4 months prior to December 2019 were defined as complete follow-up. Patients who did not meet either of these two criteria were defined as lost to follow-up.

Data retrieval

Data on baseline demographics, diagnosis, endoscopic procedures and technical details were retrieved from the prospective endoscopy database maintained at our center. Post-procedural follow-up data were retrospectively obtained from electronic medical records, including endoscopic and imaging procedures. Data from patients admitted to and cared for at outside medical centers who continued follow-up in these centers, were obtained by transfer of medical records, shared healthcare network electronic medical records, direct discussion with the attending physician and/or telephone interview with the patient. The available data were censored in December 2019.

Statistical analysis

Statistical analysis was performed using Stata (StataCorp. 2013. College Station, Texas). Categorical variables were described as percentages, continuous variables with normal distribution as mean and standard deviation, and continuous variables with non-normal distributions as medians and interquartile range.

Pearson's χ^2 test or Fisher's exact test (in case the expected frequencies in the contingency tables are less than 5) were applied to assess differences between the categorical variables.

Results

Patients included and baseline characteristics

Between January 2011 and January 2019, 57 patients (49.1% female, median age 81.4 years), with malignant biliary obstruction without an indwelling biliary stent and incomplete or failed previous ERCP underwent EUS-CDS in our Unit. The cause for ERCP failure was duodenal obstruction making the papilla inaccessible or significantly hampering cannulation of the papilla in 19 (33.3%), malignant involvement with distortion of the papilla in 16 (28.1%), and failed cannulation with ($n=15$; 26.3%) or without ($n=7$; 12.3%) pre-cut in the remaining.. Pancreatic adenocarcinoma was the most common underlying diagnosis (80.7%). Based on the American Society of Anesthesiology (ASA) classification 54.4% (31/57) of patients were ASA grades III or IV. Patient demographic data are shown in Table 1.

Table 1 Patients demographics

	LAMS (No. 37)	SEMS (No. 20)	*p*
Age, med (IQR)	81.8 (69.9–84.6)	80.2 (67.6–86.3)	0.97
Female sex, *n* (%)	17 (46%)	11 (55%)	0.51
Underlying disease, *n* (%)			0.40
Pancreatic adenocarcinoma	29 (78.4%)	17 (85%)	
Other	8 (21.6%)	3 (15%)	
ASA classification, *n* (%)			0.04
I/II	9 (24.3%)	11 (55%)	
III/IV	25(67.7%)	6 (30%)	
Not available	3 (8.1%)	3 (15%)	

LAMS lumen apposing metal stent, *SEMS* self-expandable metal stent, *ASA* American society of Anesthesiologists

Procedure description

EUS-CDS was performed during the same session of failed ERCP in all cases. Table 2 shows procedural details. All EUS-CDS (100%) were technically successful (LAMS group 95% CI 90.3–100%; SEMS group 95% CI 83.2–100%). A 10-mm diameter and 60-mm long fully covered SEMS was used in 17/20 patients. Stent sizes were not registered in the remaining three. SEMS with antimigration flaps were employed in 11 (55%) patients, and SEMS without antimigration flaps in 9 (45%). LAMS were employed in 37 cases, Hot Axios in 30 cases and (cold) Axios in the remaining 7, 5 of which were reported in a previous pilot study [9]. Coaxial double pigtail stents were placed through 22 of the 37 LAMS and through 13 of the 20 SEMS. In 19 patients with concurrent symptomatic gastric outlet obstruction, different types of uncovered duodenal metal stents were placed during the same hospital admission, either within the same session, or within 72-h of the EUS-CDS procedure.

Unplanned procedural events were registered in 6 cases. In two cases of SEMS insertion, self-limited mild bleeding was observed which required no treatment in one case and requiring adrenaline injection in another. LAMS-related unplanned procedural events were registered in 4 cases, including 2 distal flange dislodgements and 2 misdeployments. All these 4 LAMS-related unplanned procedural events were salvaged by insertion of a coaxial stent.

In the first two weeks after EUS-CDS, 9 patients (15.8%) had adverse events, 5 (13.5%; 95% CI 46.7–29.5%) in the LAMS group and 4 (20%; 95% CI 5.7–43.7%) in the SEMS group ($p=0.71$), with no significant differences between both groups. None of the patients presented post-procedure pancreatitis. Four patients, 2 in each group, developed mild cholangitis or cholecystitis. Two patients with LAMS and 1 patient with SEMS presented bile leakage requiring surgical revision and drainage placement. Thus, the incidence of severe short-term adverse events was 5.3% (3/57) overall.

Clinical success was achieved in 56 of these 57 patients (98.2% for the entire cohort), with no differences between patients with LAMS and SEMS (100% vs 95%, $p=$n.s).

Follow up

Forty-one patients had complete follow up. Patients with complete follow-up were followed for a mean of 376 ± 145 days. At the end of follow up, 6 patients with SEMS and 16 patients with LAMS had died from their underlying disease. One patient with SEMS and 5 with LAMS completed the follow up period without adverse events and were still alive at the end of data collection. 13 patients required reintervention during this period. There were no differences in overall survival between both groups.

Reintervention was required in 6 patients (16.2%; 95% CI 6.2–32%) in the LAMS group and 7 patients (35%; 95%CI 8.7–49.1%) in the SEMS group. All 13 patients were endoscopically managed. Five out of six LAMS patients who required reintervention and 4/7 SEMS patients developed symptomatic gastric outlet obstruction requiring duodenal stent placement. Additionally, one LAMS and three SEMS patients developed EUS-CDS dysfunction. The dysfunctional LAMS was managed by coaxial pig tail placement, as previously reported [17]. Two dysfunctional SEMS were converted to transpapillary stent placement by EUS-CDS stent removal and through-the-fistula antegrade guidewire passage (two-stage rendezvous). Obstruction due to an adherent clot secondary to delayed bleeding was managed

Table 2 Procedure description and outcomes

	LAMS (No. 37)	SEMS (No. 20)
Type, *n* (%)	Hot 31 (85.6%)	Hanaro: 11 (55%)
	Cold 7 (18.4%)	Wallflex 8 (40%)
		Bonastent 1 (5%)
Size (mm), *n* (%)	6×8 mm: 4 (10.8%)	60×10 mm: 17 (85%)
	8×8 mm: 27 (73%)	Not available: 3 (15%)
	10×10 mm: 5 (13.5%)	
	Not available 1 (2.7%)	
Coaxial pigtail, *n* (%)	22 (59.5%)	13 (65%)
Unplanned procedural events, *n* (%)	2 (5.4%) maldeployment	2 (10%) bleeding
	2 (5.4%) dislodgement	
Immediate adverse events, *n* (%)	1 (2.7%) cholangitis	1 (5%) cholangitis
	1 (2.7%) cholecystitis	1 (5%) cholecystitis
	2 (5.4%) bile leakage	1 (5%) bile leakage
	1 (2.7%) other	1 (5%) other
Clinical success, *n* (%)	36 (94.7%)	20 (100%)

LAMS lumen apposing metal stent, *SEMS* self-expandable metal stent

by coaxial pigtail insertion in the remaining case of EUS-CDS with SEMS dysfunction. There were no differences in reintervention rates between LAMS and SEMS groups.

Discussion

We retrospectively evaluated a large cohort of patients with distal malignant biliary obstruction and failed initial ERCP who underwent EUS-CDS, using SEMS or LAMS for biliary drainage. We found that stent placement was technically successful in all cases and that this closely translated into clinical success (jaundice resolution). Adverse events within two weeks of EUS-CDS, however, were not negligible at 15.8%. Reinterventions were required in 34% of patients with complete follow-up, largely due to new-onset gastric outlet obstruction ($n=9$), but also because of EUS-CDS dysfunction ($n=4$). We failed to find any evidence of the superiority of LAMS over SEMS for EUS-CDS in terms of technical success, clinical success, and adverse events. Conversely, the need for reintervention was not higher in LAMS versus SEMS, particularly reinterventions triggered by stent dysfunction.

Our data are consistent with previous studies on EUS-CDS reporting high technical and clinical success rates with either LAMS (Table 3) [9–14] or SEMS (Table 4) [18–25]. Despite the assumed easier stent placement of LAMS compared to SEMS or their potential for longer stent patency, this did not translate into any improved measurable clinical outcomes in our study. Given that the cost of LAMS is two to three times higher than that of SEMS, this lack of proven superiority raises concerns. The question of the relative performance of LAMS versus SEMS for EUS-CDS warrants further scrutiny, as EUS-BD is likely to play a greater role in the palliation of malignant biliary obstruction in the future. Three recent randomized trials comparing EUS-BD using SEMS to ERCP found similar technical and clinical success, with improved post-procedure adverse events and patient quality of life in the EUS-BD group [19, 22, 26]. In all these three randomized trials, EUS-CDS was performed with different types of covered SEMS.

There are several limitations to our study. As a retrospective study conducted at a single high-volume center over a relatively long timespan, inherent biases are present and lack of generalizability is a strong possibility. EUS-CDS had been performed with SEMS at our center for more than a decade before dedicated biliary LAMS became available. Thus, biliary LAMS may have greater impact on EUS-CDS outcomes in practice settings where endoscopists are less familiar with EUS-CDS with SEMS. Furthermore, no uniform type of LAMS (cautery enabled or not) or placement technique (over-the-wire or

Table 3 Endoscopic ultrasound-guided choledochoduodenostomy with lumen apposing metal stents

Study/year of publication	Study design/location	Etiology of distal biliary obstruction *n* malignant/*n* total (%)	Type of EC-LAMS	Size of EC-LAMS	Technical (%)/clinical (%) success	Early (%)/late (%) adverse events
El Chafic et al. (2019)	Retrospective Multi-center/North America	40/41 (97.5%)	EC-LAMS (Axios)	10 × 10 mm	38 (92.7%)/36 (87.8%)	4 (9.8%)/4 (9.8%)
Anderloni et al. (2019)	Retrospective Single-center/Europe	46/46 (100%)	EC-LAMS (Axios)	6 × 8 mm/8 × 8 mm/10 × 10 mm	43 (93.5%)/42 (91.3%)	1 (2.2%)/4 (8.7%)
Kunda et al. (2016)	Retrospective Multi-center/Europe	57/57 (100%)	LAMS + EC-LAMS (Axios)	6 × 8 mm/8 × 8 mm/10 × 10 mm/15 × 10 mm	56 (98.2%)/54 (94.7%)	4 (7%)/5 (8.8%)
Jacques et al. (2019)	Retrospective Multi-center/Europe	51/52 (100%)	EC-LAMS (Axios)	6 × 8 mm/8 × 8 mm/15 × 10 mm	46 (88.5%)/46 (88.5%)	2 (3.8%)/7 (13.5%)
Tsuchiya et al. (2018)	Prospective Multi-center/Asia	19/19 (100%)	EC-LAMS (Axios)	6 × 8 mm/8 × 8 mm	19 (100%)/18 (94.7%)	3 (15.8%)/5 (26.3%)
Jacques et al. (2020)	Retrospective Multi-center/Europe	63/70 (90%)	EC-LAMS (Axios)	6 × 8 mm/8 × 8 mm/15 × 10 mm	69 (98.6%)/69 (98.6%)	2 (2.8%)/7 (10%)
Total		276/285 (96.8%)			271 (98.1%)/265 (96%)	16 (5.8%)/32 (11.6)

LAMS lumen apposing metal stent, *EC-LAMS* electrocautery lumen apposing metal stent

Table 4 Endoscopic ultrasound-guided choledochoduodenostomy with self-expandable metal stents

Study/year of publication	Study design/location	Etiology of distal biliary obstruction *n* malignant/*n* total (%)	Type of stent	Size of stent	Technical (%)/ clinical (%) success	Early (%)/late (%) adverse events
Bang et al. (2018)	RCT (EUS-CD vs ERCP)/Single center/USA	33/33 (100%)	FCSEMS Viabil	8×60 mm	31 (90.9%)/32 (97%)	7 (21.2%)/1(3%)
Khashab et al. (2016)	Retrospective / Multi-center/ international	56/56 (100%) (4 plastic stents excluded)	FCSEMS	N.A	52 (93.3%)/48 (85.5%)	7 (12.5%)/7 (12.5%)
Paik et al. (2018)	RCT (EUS-BD vs ERCP)/Multi-center/South Korea	32/32 (100%)	FCSEMS	N.A	31 (96.9%)/29 (90.6%)	2 (6.3%)/1 (3.1%)
Iwashita et al. (2014)	Systematic review	97/97 (100%)	FCSEMS	N.A	91 (93.8%)/N.A	23 (23.7%)/N.A
Artifon et al. (2015)	RCT (EUS-HG vs EUS-CD)/ Single-center/ Brazil	24/24 (100%)	PCSEMS Wallflex	60×10 mm	22 (91.6%)/19 (79.2%)	4 (16.7%)/N.A
Cho et al. (2017)	Prospective / Single center/ Korea	33/33 (100%)	PCSEMS Hybrid metal stents (Standard Sci Tech Inc)	8 to 10 mm×5 to 10 cm	33 (100%)/33 (100%)	5 (15.2%)/5 (15.2%)
Poincloux et al. (2015)	Retrospective/ Single center/ Europe	27/27 (100%) (3 plastic stents excluded)	FCSEMS Wallflex Stent in stent [13]	10 mm×60 or 40 mm	26 (96.7%)/25 (93.1%)	3 (11.1%)/3 (11.1%)
Dhir et al. (2014)	Retrospective/ Multi-center/ India	68/68 (100%)	FCSEMS Wallflex	10 mm	65 (95.6%)/60 (88.2%)	6 (8.8%)/N.A
Total		370/370 (100%)			351 (94.5%)/ (90%)	57 (15.4%)/17 (9.4%)

SEMS self-expandable metal stent, *RCT* randomized clinical trial, *EUS-BD* endoscopic ultrasound-guided biliary drainage, *EUS-CD* endoscopic ultrasound-guided choledochoduodenostomy, *EUS-HG* endoscopic ultrasound-guided hepatico-gastrostomy, *ERCP* endoscopic retrograde cholangiopancreatography, *FCSEMS* fully covered self-expandable metal stent, *PCSEMS* partially covered self-expandable metal stent

free-hand) was used throughout the study period by the two operators involved. Earlier versions of the Axios stent may have been more prone to unplanned procedural events than subsequent, improved versions. The relative merits of each stent type in different patient subsets based on the degree of common bile duct dilation or other factors could not be analyzed. A significant proportion of patients referred from outside institutions lacked follow-up data, again introducing bias.

After EUS-CDS reintervention was necessary in 13 of the 38 patients with complete follow-up, mostly for duodenal stent placement (24%) and to a lesser extent for recurrent biliary obstruction (10%) Kunda et al. reported a reintervention rate of 9.3% in a 54 patients case series with LAMS EUS-CDS [9], which is comparable to our results. However, 75% of cases or recurrent biliary obstruction in our cohort occurred in SEMS patients. The placement of coaxial pigtails in 45/57 EUS-CDS might have contributed to prevent cholangitis caused by LAMS angulation in our series.

In conclusion, this is the first cohort of EUS-CDS in patients with unresectable distal malignant biliary obstruction and failed ERCP comparing clinical outcomes between SEMS and LAMS. Our study suggests equivalent outcomes for EUS-CDS for biliary drainage in patients with either type of stent in terms of technical or clinical success, unplanned procedural events, adverse events and reinterventions. As it has been the case with other interventional EUS procedures such as drainage of walled-off pancreatic necrosis, the superiority of LAMS over other type of stents has been difficult to prove [27]. Advantages of SEMS over LAMS include lower cost and their ability to be placed via CDS into the CBD even with lesser degrees of dilation. Advantages of LAMS over SEMS include one-step insertion with the attendant possibility -yet unproven- of increased procedural safety. Long-term outcomes with either type of stent also warrant further scrutiny, as changing management algorithms of malignant biliary obstruction increasingly tend to consider EUS-CDS for patients with longer life expectancy.

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Compliance with ethical standards

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11.4. COMUNICACIÓN EN CONGRESO

Lumen apposing metal stents related adverse events. Results from a nationwide prospective registry

S Bazaga, JR Aparicio, V Sanchiz, J Gornals, C Loras, R Pedraza, A Terán, E Vazquez-Sequeiros, J Vila, A Guardiola, C Guarner, C Huertas, F Garcia-Fernandez, B Bernad, A Perez, R Villanueva, F Gonzalez-Huix, I Pinto, A Vilella, JL Castro, J Colán, J Nuñez-Otero, JC Subtil, L Pérez-Carazo, I Couto, E Sanchez, F Uceda, B Martinez, FJ Garcia-Alonso, C de la Serna, M Perez-Miranda.

Endoscopy 2020; 52: S122-3.

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ESGE Days 2020 oral presentations
Saturday, April 25, 2020 11:00 – 13:00 EUS- guided therapy: From training to complications
Liffey Meeting Room 3

LUMEN APPOSING METAL STENTS RELATED ADVERSE EVENTS. RESULTS FROM A NATIONWIDE PROSPECTIVE REGISTRY

S Bazaga , JR Aparicio , V Sanchiz , J Gornals , C Loras , R Pedraza , A Terán , E Vazquez-Sequeiros , J Vila , A Guardiola , C Guarner , C Huertas , F Garcia-Fernandez , B Bernad , A Perez , R Villanueva , F Gonzalez-Huix , I Pinto , A Vilella , JL Castro , J Colán , J Nuñez-Otero , JC Subtil , L Pérez-Carazo , I Couto , E Sanchez , F Uceda , B Martinez , FJ Garcia-Alonso , C de la Serna , M Perez-Miranda

Aims: Describe the number, type and severity of adverse events associated to lumen-apposing metal stents (LAMS) in a real-life setting.

Methods: Multicenter prospective case series including all consecutive LAMS placed to access extraluminal structures between January-October 2019. Centralized follow-up was performed via standardized telephonic questionnaires, at 14 days and 3,6,9 and 12 months after placement or until LAMS removal. In case of positive or missing responses to the questionnaire, a query was raised to the local investigators, whose reports were evaluated by a commission for categorize event.

Results: A total of 283 procedures performed in 258 patients, median age: 69 years (IQR:59-82), 63% males from 27 centers, were included. Technical success was reached in 96%. Stent placement indications are summarized in Table 1. After a median follow-up of 71 (IRC:28-93) days, 128 (45.2%) stents retrieved, 52 patients (18.4%) died and 103 (36.4%) had their stent still in-situ. 62 LAMS related events were identified in 56 procedures (19.8%), 22 mild, 21 moderate, 16 severe and 3 deaths (digestive haemorrhage in walled-off-necrosis (WON) and 2 perforations, gastrojejunostomy and choledochoduodenostomy). Most frequent complications were haemorrhages (17 cases) and LAMs obstruction related infections (16 cases). Cumulative risk of LAMS related adverse events 3 months after deployment was 21.2%(16,5-27,2%), while the cumulative risk of severe/fatal events was 7.3%(4.6-11.4%). Overall, 3-month cumulative risks were higher in WONs, 31.3%(20.1-46.5%), and pseudocysts, 37.8%(21-61.5%), than in gallbladder drainages 6.2%(20.3-18.1%) or enteral anastomoses 18.6%(10.8-30.7%).

Conclusions: Our study shows an acceptable overall risks rate, although the 3 (0.9%) LAMS related deaths require further analysis of risk factors.

Table 1. Indications

Enteroanastomosis,n(%)	70(24.7%)
WON,n(%)	69(24.5%)
Gallbladder drainage,n(%)	52(18.4%)
Pseudocysts, n(%)	36(12.7%)
Others,n(%)	56(20%)

11.5. CERTIFICADO DE BECA

Junta de Castilla y León
Consejería de Sanidad

Sacyl
Gerencia Regional de Salud

RESOLUCIÓN DEL DIRECTOR GERENTE DE LA GERENCIA REGIONAL DE SALUD, POR LA QUE SE APRUEBA LA RELACIÓN DEFINITIVA DE PROYECTOS DE INVESTIGACIÓN EN BIOMEDICINA, GESTIÓN SANITARIA Y ATENCIÓN SOCIOSANITARIA SELECCIONADOS PARA DESARROLLAR EN LOS CENTROS DE LA GERENCIA REGIONAL DE SALUD DE CASTILLA Y LEÓN EN 2020.

Mediante Resolución de 7 de febrero de 2019, del Director Gerente de la Gerencia Regional de Salud, se convocaron las ayudas para la financiación de los proyectos de investigación en biomedicina, gestión sanitaria y atención sociosanitaria a desarrollar en los centros de la Gerencia Regional de Salud en 2020.

Las solicitudes presentadas fueron examinadas y evaluadas por la Comisión de Valoración con el asesoramiento técnico de la Agencia para la Evaluación de la Calidad del Sistema Universitario de Castilla y León (ACSUCYL), según los criterios objetivos que figuran en el resuelvo sexto de la convocatoria.

Con fecha 11 de septiembre de 2019, el Director General de Sistemas de Información, Calidad y Prestación Farmacéutica dictó la propuesta de resolución provisional, y se abrió un periodo de 10 días para formular alegaciones. Como consecuencia de ello, han formulado alegaciones los investigadores principales de los proyectos 1915/B/19, 1919/B/19, 1937/A/19, 2006/B/19, 2007/B/19, 2015/A/19 y 2019/A/19.

Las alegaciones formuladas fueron objeto de estudio por la Comisión de Valoración con el asesoramiento de ACSUCYL, lo que ha supuesto una modificación en la relación de los proyectos seleccionados.

En su virtud, y vista la Propuesta de Resolución dictada por el Director General de Sistemas de Información, Calidad y Prestación Farmacéutica,

RESUELVO

PRIMERO.- Aprobar la relación de proyectos de investigación en biomedicina, gestión sanitaria y atención sociosanitaria seleccionados para desarrollar en el año 2020, que se recogen en el anexo I, ordenados alfabéticamente según los apellidos del investigador principal.

El importe de la financiación será de novecientos ochenta mil doscientos cincuenta y cuatro euros (980.254,00€) con cargo a la aplicación presupuestaria 05.22.467B01.640.00 de los Presupuestos Generales de la Comunidad de Castilla y León para el año 2020, distribuidos en la forma detallada en el anexo I.

El importe correspondiente a viajes y dietas y a actividades de difusión de los resultados de la investigación, será el presupuestado con el límite máximo de 1.500,00€, de acuerdo con lo establecido en el resuelvo tercero, apartado 2, letra c) de la convocatoria.

Pso. de Zorrilla, 1 - 47007 Valladolid. Tel.: 983 32 80 00 - Fax: 983 41 23 05

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En el caso de producirse resultados de la investigación susceptibles de generar derechos de propiedad industrial o intelectual, su titularidad, gestión y explotación corresponderá a la Gerencia Regional de Salud. Todo ello sin perjuicio del derecho de los autores e inventores a ser mencionados como tales en los títulos de propiedad industrial o intelectual, y a participar en los beneficios derivados de la potencial explotación comercial de dichos títulos.

SEGUNDO.- No financiar los proyectos de investigación que se recogen en el anexo II, ordenados alfabéticamente según los apellidos del investigador principal, por haber obtenido menor puntuación en la evaluación científico-técnica que los seleccionados y haberse agotado el crédito presupuestario disponible.

TERCERO.- Excluir las solicitudes de los proyectos de investigación que se relacionan en el anexo III, ordenados alfabéticamente según los apellidos del investigador principal, porque el equipo investigador no cumple los requisitos establecidos en el resuelvo segundo de la convocatoria por alguno de los siguientes motivos:

a) El investigador principal no está vinculado laboralmente a la Gerencia Regional de Salud (apartado 1).
b) Más de un investigador pertenece a entidades no radicadas en Castilla y León (apartado 2).
c) El equipo investigador está constituido por más de un 50% de investigadores no pertenecientes a las Gerencias de Atención Especializada, Gerencias de Atención Primaria, Gerencia de Emergencias Sanitarias o centros dependientes de la Gerencia Regional de Salud que desarrollen actividad asistencial especializada (apartado 2).

CUARTO.- Estimar parcialmente las alegaciones formuladas por los investigadores principales de los proyectos 1915/B/19, 1937/A/19, 2006/B/19, 2015/A/19 y 2019/A/19. No obstante, los proyectos 1915/B/19, 1937/A/19, 2015/A/19 y 2019/A/19 no serán financiados al haber obtenido menor puntuación en la evaluación científico-técnica que los seleccionados.

QUINTO.- Desestimar las alegaciones presentadas a la propuesta de resolución provisional formuladas por los investigadores principales de los siguientes proyectos 1919/B/19 y 2007/B/19.

Valladolid, 21 de noviembre de 2019
EL DIRECTOR GERENTE DE LA
GERENCIA REGIONAL DE SALUD

Junta de Castilla y León · GERENCIA REGIONAL DE SALUD · DIRECTOR GERENTE · Sacyl · Consejería de Sanidad

Manuel Mitadiel Martínez

Junta de Castilla y León
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ANEXO I

Proyectos de investigación seleccionados.

GRS 1992/A/19	REGISTRO NACIONAL DE INCIDENCIAS DE LAS PRÓTESIS DE APOSICIÓN LUMINAL TIPO AXIOS	PÉREZ-MIRANDA CASTILLO, MANUEL	HOSPITAL UNIVERSITARIO RÍO HORTEGA	**12.679 €**