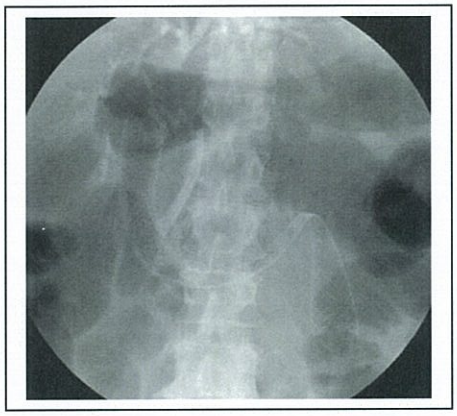
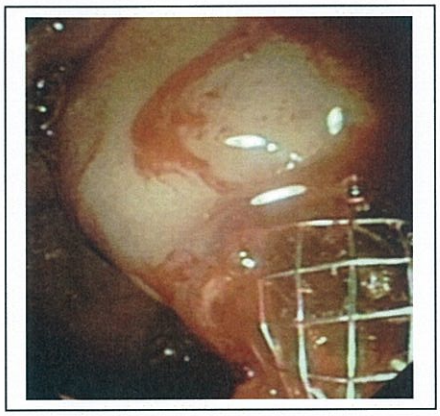
2012

JORGE MANUEL TAVARES CANENA





[Próteses no tubo digestivo: evolução e aplicações no século XXI]

Dissertação de candidatura ao grau de Doutor apresentada à Faculdade de Ciências Médicas da Universidade Nova de Lisboa

Jorge Manuel Tavares Canena

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Lisboa – 2012

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FACULDADE DE CIÊNCIAS MÉDICAS

Ao abrigo do artigo 8º - 2. do Decreto-Lei nº 388/70, fazem parte desta dissertação as seguintes publicações:

1) Canena J, Liberato M, Romão C, Coutinho AP, Neves B, Guerreiro AS. Utilização de próteses esofágicas metálicas expansíveis cobertas na paliação de estenoses malignas antro-pilóricas. GE - J Port Gastrenterol 2005; 12:150-155
2) Canena JM, Lagos AC, Marques IN, Patrocínio SD, Tomé MG, Liberato MA, Romão CM, Coutinho AP, Veiga PM, Neves BC, Além HD, Gonçalves JA. Oral intake throughout the patients' lives after palliative metallic stent placement for malignant gastroduodenal obstruction: A retrospective multicentre study. Eur J Gastroenterol Hepatol 2012 April 13; [Epub ahead of print] DOI: 10.1097/MEG.0b013e328353d9d3
3) Liberato MA, Canena J. Obstrução Colônica Aguda. In: Costa Junior AB, eds, Endoscopia Digestiva de Urgência. Edições Livraria Santos Editora Ltda, Brasil, 2009: capítulo 24, pp 261-271
4) Canena J, Liberato MA, Marques I, Rodrigues C, Lagos A, Patrocínio S, Tomé M, Pires E, Romão C, Coutinho A, Veiga P, Neves B, Deus J, Além D, Gonçalves J. Sustained relief of obstructive symptoms for the remaining life of patients following placement of an expandable metal stent for malignant colorectal obstruction. Rev Esp Enferm Dig 2012 (aceite para publicação)
5) Canena J, Liberato M, Rio-Tinto R, Pinto-Marques P, Romão C, Coutinho A, Neves B, Silva MF. A comparison of the temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures: A prospective multicentre study (enviado para publicação)
6) Canena J, Liberato M, Horta D, Romão C, Coutinho P. Short-term stenting using fully covered self-expandable metal stents for the treatment of refractory biliary leaks, post-sphincterotomy bleeding and perforations. Surg Endosc 2012 (aceite para publicação)
7) Liberato M, Canena J. Endoscopic stenting for hilar cholangiocarcinoma: Efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients (enviado para publicação)

Nos artigos 1 a 6 o autor da tese foi o executante de 60-90% dos procedimentos endoscópicos, promoveu a recolha de dados, e foi o responsável pela hipótese original, análise, interpretação dos dados, elaboração e revisão final do manuscrito. No artigo 3 a forma final publicada foi revista integralmente e aprovada pelo primeiro autor. No artigo 7, o autor executou 20-30% dos procedimentos endoscópicos, elaborou o manuscrito inicial e executou, juntamente com o primeiro autor a interpretação dos dados e a revisão final do manuscrito.

"Omnia tempus est, et tempus spatiis transeunt universa sub caelo:

Tempus nascendi et tempus moriendi;

Tempus plantandi et tempus evellendi quod plantatum est;

Tempus occidendi et tempus sanandi;

Tempus destruendi et tempus aedificandi"

Eclesiastes, em latim, traduzido do hebraico original

"Para tudo existe um propósito e um tempo sob o céu:

Um tempo para nascer e um tempo para morrer;

Um tempo para semear e um tempo para colher o que foi semeado;

Um tempo para matar e um tempo para curar;

Um tempo para destruir e um tempo para construir"

Eclesiastes, numa tradução livre e pessoal

Dedicatória

Ao Vicente, luz dos meus olhos, para que ele possa sempre vislumbrar que o esforço e o trabalho são o caminho a seguir.

Aos meus Pais, que sempre estiveram na minha retaguarda numa busca incessante do melhor para mim.

À Telma, que sempre me disse que isto era possível e me incentivou pela sua constante presença.

Agradecimentos

Ao meu mestre e amigo, Manuel Liberato que muito fez para eu ser melhor endoscopista, melhor médico e melhor pessoa.

Ao Professor Mário Quina, mestre insigne da Medicina e da Academia, de quem tenho o raro privilégio de ter sido colaborador e a honra de poder chamar amigo, fonte de inspiração e principal razão de eu ser Gastrenterologista e estar ligado à Academia.

Ao Carlos Romão, personalidade de grande generosidade, que me ajudou, incentivou e me fez crescer como homem e endoscopista.

À Beatriz Neves, directora e amiga que sempre apostou na minha carreira e formação e tudo fez para que fosse possível a realização deste projecto.

Aos meus queridos amigos António Pinto, Jorge Reis e José Leitão Luís que me acompanharam em todo o meu percurso e me incentivaram a ir mais além.

Ao meu amigo António Mário Santos que me ensinou muito sobre investigação, que promoveu os primeiros projectos em que estive envolvido, que sempre esteve presente nos momentos difíceis e a quem eu dedico muito particularmente esta obra.

Ao Doutor Fernando Moura Pires, esteja ele onde estiver. No primeiro dia em que me conheceu alvitrou que estas provas iriam chegar.

A todos os co-autores dos artigos incluídos nesta tese pelo seu contributo, e muito em especial ao meu colaborador e amigo dilecto, David Horta, para que ele possa seguir nas minhas pegadas.

Finalmente ao Professor António Sousa Guerreiro. Dele fui aluno, interno, discípulo e com honra e satisfação, amigo e colaborador. No percurso de 22 anos de conhecimento mútuo, de altos e baixos, nunca me faltou com estímulo, saber, amizade e incentivo. Só através do seu empenho e orientação esta obra ficou pronta. O meu muito obrigado.

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Resumo

RESUMO

O final do século XX e a primeira década do século XXI assistiram ao nascimento e disseminação da utilização de próteses expansíveis em vários segmentos do tubo digestivo. Contudo, continuam a persistir focos de conflito científico sobre as melhores aplicações para os diferentes tipos de próteses em várias patologias, benignas e malignas, nos vários segmentos do tracto gastro-intestinal. Esta tese pretendeu clarificar: 1) o papel das próteses metálicas auto-expansíveis no tratamento paliativo de obstruções malignas gastro-duodenais e colo-rectais; 2) o interesse e aplicações de próteses expansíveis em situações benignas, quer esofágicas, quer biliares; 3) a melhor abordagem endoscópica para o tratamento paliativo do colangiocarcinoma hilar. Para tal foram desenvolvidos 7 estudos, totalmente realizados em Portugal, e que se descrevem de seguida.

I. Canena J, Liberato M, Romão C, Coutinho AP, Neves B, Guerreiro AS. Utilização de próteses esofágicas metálicas expansíveis na paliação de estenoses malignas antro-pilóricas. GE - J Port-Gastrenterol 2005; 12:150-155

Estudo prospectivo com 10 doentes, em que se realizou um ensaio piloto e original sobre a utilização de próteses esofágicas parcialmente cobertas na paliação de estenoses pilóricas malignas. Estudo realizado numa época em que não existiam próteses entéricas cobertas com possibilidade de serem colocadas através do canal do endoscópio. Este trabalho pretende sugerir que, sendo tecnicamente possível a colocação de próteses esofágicas no piloro, a utilização de dispositivos cobertos seria uma opção futura a considerar. Esta realidade era sugerida pelo facto de, neste estudo, todos os doentes mantiveram alimentação oral até à morte, sem necessidade de reintervenção e com morbilidade mínima.

II. Canena JM, Lagos AC, Marques IN, Patrocínio SD, Tomé MG, Liberato MA, Romão CM, Coutinho AP, Veiga PM, Neves BC, Além HD, Gonçalves JA. Oral intake throughout the patients' lives after palliative metallic stent placement for malignant gastroduodenal obstruction: A retrospective multicentre study. Eur J Gastroenterol Hepatol 2012 April 13; [Epub ahead of print] DOI: 10.1097/MEG.0b013e328353d9d3

Estudo retrospectivo, multicêntrico, com 74 doentes, em que se avaliou a eficácia clínica das próteses metálicas em doentes com obstrução maligna gastro-duodenal.

Observámos um sucesso técnico de 100% e uma eficácia clínica (restabelecimento da alimentação oral) durante o resto da vida dos doentes em 95.9% dos casos. Numa população com uma sobrevida mediana de 8 semanas, 78.4% dos doentes não necessitaram de intervenção adicional. A taxa de complicações foi de 18.9% e numa análise multivariada pelo modelo de Cox, a localização duodenal da estenose maligna foi o único factor independente associado à patência das próteses.

III. Liberato MA, Canena J. Obstrução Colônica Aguda. In: Costa Junior AB, eds, Endoscopia Digestiva de Urgência. Edições Livraria Santos Editora Ltda, Brasil, 2009: capítulo 24, pp 261-271

Capítulo de livro, publicado no Brasil, em que se faz uma revisão da literatura e da metodologia endoscópica. Está inserido no capítulo um estudo inicial, prospectivo, com 28 doentes com obstrução colo-rectal e tratados de forma paliativa com próteses metálicas. Este estudo apresentou um sucesso técnico e clínico de 100% e um tempo médio de hospitalização de 9.2 dias após a colocação das próteses. Vinte doentes (71.4%) não necessitaram de intervenção adicional até à morte, 4 doentes (14.3%) foram submetidos a colostomia por carcinomatose peritoneal e 4 doentes (14.3%) que desenvolveram reosbtrução tumoral da prótese foram tratados pela colocação de outra prótese. Dez doentes (35.7%) tinham lesões no cólon transverso e ângulo hepático sugerindo que qualquer localização colónica pode ser paliada endoscopicamente de uma forma eficaz e por longos períodos.

IV. Canena J, Liberato M, Marques I, Rodrigues C, Lagos A, Patrocínio S, Tomé M, Pires E, Romão C, Coutinho A, Veiga P, Neves B, Deus J, Além H, Gonçalves J. Sustained relief of obstructive symptoms for the remaining life of patients following placement of an expandable metal stent for malignant colorectal obstruction. Rev Esp Enferm Dig 2012 (aceite para publicação)

Estudo retrospectivo, multicêntrico, englobando 89 doentes com obstrução maligna colo-rectal inoperável nos quais se tentou a colocação de uma prótese metálica como tratamento paliativo. Observámos um sucesso técnico e clínico em 95.5% e 91.0% dos doentes respectivamente. No total 68 dos 89 doentes (76.4%) mantiveram-se livres de sintomas obstrutivos, sem intervenção adicional, até à morte. A taxa de complicações foi de 22.5% e a mortalidade associada ao procedimento foi de 1.1%. Com o recurso a um modelo de regressão logística, e mesmo sem atingir significância estatística, verificou-se que a terapêutica concomitante com quimioterapia foi um factor de risco para migração.

V. Canena J, Liberato M, Rio-Tinto R, Pinto-Marques P, Romão C, Coutinho A, Neves B, Silva MF. A comparison of the temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures: A prospective multicentre study (enviado para publicação)

Estudo prospectivo, multicêntrico, englobando 30 doentes e que comparou a colocação temporária de 3 tipos de próteses expansíveis (plásticas, metálicas totalmente cobertas e biodegradáveis) no tratamento de estenoses esofágicas refractárias à dilatação. Observámos que a colocação temporária de uma prótese biodegradável ou de uma prótese metálica totalmente coberta pode levar ao desaparecimento da disfagia em 30% e 40% dos doentes respectivamente. A utilização das próteses plásticas é a menos recomendável pois o seu uso está associado a elevadas taxas de migração e intervenção adicional bem como poucos casos (10%) de melhoria a longo prazo. Um modelo multivariado de Cox identificou o tamanho da estenose como o único factor independente associado à recidiva da disfagia após o tratamento temporário com próteses.

VI. Canena J, Liberato M, Horta D, Romão C, Coutinho P. Short-term stenting using fully covered self-expandable metal stents for the treatment of refractory biliary leaks, post-sphincterotomy bleeding and perforations. Surg Endosc 2012 (aceite para publicação)

Estudo retrospectivo, multicêntrico, englobando 25 doentes submetidos à colocação temporária de próteses metálicas auto-expansíveis para o tratamento de várias condições benignas biliares (fugas biliares pós-colecistectomia refractárias, hemorragia de difícil controlo pós-esfincterotomia e perfurações pós-esfincterotomia). Neste estudo concluímos que a estratégia de colocação temporária das próteses (30 dias ou menos) é eficaz em todos os casos. Este curto período de colocação evita complicações e o tempo ideal de permanência das próteses na via biliar deve ser diferente para cada condição.

VII. Liberato M, Canena J. Endoscopic stenting for hilar cholangiocarcinoma: Efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients (enviado para publicação)

Estudo retrospectivo, realizado num único centro ao longo de 15 anos, englobando 480 doentes com colangiocarcinoma inoperável e em quem foi tentada a colocação de próteses plásticas e metálicas de forma unilateral e bilateral. Observámos um sucesso técnico global em 93.8% dos casos e que a inserção paliativa de uma prótese metálica está

significativamente associada a um maior sucesso técnico e clínico, maior tempo de patência das próteses e menor taxa de complicações, quando comparada com a colocação de próteses plásticas, em todas as classes de Bismuth, numa análise por intenção de tratar. Neste estudo a patência cumulada da colocação bilateral de próteses metálicas e plásticas foi superior à colocação unilateral em doentes com lesões tipo Bismuth II.

As principais conclusões desta tese são:

1) A utilização de próteses metálicas auto-expansíveis é um tratamento paliativo e definitivo muito eficaz em doentes com obstrução maligna colo-rectal e gastro-duodenal. Este procedimento está associado a taxas de morbilidade e de intervenção adicional aceitáveis.
2) O recurso a próteses expansíveis em doenças benignas pode constituir uma opção terapêutica válida. As próteses biodegradáveis e as próteses metálicas totalmente cobertas podem ser utilizadas, com eficácia aceitável, num grupo de doentes com estenoses refractárias do esófago e para os quais não estão disponíveis grandes opções de tratamento. As próteses metálicas totalmente cobertas podem ser um tratamento de excepção em situações benignas biliares onde anteriormente a cirurgia era a única opção disponível.
3) As próteses metálicas são a opção de escolha no tratamento paliativo do colangiocarcinoma hilar, independentemente do tipo de lesão. Em doentes com estenoses do tipo II de Bismuth a colocação bilateral de próteses metálicas, sempre que tecnicamente possível, deve ser recomendada, pois está associada a uma maior patência das próteses e a uma menor taxa de reintervenção.

INTRODUÇÃO

INTRODUÇÃO

"...life, like evolution always finds a way...."

Charles Darwin, Voyage of the Beagle

O tubo digestivo é sobretudo um sistema de condutância luminal, sede frequente de tumores malignos incuráveis e obstrutivos, onde a cirurgia de ressecção ou derivação se apresentava como a única alternativa. Esta abordagem, muitas vezes realizada em doentes idosos e com várias co-morbilidades, era habitualmente traduzida, do ponto de vista clínico, numa elevada carga de morbilidade e mortalidade que, em algumas séries cirúrgicas, alcançava valores na ordem dos 40%[1,2].

O aparecimento das próteses metálicas auto-expansíveis destinadas ao uso da gastrenterologia e endoscopia veio revolucionar o tratamento das estenoses malignas no tracto gastro-intestinal. Estes dispositivos, originalmente desenhados para utilização nas áreas cardio-vascular e de radiologia de intervenção, sofreram enorme evolução nos últimos 20 anos que por estranho que pareça é a idade real da utilização de próteses metálicas no tubo digestivo. Tendo sido inicialmente concebidas para a paliação de estenoses malignas esofágicas e biliares, em breve se expandiram a outras áreas do tubo digestivo como a região gastro-duodenal e colo-rectal. Os últimos anos assistiram a um extraordinário desenvolvimento tecnológico associado à procura, por parte dos fabricantes e comunidade médica, de novas próteses com diferentes tamanhos, matérias e desenhos diversos, de forma a preencherem as constantes necessidades e novas aplicações nesta disciplina. O aparecimento de próteses metálicas totalmente cobertas, passíveis de remoção ao fim de algum tempo após a sua colocação, uma vez que não são integradas na parede do órgão onde foram colocadas, associadas ao surgimento de próteses expansíveis plásticas e biodegradáveis alargou ainda mais as fonteiras do admirável mundo novo das próteses do tubo digestivo. Assim, dispositivos que inicialmente eram colocados definitivamente com intuito paliativo, em virtude do aparecimento de novos modelos, entraram no tratamento de lesões benignas, (estenoses e fístulas), sendo removidos ao fim de um período variável de tempo. Hoje em dia existem múltiplos desenhos e modalidades de próteses que têm variadas aplicações, riscos e benefícios, os quais devem ser aplicados às necessidades dos doentes.

Perspectiva histórica – da origem da palavra às primeiras próteses

A palavra prótese tem a sua origem na palavra grega, *prothesis (πρόθεσις)*, que significa originalmente adição e que pretende designar a colocação de um aparelho que substitui ou melhora a função de uma parte natural do nosso organismo. Contudo, a utilização da palavra prótese em endoscopia, mesmo na nossa língua é pouco frequente sendo substituída muitas vezes pelo termo *stent*, oriundo da linguagem inglesa e que é universalmente empregue quando existe referência a este tipo de dispositivos, independentemente do país e língua utilizada.

Quando Charles Thomas Stent nasceu, a 17 de Outubro de 1807 em Brighton, estava longe de imaginar a difusão que o seu nome iria merecer nos séculos vindouros. Foi o sexto filho de William e Hannah Stent, tendo vindo a falecer em Londres em 1885 com a idade de 77 anos. Charles Stent ganhou fama como dentista, sobretudo por ter sido o autor de um composto designado como composto de Stent, utilizado em moldes dentários e constituído por *gutta-percha*, que é a seiva de uma árvore malaia ao qual Stent adicionou estearina e talco de forma a aumentar a plasticidade e estabilidade do produto[3]. Subsequentemente, em 1917, um cirurgião, Johannes F. S. Esser (1877-1946), usou o composto para uma cirurgia plástica facial tendo-o designado como molde de Stent[4]. Em 1954, William H. ReMine e John H. Grindlay usaram o princípio e o composto de Stent para criar um tubo de polietileno na anastomose e reconstrução de canais biliares num modelo experimental canino e foram os primeiros a usar a palavra *stent** (propositadamente a palavra stent passou de maiúscula a minúscula) numa publicação[5]. Na mesma área e com o mesmo modelo de tubo Chenoweth usou a expressão *stent* num artigo que visava a discussão do seu trabalho no campo da intervenção biliar[6]. Em 1972, dois urologistas, Firlit e Brown usaram a palavra *stent* no título de um artigo, referindo que era a palavra lógica para os tubos de plástico utilizados para a resolução de uma obstrução ureteral[7]. Por outro lado, a palavra *stent* ganhou extraordinária difusão no campo da medicina cardiovascular. A primeira referência a esta palavra na literatura cardiovascular pertence a Weldon et al., em 1966, quando estes autores descreveram a substituição de uma válvula mitral[7]. Já o conceito de um tubo endo-arterial parece pertencer a Dotter cuja descrição inicial deste princípio foi feita em 1969[9]. Este autor passa a utilizar a palavra *stent,* numa publicação em 1983, referindo-se a um tubo endo-arterial que visava resolver o problema das estenoses vasculares[10]. Em gastrenterologia, Molnar e Stockum em 1974, foram os primeiros a utilizar a expressão *stent* para descrever a colocação percutânea de uma prótese biliar plástica[11]. Posteriormente, em 1979 Nib Soehendra e Reynders-Frederix descreveram a colocação endoscópica de uma prótese biliar

de plástico na paliação de uma obstrução biliar maligna[11]. Assim a palavra *stent* é um dos raros exemplos em que um nome próprio se tornou numa palavra comum, tendo aplicações em vários campos da medicina. Na realidade e no momento da elaboração desta tese uma pesquisa com a palavra *stent* no PubMed produziu 57199 artigos, mostrando a sua importância e difusão.

As primeiras próteses a serem utilizadas no tubo digestivo, na década de oitenta do século XX, eram plásticas, de natureza rígida e foram inicialmente aplicadas, nas vias biliares e posteriormente no esófago. Em 1991 surgiram as primeiras próteses metálicas auto-expansíveis, de aço inoxidável, comercializadas pela marca Wilson-Cook e que foram designadas por Gianturco Z-stent. Os primeiros relatos da sua colocação em 8 doentes com cancro esofágico inoperável foram publicados em 1991[13], abrindo caminho a uma era de publicações e investigação nesta área.

Próteses expansíveis: princípios e resposta tecidular

O grande objectivo da colocação de uma prótese metálica auto-expansível através de um segmento estenosado do tubo digestivo é providenciar um lúmen amplo evitando a utilização de introdutores muito largos (característicos das próteses plásticas) através dos segmentos estenosados, manobra que por si pode associar-se a complicações como a perfuração. Como facilmente se depreende, e para fácil ultrapassagem da estenose, as próteses metálicas estão comprimidas num introdutor de baixo diâmetro, sendo libertadas gradualmente sob controlo endoscópico e fluoroscópico na grande maioria dos casos.

a) Técnica e características das próteses

O primeiro passo para a colocação de uma prótese é a ultrapassagem da estenose com fio-guia, permitindo a posterior condução do introdutor da prótese através do segmento estenosado. A dilatação da estenose é ocasionalmente necessária, em casos de lesões muito longas, apertadas, anguladas ou esofágicas, mas deve ser limitada ao mínimo indispensável de forma a minimizar o risco de perfuração e sobretudo de migração após a colocação da prótese. Um outro aspecto importante é a selecção do tamanho da prótese. Esta deve ter uma dimensão que permita, não só cobrir todo o tumor, mas evitar ao máximo um risco de crescimento tumoral ao longo da prótese com cobertura dos topos. Habitualmente é recomendável a selecção do tamanho da prótese de forma a acrescentar 2-3 cm a cada margem do tumor. Assim uma estenose com 4 cm de comprimento deve ser tratada com uma prótese de 8 a 9 cm. Um outro aspecto que pode ser importante é a força radial da prótese,

que é definida como sendo a força exercida pelo dispositivo nas estruturas vizinhas durante e após a sua expansão. Se de um modo geral próteses com maior força radial atingem mais rapidamente o seu diâmetro (mais rápido efeito clínico) e apresentam uma probabilidade menor de migração, nem sempre a sua selecção é aconselhável. É o caso de lesões malignas do esófago cervical em que próteses de elevada força radial podem comprimir excessivamente a traqueia com os problemas respiratórios inerentes[14]. Outro aspecto a ser equacionado é a arquitectura e forma da prótese. Algumas próteses apresentam as extremidades (ou apenas uma delas) mais largas de forma a diminuírem o risco de migração, embora isso possa reagir com o tecido circundante (ver adiante) e causar marcada reacção inflamatória traduzida em tecido hiperplásico, cujo excesso pode levar à obstrução da prótese. Finalmente é fundamental a adequada escolha do desenho da prótese em função do tumor ou do efeito pretendido. Estão disponíveis 3 tipos de próteses: a) totalmente coberta; b) parcialmente coberta, e c) descoberta. Nas estenoses malignas o uso de próteses descobertas e parcialmente cobertas associadas ao crescimento tumoral através das malhas da prótese e ao surgimento de tecido hiperplásico devem ser contrapostos ao risco de migração que é habitualmente encontrado no uso destes dispositivos totalmente cobertos, cuja principal finalidade é evitar o crescimento de tumor através da malha. Em seguida, analisaremos a resposta tecidular do organismo à presença de uma prótese.

b) Resposta tecidular à colocação de próteses

Como referido anteriormente, existem em 3 apresentações de próteses metálicas: descobertas, parcialmente cobertas e totalmente cobertas. As primeiras são constituídas por uma malha metálica nua que entra em contacto directo com a mucosa normal e com o tecido tumoral. As próteses parcialmente cobertas apresentam uma membrana em quase toda a sua extensão deixando as extremidades livres e as totalmente cobertas apresentam uma membrana que cobre toda a malha metálica.

Após a colocação de uma prótese metálica descoberta a expansão do dispositivo faz com que a parte central da prótese expanda contra a massa tumoral e as extremidades (proximal e distal) contra a mucosa normal. A força radial da expansão da prótese causa necrose das camadas superficiais do tumor e da mucosa aparentemente poupada, levando a que a prótese penetre na submucosa normal e no tumor[15,16]. A penetração do dispositivo na submucosa leva a uma reacção inflamatória nas extremidades da prótese, em mucosa normal, desencadeando fibrose que acaba por cobrir a prótese devido ao surgimento de tecido reaccional designado por hiperplásico. Por sua vez, na zona tumoral, em breve as células tumorais vão cobrir as

malhas da prótese. Ao fim de semanas a meses a malha da prótese deixa de ser visível, a prótese torna-se parte integrante da parede do órgão (fica embebida) e estão criadas condições para o crescimento do tumor através da malha levando a nova obstrução se a sobrevida do doente possibilitar esse acontecimento[15,16]. Já o comportamento das próteses totalmente cobertas é diferente. A sua expansão e pressão sobre o tumor e sobre a mucosa normal levam à criação de necrose isquémica nestas estruturas. Este evento cria condições para o desenvolvimento de um exsudado fibrinoso e posterior fibrose organizada na superfície da prótese, mas se a membrana responsável pela cobertura se mantiver íntegra, a malha do dispositivo não penetra na parede do órgão e não fica embebida[15,16]. Naturalmente que este facto implica que a cobertura da prótese se mantenha íntegra durante a sobrevida do doente. Este comportamento leva a que próteses totalmente cobertas possam ser colocadas em estenoses benignas que não respondem adequadamente às dilatações[17]. A força radial da prótese dilata a estenose e a cobertura impede a aderência da prótese à parede do órgão permitindo a remoção do dispositivo. Em consequência do que foi descrito anteriormente e dependendo do órgão, uma excessiva permanência da prótese totalmente coberta pode, por fenómenos de fibrose, levar ao surgimento de uma nova estenose (nas extremidades) após a sua retirada. Este tema, ou seja a utilização de próteses metálicas totalmente cobertas em estenoses e lesões benignas, está muito em voga no momento actual, sendo explorado em 2 dos artigos integrantes desta tese. As próteses parcialmente cobertas têm propriedades mistas das próteses cobertas e descobertas. As suas extremidades descobertas reagem com os tecidos normais ficando embebidas na parede do órgão ao fim de algum tempo; já a porção média da prótese (em contacto com o tumor) mantem a permeabilidade do conjunto impedindo que a massa tumoral penetre na malha e invada a malha do dispositivo.

Dois assuntos adicionais neste tema merecem reflexão: 1) a utilização de quimioterapia e radioterapia após colocação de próteses. A quimioterapia está associada a necrose e diminuição da massa tumoral predispondo a situações de migração da prótese. A radioterapia provoca marcado edema e ulceração da mucosa, causando com frequência extensa fibrose da camada muscular, o que pode levar a que a parede do órgão se torne bastante fina. Próteses com marcada força radial podem condicionar extensa necrose e em órgãos como o esófago a parede fina e fibrosada pode necrosar por completo levando à formação de fístulas para o mediastino/árvore respiratória cujo local mais frequente são no topo da prótese; 2) o surgimento de próteses biodegradáveis, nomeadamente a prótese Ella®, feita de um material de sutura absorvível a polidioxanona. Este material é uma estrutura semicristalina e biodegradável que se degrada por hidrólise das ligações éster da molécula, sende este

fenómeno acelerado por baixo pH. O número de relatos na literatura não é suficiente para o conhecimento profundo da resposta do tecido humano à polidioxanona, mas aparentemente é bem tolerado pelo organismo ainda que existam relatos de reacção hiperplásica severa à prótese. Este tema é abordado por nós num dos artigos da dissertação (artigo 5) com fotografias da reacção da mucosa esofágica após a degradação da polidioxanona.

Próteses metálicas na paliação endoscópica de estenoses malignas gastro-duodenais

A obstrução gastro-duodenal é uma complicação tardia de vários tumores malignos como o gástrico, o pancreático, o colangiocarcinoma, o duodenal, e o da ampola de Vater, sendo o local da obstrução variável e estendendo-se desde o antro até ao jejuno proximal consoante a etiologia[1,19-21]. Adicionalmente, a obstrução pode ser resultante da invasão directa por metástases de tumores, mais frequentemente, localizados na cavidade abdominal. O cancro gástrico e o pancreático são as duas causas mais frequentes da obstrução, dependendo a sua frequência como etiologia da estenose consoante a localização no globo da população estudada. Os sintomas clínicos da obstrução gastro-duodenal incluem náusea intensa, vómitos frequentes, dor abdominal, desidratação e desnutrição[1,20,21]. A obstrução maligna gastro-duodenal surge, muitas vezes, como um evento pré-terminal e está habitualmente associada à irresecabilidade tumoral[1,20,21]. Mais frequentemente os doentes com este problema apresentam-se desnutridos e são maus candidatos a cirurgias paliativas[1,19-28]. Após o diagnóstico desta entidade a esperança de vida é curta, não ultrapassando com frequência as 20 semanas[1,19-28].

Durante décadas a abordagem paliativa clássica da obstrução gastro-duodenal foi a derivação cirúrgica (gastro-jejunostomia), por via aberta ou por laparoscopia[1,21]. A cirurgia laparoscópica parece constituir uma vantagem sobre a cirurgia convencional no que diz respeito à menor morbilidade e ao tempo de internamento[29]. Contudo, os últimos 20 anos assistiram ao início e disseminação do recurso a próteses metálicas auto-expansiveis para a paliação da obstrução gastro-duodenal[1,18-28]. Esta técnica tem-se vindo a afirmar como uma alternativa viável à cirurgia e a outros tratamentos como a nutrição entérica pós jejunostomia cirúrgica, nutrição parentérica e colocação de sondas naso-entéricas[30].

A suspeita da obstrução deve basear-se na clínica e no surgimento de sintomas típicos em doentes com tumor maligno já conhecido e muitas vezes em tratamento paliativo com quimioterapia e radioterapia. O diagnóstico é feito habitualmente por endoscopia. Com frequência os doentes são submetidos a exames imagiológicos adicionais (tomografia computorizada e trânsito gastro-intestinal), que visam, sobretudo, despistar outros locais de

obstrução para além de uma melhor caracterização do local de estenose, em especial se a lesão for inultrapassável pelo endoscópio, o que é o mais frequente. A técnica de colocação não se tem alterado substancialmente com o passar dos anos[31-33]. A estenose é ultrapassada com fio guia e catéter de triplo-lúmen; a injecção de contraste permite medir com exactidão a estenose (importante para seleccionar o comprimento da prótese) para além de assegurar que o fio guia progrediu adequadamente no tubo digestivo a jusante da obstrução. É habitual a marcação da extremidade proximal da lesão com uma estrutura radiopaca (mais frequentemente um clip hemostático) para facilitar o correcto posicionamento do dispositivo durante a sua libertação, o que é feito, habitualmente, sob controlo fluoroscópico e endoscópico. Alguns endoscopistas preferem trocar o fio guia inicial, de ponta hidrofílica, por um fio guia mais rígido, de forma a permitir um melhor avanço da prótese mas não existe consenso quanto a esta manobra. A prótese é avançada sobre o fio-guia através do canal de um endoscópio terapêutico ou de um colonoscópio (canal mínimo de 3.8 mm). Esta técnica é designada por colocação TTS, baseada na nomenclatura anglo-saxónica (*through-the-scope*) e permite com um colonoscópio colocar uma prótese até uma obstrução localizada nos primeiros cm do jejuno (Figura 1). Existe uma outra abordagem, designada por não-TTS que foi a utilizada na década de 90 (quando ainda não haviam próteses TTS) em que o fio guia era colocado em posição por via endoscópica. Posteriormente e sob controlo fluoroscópico avançava-se uma prótese sobre o fio-guia até à estenose. Interessante é que ainda hoje existem séries de colocação não TTS oriundas da radiologia de intervenção sendo que a maior série publicada na literatura, com 213 doentes é proveniente desta área. Para além disso esta técnica não-TTS também foi utilizada na colocação das primeiras próteses cobertas, habitualmente esofágicas com o catéter de implantação original ou modificado[34-35], uma vez que as próteses TTS cobertas só surgiram já em pleno século XXI. Um dos artigos desta dissertação (artigo 1) é um ensaio original sobre este tema, avaliando a utilização de próteses esofágicas não modificadas e cobertas para paliar estenoses malignas pilóricas em doentes com adenocarcinoma gástrico.

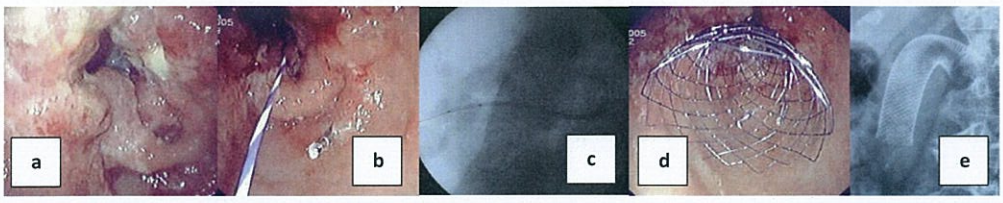

Figura 1. Técnica de colocação de prótese pilórica – a: visualização da neoplasia; b: fio guia em posição com clip de marcação; c: libertação da prótese sob controlo fluoroscópico; d: visualização endoscópica após libertação; e – Rx às 48H com a prótese totalmente expandida

a) Tipos de próteses disponíveis

As próteses entéricas/piloro-duodenais são compostas por diferentes ligas metálicas, e apresentam diferentes comprimentos, diâmetros e forças radiais. No momento actual, as próteses disponíveis para o tratamento das estenoses malignas gastro-duodenais (Tabela 1) tem um catéter de introdução que permite a sua passagem no canal de um endoscópio terapêutico (superior a 3.8 mm de diâmetro). A primeira prótese disponível no mercado, provavelmente a mais utilizada desde 1998 a 2005, foi uma prótese descoberta designada por Wallstent® (Boston Scientific, MA, Natick, EUA), feita numa liga de elgiloy (liga com aço inoxidável). Posteriormente foi substituída por uma nova versão, apelidada de WallFlex®, mais flexível, de extremidades arredondadas e com a extremidade proximal com maior diâmetro de forma a reduzir a possibilidade de migração. Existem outras próteses disponíveis como as Choostent® e Hanarostent® (MI Tech, Seoul, Coreia), a Song® (Stentech, Seoul, Coreia) e a Evolution® (Cook Medical, Winston-Salem, NC, EUA). A Hanarostent® está disponível nas versões descoberta e parcialmente coberta em nitinol (liga flexível de níquel e titânio). A Choostent® apresenta uma porção central coberta e as extremidades descobertas, sendo neste desenho idêntica à prótese Song®. As próteses Evolution® foram recentemente introduzidas no mercado, e apenas estão disponíveis na versão descoberta. Não está provado cientificamente que nenhum dispositivo descoberto seja melhor que outro nem que nenhum modelo coberto apresente melhores resultados do que um modelo alternativo de natureza coberta.

Tabela 1. Algumas das próteses metálicas para o piloro/duodeno

Marca	**Diâmetro (mm)**	**Comprimento (mm)**	**Diâmetro do sistema (Fr)**	**Casa Comercial**
WallFlex	22	60, 90	10	Boston Scientific
Evolution	22	60, 90, 120	10	Wilson-Cook
Hanarostent*	18,20,22	60-170	10.2	MI Tech
Niti-S*	16,18,20,22,24	40,60,80,100,120	10.5	Taewoong Medical

*Disponível em formas totalmente cobertas e parcialmente cobertas

Por outro lado, existe alguma controvérsia sobre as eventuais vantagens das próteses cobertas. As próteses cobertas foram construídas para diminuir a taxa de reobstrução maligna das próteses. Contudo, alguns relatos referem uma taxa de migração elevada (17% a 26%) o que desde logo questiona a utilidade das próteses cobertas[36-38]. Dois estudos recentes

avaliaram este problema[39-40]. Um trabalho retrospectivo com 60 doentes comparou próteses cobertas e não cobertas, tendo encontrado resultados similares no sucesso técnico e sucesso clínico[39]. Contudo as próteses cobertas estiveram associadas a um maior número de reintervenções. Por outro lado, um ensaio clínico randomizado entre os 2 tipos de próteses, não mostrou quaisquer vantagens na utilização de formas cobertas[40]. No momento actual, a grande maioria dos endoscopistas utiliza próteses descobertas, não parecendo haver vantagens na utilização de próteses cobertas.

b) Sucesso técnico e sucesso clínico imediato

O sucesso técnico, definido como o correcto posicionamento da prótese através da estenose varia entre os 91 e os 100% em vários estudos[1,19-28]. Uma revisão sistemática de 606 casos apresenta um sucesso técnico de 96%[41]. Em unidades com experiência na colocação de próteses, o sucesso técnico é superior a 90%. As causas mais frequentes para o insucesso técnico são a impossibilidade de ultrapassar a estenose com um fio guia (o mais frequente), deficiência técnica do sistema de libertação da prótese e migração imediatamente após a libertação do dispositivo. O sucesso clínico imediato é definido, em múltiplos trabalhos, pela melhoria dos sintomas e pela capacidade do doente retomar a alimentação oral. Na maior parte dos estudos é utilizado uma pontuação (*score*), o GOOSS (Gastric Outlet Obstruction Scoring System), publicado pela primeira vez em 2002 e que pretende quantificar de forma objectiva o nível de alimentação oral antes e após a colocação da prótese[19] (Tabela 2).

Tabela 2. Pontuação para quantificar o nível de alimentação oral. GOOSS (Gastric Outlet Obstruction Scoring System)

Pontuação (score)	**Tipo de alimentação oral**
0	Intolerância alimentar
1	Tolerância para líquidos
2	Tolerância para alimentação mole/pastosa
3	Dieta geral ou pobre em resíduos

O sucesso clínico imediato varia na literatura entre 77.7% a 97.2%. A meta-análise de Dormann et al. que analisou 32 estudos reporta um sucesso clínico em 86.8%, e com um tempo médio de resolução dos sintomas de 4 dias[41]. Uma outra revisão sistemática avaliou 44 publicações com um total de 1000 doentes submetidos a próteses gastro-duodenais e refere um sucesso clínico de 89%[42]. Antes da intervenção as pontuações de GOOSS eram 0 em 62%, 1 em 33% e 2 em 5%. Após a colocação das próteses as pontuações passaram a ser 0 em 6%, 1

em 22%, 2 em 40% e 3 em 32%. A maioria dos doentes passou a tolerar uma dieta oral, num período inferior a 24H após a colocação da prótese.

c) Esperança e qualidade de vida após colocação das próteses

Como discutido anteriormente a obstrução gastro-duodenal é um evento tardio na história natural de vários tipos de neoplasias. Vários estudos referem um tempo mediano de sobrevida variando entre os 49 a 121 dias e que parece não ser diferente para os diversos tipos de neoplasias[1,19-28,41,42]. Naturalmente que o restauro da capacidade de um doente terminal em alimentar-se oralmente implica uma melhoria da qualidade de vida. Alguns estudos avaliaram especificamente este problema e a grande maioria reporta uma clara melhoria da qualidade de vida após colocação da prótese[43,44]. Um estudo recente proveniente da Holanda, recorrendo a várias escalas de qualidade de vida não encontrou melhoria na qualidade de vida[1], embora este facto possa reflectir o estadio avançado da doença e não necessariamente a qualidade de vida após a colocação da prótese.

d) Complicações

As complicações são habitualmente categorizadas em minor (não são fonte de risco de vida) ou major (severas ou implicando risco de vida). As complicações minor incluem dor moderada, migração, obstrução e hemorragia auto-limitada); as complicações major incluem dor severa necessitando de analgésicos centrais opiáceos, hemorragia necessitando de suporte transfusional e perfuração. Na literatura, a taxa de complicações varia entre os 9 e os 30%[1, 19-28,41-44]. Uma das complicações mais frequentes é a obstrução da prótese por crescimento tumoral. Num estudo prospectivo com 43 doentes a taxa de reobstrução foi 9%[21]; noutro estudo prospectivo recente com 51 doentes a taxa de obstrução foi 14%[1]. Na revisão sistemática de Doorman *et al.* a obstrução da prótese ocorreu em 18% dos doentes[41]. De um modo geral o tempo mediano para a obstrução da prótese é superior a 100 dias, valor superior ao tempo mediano de sobrevida das populações estudadas sugerindo que na grande maioria dos casos a colocação de uma prótese assegura a manutenção do aporte alimentar pela via oral até à morte. Por outro lado, a obstrução da prótese pode ser resolvida, com sucesso, na generalidade dos casos, através da colocação de nova prótese. Uma outra complicação importante é a perfuração, sendo um evento raro. Na meta-análise citada anteriormente, esta complicação foi encontrada em 1,2% dos casos[41]. No trabalho publicado, com a maior da literatura (213 doentes), não houve nenhum caso de perfuração[20].

e) Obstrução biliar concomitante

A obstrução biliar é um evento que, com frequência, se pode associar à obstrução gastro-duodenal[19,45,46]. A taxa de obstrução biliar varia consoante a etiologia, sendo mais elevada em séries em que a causa de obstrução é a neoplasia pancreática. Habitualmente a obstrução biliar antecede ou desenvolve-se ao mesmo tempo que a obstrução duodenal[19,45,46]. Nos casos em que a obstrução decorre ao mesmo tempo a técnica habitual consiste em colocar, inicialmente, uma prótese metálica entérica de modo a que a extremidade distal desta fique localizada antes da ampola de Vater. Após a expansão da prótese (48 a 72h) a abordagem da via biliar deverá ser feita atravessando a estenose através da prótese entérica, de forma a chegar em frente da papila. Existe alguma controvérsia sobre a drenagem profiláctica das vias biliares em doentes sem colestase/icterícia, nos quais a colocação de uma prótese entérica pode, hipoteticamente, cobrir a papila após a sua libertação. Alguns autores defendem que esta colocação profiláctica não é necessária uma vez que o evento obstrução biliar após a obstrução gastro-duodenal é um evento raro (cerca de 1-3% dos casos), podendo ser resolvido por uma abordagem percutânea, ou por endoscopia. Nesta opção a canulação da via biliar é obtida através das malhas da prótese previamente colocada[19,45,46]. Outros autores consideram que a abordagem endoscópica através das malhas da prótese nem sempre é possível, sendo a taxa de sucesso baixa; para além disso a abordagem percutânea é muito invasiva e não desprovida de complicações. Estes autores advogam que a colocação de uma prótese biliar profiláctica não aumenta as complicações do procedimento e a sua colocação profiláctica deve ser sempre equacionada[1,30].

f) Sucesso clínico a longo prazo e comparação com a gastrojejunostomia

Existem múltiplos relatos que pretendem comparar a colocação paliativa de próteses com a derivação cirúrgica, seja pela via clássica, seja por laparoscopia. Uma revisão sistemática recente, sobre 307 procedimentos comparativos, refere que a colocação de próteses entéricas apresenta melhores resultados, nomeadamente, maior taxa de sucesso clínico, menor morbilidade, menor tempo de internamento e um início mais precoce da alimentação oral[47]. Apenas estão disponíveis 3 estudos randomizados comparando as duas abordagens terapêuticas e todos eles envolvendo um reduzido número de doentes[48,49,50]. O estudo mais antigo refere melhores resultados na terapêutica com próteses no que diz respeito ao tempo de intervenção, tempo de internamento e tempo para início da alimentação, embora os resultados dos dois métodos fossem similares em termos de morbilidade, mortalidade e sucesso clínico a 3 meses[48]. Um outro estudo refere vantagens na utilização das próteses sobre

a paliação cirúrgica, em termos de tempo de internamento, complicações e bem-estar físico[49]. Contudo, um estudo randomizado recente sugere que a cirurgia, apesar de um início lento e gradual na melhoria dos sintomas, apresenta melhores resultados a longo prazo e deve ser o tratamento de escolha para doentes com uma expectativa de vida superior a 2 meses[50]. Os autores deste trabalho sugerem, num estudo posterior, que a pontuação da organização mundial de saúde, visando a *performance status*, deve ser o factor discriminativo de sobrevida e todos os doentes com uma pontuação de 0 ou 1 (a pontuação 2 pode igualmente ser incluída), devem ser propostos para cirurgia[51]. Este trabalho deve ser analisado com algum cuidado por dois motivos: a) primeiro, o número de doentes envolvidos no estudo foi limitado e no grupo das próteses (n=21) a sobrevida mediana foi 56 dias, o que quer dizer que no momento da data discriminativa de 60 dias existiam apenas 9 doentes vivos; b) segundo, a grande maioria destes 9 doentes morreram rapidamente, sendo difícil assegurar que a partir dos 60 dias o aporte alimentar degradou-se.

Umas das grandes dificuldades na valorização a longo prazo, numa população com tempo mediano de vida curto, da terapêutica com próteses é a falta de trabalhos que sigam a grande maioria dos doentes até à morte, já que a maioria dos estudos tem um seguimento limitado ou o número de doentes perdidos é elevado. Um dos artigos da dissertação explora esta lacuna da literatura com o seguimento de 74 doentes até a morte, analisando diversos parâmetros clínicos associados à colocação de próteses e ao sucesso a longo prazo (artigo 2).

Em resumo poder-se-á dizer que a utilização de próteses na paliação definitiva da obstrução gastro-duodenal apresenta um elevado sucesso técnico e clínico a curto prazo e a grande maioria dos doentes mantêm alimentação oral até á morte. Os doentes podem ser retratados com novas próteses e o número de complicações graves é muito baixo. A cirurgia deve ser reservada para doentes em que a colocação de próteses não é possível e em doentes com esperança de vida provavelmente superior a 6 meses que como vimos é um evento raro, ainda que provavelmente, muitos desses doentes não pretendam ser operados.

Próteses metálicas auto-expansíveis como terapêutica paliativa da obstrução maligna colo-rectal

Cerca de 15 a 20% dos doentes com cancro colo-rectal podem apresentar-se, durante a evolução da doença, com sintomas obstrutivos[52]. A grande maioria destes doentes tem doença em estadio avançado, são frequentemente idosos, apresentam co-morbilidades importantes e não tem o cólon limpo[53-55]. Todos estes factores representam um risco cirúrgico aumentado implicando valores acrescidos de morbilidade e mortalidade. Na realidade, a

descompressão cirúrgica de emergência anda associada a taxas de mortalidade e morbilidade na ordem dos 10% e 50% respectivamente[56-57]. A intervenção cirúrgica é habitualmente realizada em duas etapas, com a criação inicial de uma colostomia que em cerca de 50% dos casos se torna definitiva, criando um profundo impacto negativo na qualidade de vida, em doentes com uma esperança de vida limitada[56-58].

Devido a estas considerações o uso de próteses metálicas auto-expansíveis no tratamento de doentes com obstrução maligna colo-rectal ganhou grande popularidade e difusão, sendo a comunidade cirúrgica uma das grandes impulsionadoras desta técnica. A obstrução colo-rectal causada, quer por neoplasia primária colo-rectal, quer por compressão extrínseca no contexto de outro tipo de cancros é uma situação de urgência, que se não for abordada com celeridade causa invariavelmente a morte. Normalmente, o diagnóstico inicial é clínico e é feito pelo aparecimento de dor e de distensão abdominal, associados a náuseas e vómitos. Perante a suspeita clínica o diagnóstico é feito, inicialmente, por métodos de imagem como a radiografia simples do abdómen e a tomografia computorizada, sendo posteriormente confirmado por colonoscopia. A colocação de próteses na obstrução aguda é realizada em duas grandes indicações: 1) descompressão colónica aguda, de forma a permitir uma correcta preparação do cólon e posterior ressecção cirúrgica, realizada numa única etapa, sendo esta abordagem designada como ponte para cirurgia; 2) como terapêutica paliativa definitiva em doentes com tumores em estadio avançado e sem indicação cirúrgica.

Contra-indicações absolutas para esta técnica incluem a perfuração documentada, lesões rectais muito distais e com uma margem para o esfíncter anal inferior a 4cm e carcinomatose peritoneal[53,59]. A obstrução colo-rectal pode estar associada a lesões malignas extra-colónicas como as ginecológicas, vesicais, prostáticas, pancreáticas, gástricas e do intestino-delgado. Contudo e ao contrário do cancro colo-rectal primário, estes doentes tem, frequentemente, mais do que um local de obstrução, bem como, por vezes, lesões de cirurgia e radioterapia prévias. A combinação destes múltiplos factores está, muitas vezes, associada ao insucesso clínico e a uma taxa acrescida de complicações. Como consequência a utilização de próteses metálicas na obstrução causada por lesões extra-colónicas deve ser sempre ponderada e a selecção dos doentes ser adequada[60,61].

A colocação de próteses na obstrução maligna colo-rectal está associada a elevadas taxas de sucesso técnico e clínico. A revisão sistemática com maior número de doentes na literatura refere um sucesso técnico global de 93.24% (intervalo de 64 a 100%)[62]. No que diz

respeito ao sucesso clínico imediato a mesma meta-análise refere valores médios de 88.56% (intervalo 55-100%).

a) Preparação, técnica e próteses disponíveis

Perante uma oclusão, em especial completa, deve considerar-se a utilização de antibioterapia de largo espectro, já que a introdução de ar no cólon pode provocar fenómenos de micro-perfuração e bacteriémia. A preparação oral está contra-indicada, sendo esta efectuada através de 2-4 enemas de limpeza, número dependente, não só do tipo de oclusão (total ou sub-total), mas também do local provável de obstrução. A técnica é iniciada com o doente em decúbito lateral esquerdo. Algumas vezes, em especial quando as lesões se encontram no colon esquerdo, o doente é mudado para o decúbito dorsal durante o procedimento, para uma melhor visualização fluoroscópica. À semelhança das próteses gastro-duodenais também a colocação de próteses colo-rectais apresenta, do ponto de vista técnico, duas modalidades: TTS e outra não TTS. Ambas iniciam-se com a canulação da estenose através da técnica descrita anteriormente, associada à marcação da extremidade proximal da lesão com um clip hemostático. Após o fio guia estar em posição existem, como dito anteriormente, duas abordagens: a colocação TTS, implicando um avanço da prótese através do canal de um colonoscópio e que permite a libertação do dispositivo em qualquer local do cólon. A técnica não TTS deve ser reservada para estenoses localizadas no recto e na sigmóide distal a cerca de 20-30 cm da margem anal.

Descrita, originalmente, no início da década de 90 do século XX por Dohmoto et *al.*[63], a técnica manteve-se idêntica nos seus princípios básicos[53,59], embora o material e as próteses utilizadas tenham sofrido grande evolução. Existem vários tipos de próteses disponíveis, numa grande variedade de diâmetros e tamanhos, permitindo uma selecção adequada da prótese em relação com a anatomia, com o diâmetro da obstrução e comprimento da estenose (Tabela 3). As próteses podem ser constituídas por vários materiais como o aço inoxidável, o elgiloy e o nitinol, podendo ser descobertas ou cobertas. Os revestimentos podem ser de diferentes materiais como o poliuretano, o polietileno e o silicone, tendo como objectivo principal impedir o crescimento tumoral através das malhas da prótese. O aço inoxidável e o elgiloy são materiais praticamente abandonados e na generalidade as próteses são compostas por nitinol. Este composto, para além da sua maleabilidade, não é ferromagnético, o que permite a realização de ressonâncias magnéticas aos doentes, ainda que nas zonas anatomicamente vizinhas da prótese possam existir alguns artefactos. Uma questão importante é a utilidade clínica das próteses cobertas. No momento actual e em função dos estudos disponíveis não

existem vantagens na utilização de dispositivos cobertos em detrimento de formas descobertas, quer na ponte para a cirurgia quer na paliação[62,64,65]. Quando usadas na paliação definitiva de lesões obstrutivas as próteses cobertas podem ter o potencial de evitar o crescimento do tumor através das malhas e consequentemente impedirem a reobstrução tumoral da prótese. Contudo, estudos comparativos entre formas cobertas e descobertas, associados a análises retrospectivas sugerem que a potencial vantagem dos dispositivos cobertos é limitada pela importante taxa de migração destas próteses com a consequente reobstrução tumoral[62,64,65,66]. Um estudo recente de Lee *et al.* comparou o uso de próteses cobertas com dispositivos descobertos em 80 doentes com obstrução maligna colorectal[66]. No grupo das próteses cobertas registaram-se 9 complicações tardias, incluindo 6 migrações, 1 reobstrução da prótese e 2 casos de impactação fecal. No grupo dos dispositivos sem cobertura apenas se verificaram 3 casos de reobstrução das próteses por crescimento tumoral através da malha, sugerindo que não existe nenhuma vantagem óbvia no recurso a próteses cobertas quando comparadas com as formas descobertas na paliação de estenoses malignas colo-rectais.

Tabela 3. Algumas das próteses metálicas para o cólon

Marca	**Diâmetro (mm)**	**Comprimento (mm)**	**Diâmetro do sistema (Fr)**	**Casa Comercial**
WallFlex	22,25	60, 90,120	10	Boston Scientific
Evolution	25	100, 120	10	Wilson-Cook
Hanarostent*	20,22,24	70-120	10.2	MI Tech
Niti-S*	18,20,22,24	60,80,100,120	10.5	Taewoong Medical

*Disponível em formas totalmente cobertas e parcialmente cobertas

b) Resultados clínicos da utilização de próteses na obstrução maligna colo-rectal

1. Ponte para cirurgia

Aceita-se, no momento actual, que a melhor opção para o tratamento emergente de uma obstrução colo-rectal é a utilização de próteses expansíveis. Como descrito anteriormente a cirurgia encontra-se associada a elevadas taxas de morbilidade e mortalidade[53,56,57]. A utilização de próteses permite uma elevada taxa de sucesso clínico e um número de complicações inferiores a 5%[59]. A descompressão do cólon permite equilibrar o doente em termos iónicos e metabólicos, para além de possibilitar a preparação adequada do cólon. A grande vantagem desta abordagem resulta na possibilidade de realizar uma cirurgia

potencialmente curativa numa só etapa e com reduzidos riscos para o doente. Uma revisão sistemática recente incluindo 88 estudos sugere que a utilização de próteses expansíveis é uma estratégia segura e clinicamente eficaz, permitindo a resolução da obstrução e a realização de cirurgias numa só etapa[57]. Contudo, validade destes resultados é limitada tendo em conta que a maioria dos estudos analisados apresentam um pequeno número de doentes e são na sua maioria retrospectivos. Apenas existem dois estudos randomizados que abordam este problema e apresentam resultados completamente díspares[67,68]. Cheung *et al.* publicaram em 2009 um trabalho com 48 doentes (24 em cada grupo)[67]. O sucesso técnico e clínico no grupo das próteses foi de 83%. No grupo endoscópico do estudo os doentes apresentaram significativamente melhores resultados no que diz respeito à taxa de complicações, ao número de doentes nos quais a cirurgia foi realizada numa só etapa e ao número de colostomias definitivas. Um outro estudo recente multicêntrico incluiu 60 doentes (30 em cada grupo)[68]. No grupo da cirurgia 17 doentes foram submetidos a uma colostomia definitiva em comparação com 13 doentes no grupo das próteses (P=0.3). O sucesso técnico no grupo das próteses foi muito baixo e existiram 3 perfurações levando ao encerramento precoce do estudo. Uma das grandes críticas a esta investigação é o baixo sucesso técnico sugerindo que em alguns dos centros foram envolvidos endoscopistas com pouca experiência.

Um outro assunto de debate é a relação custo-benefício da colocação de próteses já que, de um modo geral, estes dispositivos são caros, rondando valores entre 1000 e 2000 euros. Vários estudos sugerem que a estratégia de colocação de próteses seguida de cirurgia apresenta menores custos que da cirurgia de emergência isolada. Esta vantagem assenta em 2 aspectos fundamentais: o tempo de hospitalização e os custos inerentes à criação de colostomias são muito maiores quando os doentes são operados num contexto de emergência, sem o cólon preparado[69,70].

Em resumo e apesar de necessitarmos de mais estudos randomizados, existe um forte consenso que numa situação de emergência e sempre que possível deve ser oferecido ao doente a possibilidade de colocação de uma prótese como ponte para a cirurgia já que este procedimento está associado a uma menor taxa de complicações, menor tempo de hospitalização, maior número de cirurgias numa só etapa e menor número de colostomias com melhoria de qualidade de vida, quando comparado com a cirurgia de emergência.

2. Terapêutica paliativa

Como descrito anteriormente, uma percentagem importante dos doentes que se apresentam com obstrução maligna colo-rectal tem doença incurável e a paliação é a única

alternativa disponível. No contexto da paliação e independentemente da estratégia terapêutica adoptada a recuperação do trânsito intestinal e a manutenção da patência do lúmen colónico é fundamental. A pergunta que se coloca é se a utilização de próteses metálicas auto-expansíveis na paliação definitiva apresenta o mesmo grau de sucesso que o recurso a estes dispositivos como ponte para a cirurgia?

Três estudos randomizados compararam a cirurgia paliativa com a colocação de próteses em doentes com obstrução colo-rectal[71,72,73]. Um estudo inicial, com 30 doentes, sugere que os resultados são similares entre os 2 grupos, mas a colocação de próteses está associada a uma melhoria da qualidade de vida e a uma redução dos custos[71]. Um outro trabalho, englobando 22 doentes, refere que a abordagem endoscópica apresentou melhores resultados em termos de tempo de hospitalização, resolução dos sintomas obstrutivos e tempo de retoma da alimentação oral[72]. Um estudo recente foi terminado prematuramente devido ao elevado número de perfurações no grupo do tratamento endoscópico, resultando numa mortalidade de 30%. Uma das grandes críticas a este trabalho é o elevado número de perfurações (60%), muito acima das taxas referidas em múltiplos trabalhos existentes na literatura[73].

Alguns estudos prospectivos e trabalhos retrospectivos recentes parecem sugerir o inequívoco valor das próteses metálicas no cenário paliativo. Um estudo prospectivo com 44 doentes seguiu 14 doentes até à morte e destes 12/14 (86%) mantiveram-se livres de sintomas obstrutivos até à morte[58]. Uma comparação retrospectiva recente entre colocação de próteses (71 doentes) e cirurgia (73 doentes) sugere que com a estratégia de tratamento endoscópico é possível obter não só uma descompressão inicial eficaz, como também um sucesso a longo prazo, comparável ao da cirurgia[52]. Neste trabalho, embora a colocação inicial de uma prótese tenha um tempo livre de obstrução inferior à cirurgia, a colocação de uma segunda prótese, em doentes com reosbtrução tumoral da prótese inicial, permite obter um tempo de patência luminal semelhante ao obtido no grupo cirúrgico. Mais argumentos a favor da colocação de próteses foram apresentados num largo estudo retrospectivo: aos 6 meses a taxa de sucesso clínico estimado foi de 77.2%, enquanto a patência do lúmen colónico, até á morte, manteve-se em 108/122 doentes (88.5%)[74]. Um outro estudo de análise económica sugere que apesar do sucesso técnico e clínico dos 2 tratamentos (endoscopia e cirurgia) serem semelhantes, a colocação de uma prótese está associada a menor tempo de internamento, menor taxa de complicações e um custo inferior a 30-50%, quando comparada com uma colostomia[75]. Finalmente estudos sobre a qualidade de vida sugerem que a colocação de próteses está associada a uma melhor qualidade de vida em comparação com a cirurgia[76]. Perante estes

argumentos alguns autores referem que a cirurgia em doentes com esperança de vida muito limitada pode mesmo ser considerada uma atitude terapêutica não ética, levando a profundas implicações de carácter negativo na qualidade de vida[53,78].

Apesar destes argumentos existem poucos trabalhos que tenham seguido um largo número de doentes, no cenário paliativo, até à morte e alguns desses estudos mostraram resultado antagónicos. Nesta dissertação procura-se avaliar este problema através de um estudo retrospectivo multicêntrico em que uma larga população de 89 doentes é seguida desde a colocação da prótese até à morte (artigo 4).

c) Complicações

Existe algum consenso em que a colocação de uma prótese colo-rectal é um procedimento associado a uma taxa de mortalidade inferior a 1%[58,74,77,78]. Globalmente e em muitos estudos a taxa de complicações está próxima dos 25%[57,58,62,74,77,78]. Uma das complicações mais frequentes é a oclusão da prótese por invasão tumoral. A probabilidade de obstrução da prótese aumenta com o acréscimo de sobrevida dos doentes, devido ao natural crescimento da massa tumoral. A revisão sistemática de Khot *et al.* refere uma taxa de obstrução da prótese de 16% em doentes submetidos a paliação definitiva por próteses metálicas[79]. O tratamento de escolha, no momento actual, é a inserção de uma nova prótese através da prótese inicial invadida por tecido neoplásico. Num estudo recente a taxa de obstrução foi de 15.4% após um tempo médio de 127 dias e foi resolvida com sucesso, na maioria dos casos, com a colocação de novo dispositivo[80]. Este tema é abordado num artigo desta dissertação (artigo 4).

Outra complicação importante é a migração da prótese, que pode ser assintomática, associar-se a sintomas obstrutivos ou ainda a hemorragia e tenesmo se a prótese encravar no recto. Estudos recentes apresentam taxas de migração entre os 3-12% nas próteses descobertas[62,81], valores muito inferiores às taxas de migração dos dispositivos cobertos que podem apresentar valores entre os 30-50%[80]. Vários factores podem aumentar a taxa de migração: a) quimioterapia pela redução da massa tumoral; b) estenoses por compressão extrínseca; c) localização rectal. Este assunto é também abordado nesta dissertação através de análise univariada e multivariada de factores que podem influenciar a migração (artigo 4).

A complicação mais grave é a perfuração que pode ocorrer em diferentes momentos da terapêutica paliativa: a) a relacionada com o procedimento, com uma taxa de 15-20% do valor total da complicação, e que está associada à manipulação e à dilatação da estenose[53]. A

restante taxa de perfuração resulta da expansão da prótese contra a massa tumoral ou pela erosão das extremidades da prótese num tecido normal, ainda que fragilizado. A taxa global de perfuração ronda os 5% em vários estudos[58,62,74,78,81]. Um trabalho recente englobou 2287 doentes de 82 artigos, e refere uma taxa de perfuração de 4.9%[82]. As taxas desta complicação na ponte para cirurgia e na paliação não foram significativamente diferentes (4.8% versus 5.4%, *P*=0.66), sendo que a grande maioria destes eventos ocorrem menos de 30 dias após a colocação da prótese (cerca de 50% ocorrendo menos de 24H após a colocação). A mortalidade relacionada com a perfuração foi de 0.8% por doente submetido a prótese, mas quando se analisam os valores de mortalidade apenas dos doentes onde este evento ocorre os números são mais assustadores (16.2%). Parecem existir vários factores de risco para perfuração incluindo a dilatação da estenose com balão, quimioterapia e o uso de um agente anti-angiogénico, o bevacizumab[73,74,78,82,83]. Este fármaco pode, por si só, aumentar o risco de perfuração em doentes com neoplasia colo-rectal, estando esse risco acrescido em doentes tratados de uma forma paliativa com próteses metálicas expansíveis[83].

Em resumo e apesar dos estudos randomizados apresentarem resultados divergentes, o uso de próteses metálicas como ponte para cirurgia na obstrução maligna aguda colo-rectal parece ser a terapêutica de escolha e isso é suportado por vários relatos prospectivos e retrospectivos bem como por estudos de análise económica. Apesar de não ser um consenso global parece existir uma evidência crescente nas vantagens da colocação paliativa de próteses em detrimento da cirurgia paliativa.

Próteses expansíveis no tratamento de estenoses esofágicas benignas

A utilização de próteses metálicas auto-expansíveis na paliação de estenoses malignas do esófago é uma das abordagens terapêuticas mais consensuais na endoscopia. O recurso a sistemas de implantação de baixo diâmetro associados a uma expansão lenta e gradual das próteses permite, não só um sucesso técnico elevado, bem como a obtenção de largos diâmetros e um alívio sintomático rápido e relevante. De forma a evitar o crescimento tumoral através das malhas do dispositivo, a maioria das próteses usadas no esófago são cobertas por uma membrana plástica (constituída por diversos materiais, como descrito anteriormente). Uma vez que qualquer cobertura facilita a migração das próteses, estes dispositivos não são cobertos nas suas extremidades de forma a facilitar (como explicado anteriormente) o crescimento tumoral e a sua fixação na parede esofágica. A consequência imediata deste fenómeno é a impossibilidade de remoção da prótese a breve prazo, o que se torna irrelevante em doentes com esperança de vida limitada. Todavia, este aspecto torna-se relevante quando

falamos de lesões benignas onde a retirada da prótese é fundamental. Recentemente foram introduzidas no arsenal terapêutico próteses totalmente cobertas, que não aderem à parede do esófago, e que podem ser removidas quando necessário: a) próteses plásticas expansíveis, feitas de poliéster e cobertas por uma membrana de silicone; b) próteses metálicas auto-expansíveis, totalmente cobertas. Um outro conceito emergente e com grande potencial é o aparecimento de próteses biodegradáveis, que sofrem degradação metabólica e absorção pelos tecidos onde são colocadas.

a) O problema: o conceito de estenoses esofágicas refractárias

Antes do tratamento de uma estenose esofágica é necessário equacionar vários factores que podem condicionar a resposta da estenose á dilatação: se a estenose é simples (<2cm) ou complexa (>2cm), linear ou tortuosa, se permite ou não a passagem do endoscópio convencional (>9.5cm) e a sua etiologia. Estenoses pépticas, corrosivas, pós radioterapia, pós cirurgia e até pós terapêutica fotodinâmica são as principais causas de estenoses esofágicas encontradas. A dilatação seriada com balões ou dilatadores rígidos como as velas de Savary-Guilliard é o tratamento de escolha para as estenoses esofágicas. Contudo, até cerca de 40% das estenoses esofágicas recidivam durante o período de dilatações[84-86]. As Estenoses mais difíceis de tratar são habitualmente as mais complexas e que recidivam precocemente (dias a semanas). Estenoses com recidiva frequente são habitualmente designadas por refractárias, embora existam várias definições para este conceito. Actualmente a mais aceite é a de Kochman et *al.*[87] que propuseram a seguinte definição: restrição anatómica esofágica de carácter fibrótico, na ausência de inflamação ou distúrbio da motilidade e em que não existe a possibilidade de manter um diâmetro esofágico igual ou superior a 14mm após 5 sessões de dilatação com intervalos de duas semanas ou não existe a possibilidade de manter um diâmetro esofágico igual ou superior a 14mm durante 4 ou mais semanas após se ter obtido um diâmetro luminal esofágico de 14mm. Esta definição, apesar de ser a mais usada, tem várias limitações, sendo a principal o facto de não considerar diferentes etiologias para a estenoses, já que estenoses de diferentes causas podem responder de diferentes formas às dilatações. Para além das dilatações seriadas, tem-se recorrido a outras abordagens endoscópicas, incluindo a injecção intra-lesional de corticosteróides, o corte de fibrose por electro-cautério, próteses expansíveis e a combinação destas tratamentos. Finalmente, resta a cirurgia para os casos mais difíceis e que não está isenta de morbilidade e mortalidade.

b) A ideia: o recurso a próteses expansíveis temporárias como dilatadores permanentes.

Se durante uma dilatação, os poucos segundos em que a estenose é submetida à força de um dilatador pode provocar o alívio da disfagia durante dias ou semanas, conceptualmente, a presença desse dilatador durante semanas ou meses pode levar a um alívio permanente da disfagia. Idealmente, as próteses expansíveis podem cumprir esse objectivo uma vez que não só permitem a dilatação permanente como aliviam a disfagia enquanto estão em posição. Apesar disso, e uma vez que estamos a lidar com estenoses benignas é necessária a remoção da prótese após algum tempo. Tem-se utilizado, na função de dilatadores temporários, diversos tipos de próteses: a) próteses metálicas (parcialmente cobertas e totalmente cobertas); b) próteses expansíveis plásticas; e c) próteses biodegradáveis. Infelizmente a maior parte dos estudos abordando este assunto são retrospectivos, com poucos doentes e onde a definição de estenose refractária é questionável. Na actualidade não dispomos de estudos prospectivos e randomizados, sobretudo comparando diferentes tipos de próteses. Num dos artigos desta dissertação e de uma forma prospectiva comparámos a eficácia dos 3 tipos de próteses disponíveis: metálicas totalmente cobertas, plásticas e biodegradáveis (artigo 5).

c) Próteses metálicas auto-expansíveis totalmente cobertas

Este tipo de próteses foram inicialmente designadas para o tratamento de estenoses malinas. Como se descreveu anteriormente as extremidades descobertas deste tipo de próteses permitem que estes dispositivos se integrem na parede esofágica, reduzindo o risco de migração, mas ao mesmo tempo tornando a sua remoção um procedimento difícil e de risco. Este facto torna-se irrelevante quando as próteses são utilizadas no contexto paliativo, mas revela-se importante se pretendemos remover as próteses. A sua permanência numa estenose benigna pode levar a complicações como ulcerações, fístulas, formação de novas estenoses e até perfurações[88,89]. Numa revisão de 29 doentes submetidos à colocação de próteses metálicas parcialmente cobertas, Sandha *et al.* referem uma taxa de complicações de 80%, incluindo formação de novas estenoses (40%), migração (31%) e fístulas traqueo-esofágicas (6%)[89]. Devido à elevada taxa de complicações a próteses metálicas parcialmente cobertas não podem ser recomendadas para a colocação temporária em estenoses esofágicas benignas refractárias[90].

d) Próteses plásticas

As próteses plásticas existentes são designadas por Polyflex® (Boston Scientific, Natick, Massachusetts, EUA). As próteses são feitas de uma malha de poliéster, tendo uma cobertura de silicone ao longo de toda a prótese. Devido a esta cobertura a prótese não induz ou induz minimamente a formação de tecido de granulação. Como consequências as próteses

plásticas não aderem à parede esofágica, o que facilita a sua remoção. A prótese apresenta, na sua extremidade proximal, um diâmetro superior ao do corpo, em forma de tulipa, de forma a reduzir a taxa de migração. Para mais fácil visualização sob fluoroscopia a prótese apresenta 3 marcas radiopacas localizadas nas suas extremidades e porção média A prótese está disponível em vários tamanhos e diâmetros (Tabela 4). Este dispositivo necessita de ser montado num introdutor, que apresenta um calibre que vai de 12 a 14mm consoante o diâmetro da prótese. Este dispositivo não tem qualquer fio de sutura na sua extremidade proximal e a remoção da prótese pode ser realizada com o auxílio de uma pinça que agarre a sua extremidade superior. Nos últimos anos assistiu-se a uma grande utilização das próteses plásticas no tratamento de condições esofágicas benignas incluindo fístulas, fugas pós anastomóticas, perfurações e estenoses benignas. Existem várias séries prospectivas e retrospectivas analisando o uso temporário de próteses plásticas no tratamento de estenoses esofágicas refractárias, muitas delas com resultados antagónicos. Os estudos iniciais apresentaram bons resultados, levando a uma elevada taxa de doentes sem disfagia no final do estudo. Num trabalho prospectivo com 21 doentes (17 com estenoses benignas), a colocação temporária das próteses foi curativa em 13/17 doentes (76.5%)[91]. As próteses permaneceram no esófago durante um período que variou entre os 2 dias e os 12 meses e a taxa de migração foi de 52.9%. Num outro estudo, 15 doentes com estenoses refractárias foram tratados com a colocação temporária (6 semanas) de próteses de plástico e no final do estudo 12/15 doentes (80%) estavam livres de disfagia. Os autores não encontraram complicações significativas e a taxa de migração foi baixa (6.7%). Contudo, estudos posteriores moderaram o entusiasmo inicial apresentando taxas de sucesso muito inferiores, variando entre os 0 e os 30%[93-98]. Holm *et al.* apresentam um estudo retrospectivo de 30 doentes com condições esofágicas benignas (22 doentes com estenoses)[93]. A melhoria clínica, a longo prazo, foi apenas obtida em 17% dos doentes e a taxa de migração foi de 62.1%. Um estudo prospectivo com 40 doentes com estenoses benignas submetidos à colocação, durante um mês, de próteses plásticas apresentou uma taxa de sucesso de 30% no final do estudo[95]. Neste trabalho a taxa de migração foi de 22% e os autores apresentaram uma lista de complicações importantes, incluindo hemorragia, dor torácica severa, perfuração e até uma caso de morte. Também um relato de 5 doentes refere um sucesso clínico de 0%, e complicações em todos os doentes, incluindo migração (60%), perfuração e dor torácica grave[97]. Numa revisão sistemática, incluindo 10 estudos, e 130 doentes submetidos a próteses plásticas para o tratamento de estenoses refractárias do esófago Repici *et al.*[99], descreveram uma taxa de sucesso técnico em 98% dos casos. O sucesso clínico, a longo prazo, foi obtido em 52% dos doentes, embora esta taxa possa reflectir o sucesso muito elevado dos 3 estudos iniciais. Com os dados disponíveis o sucesso clínico a longo prazo das próteses plásticas é

incerto, mas provavelmente inferior a 30%. De igual modo o tempo de colocação não está definido e o uso das próteses não é desprovido de complicações, em especial migrações e elevada taxa de reintervenções.

Tabela 4. Características das próteses plásticas expansíveis

Marca	Diâmetro (mm)	Comprimento (mm)	Diâmetro do sistema (mm)	Casa Comercial
Polyflex	16	90, 120, 150	12	Boston Scientific
	18	90, 120, 150	13	
	21	90, 120, 150	14	

e) Próteses metálicas totalmente cobertas

Uma vez que a porção descoberta de uma prótese adere facilmente à mucosa esofágica, podendo ficar embebida na parede do órgão, a melhor forma de o prevenir é recorrendo a próteses em que toda a malha metálica está envolvida por uma cobertura. A generalidade das próteses cobertas existentes (Tabela 5) tem duas extremidades de maior diâmetro, em relação ao corpo para reduzir a taxa de migração. A maioria das próteses tem um fio de sutura na sua extremidade proximal, de forma a permitir a sua captura por uma pinça, e consequente remoção da prótese. Ao contrário daquilo que se passa com as próteses plásticas o introdutor das próteses metálicas é de baixo calibre e permite, na maior parte dos casos, o reposicionamento da prótese, durante a sua libertação. Num estudo em modelos animais (porco), Baron *et al.* demonstrou que as próteses parcialmente cobertas induziam marcado tecido de granulação o qual ao provocar a adesão da prótese à parede do esófago tornava a sua retirada especialmente traumática[100]. Por outro lado, e no mesmo trabalho, a utilização de próteses totalmente cobertas estava associado a uma resposta tecidular mínima o que possibilitava uma fácil retirada destes dispositivos. A grande limitação das próteses totalmente cobertas, neste modelo animal, foi a sua importante taxa de migração. Existem, na literatura, alguns estudos, a maioria de carácter retrospectivo, e com resultados variáveis[101,102,103]. Um trabalho, proveniente da área da radiologia de intervenção, avaliou a eficácia de 3 tipos de próteses cobertas em 55 doentes[101]. As próteses estiveram colocadas durante um tempo variável (1 semana a seis meses), e a taxa de sucesso clínico a longo prazo foi de 31%. As complicações mais frequentes foram: hiperplasia tecidular (31%), migração (25%) e dor severa necessitando de analgésicos centrais (24%). Eloubeidi *et al.* apresentaram recentemente os resultados de um estudo retrospectivo envolvendo 19 doentes em dois

centros de referência nos Estados Unidos[102]. No final do seguimento a taxa de doentes sem disfagia foi de 21% e a complicação mais frequente foi a migração (37%). Um trabalho recente, proveniente da China, analisou retrospectivamente 24 doentes submetidos à colocação temporária (4-8 semanas) de próteses em estenoses pós cirurgia (estenoses da anastomose esófago-gástrica). Os autores referem apenas um caso de migração e a taxa de doentes sem disfagia após um ano foi de 70.8%.

Tabela 5. Algumas das próteses metálicas totalmente cobertas para o esófago

Marca	**Diâmetro (mm)**	**Comprimento (mm)**	**Diâmetro do sistema (Fr)**	**Casa comercial**
WallFlex	18	103, 123, 153	6.2	Boston Scientific
	23	105, 125, 155	6.3	
Alimaxx	18	70, 100, 120	7.4	Merit Medical
	22	70, 100, 120	7.4	
Evolution	18	80, 100, 120	8	Wilson-Cook
	20	80, 100, 120	8	
Niti-S	16	60, 80, 100, 120, 150	5.8	Taewoong
	18	60, 80, 100, 120, 150	6.5	Medical
	20	60, 80, 100, 120, 150	6.5	

Baseados em estudos retrospectivos, com um número limitado de doentes, parece evidente que este tipo de próteses não induz uma quantidade significativa de tecido hiperplásico, o que as pode tornar facilmente removíveis. A experiência inicial, com estes dispositivos, no tratamento de estenoses esofágicas refractárias parece encorajadora, com uma taxa de sucesso razoável e com um número de complicações graves baixo. São necessários mais estudos para definir melhor a duração da colocação das próteses e melhores desenhos destes dispositivos para reduzir a taxa de migração.

f) Próteses biodegradáveis

As próteses biodegradáveis, actualmente disponíveis, são feitas de um material existente nas suturas cirúrgicas e que o organismo pode metabolizar: a polidioxanona, um polímero poliláctico, de degradação pH-dependente. Como vimos anteriormente a prótese designa-se por Ella®, é proveniente da República Checa, necessita de ser montada manualmente no sistema de introdução e está disponível em vários tamanhos e diâmetros

(Tabela 6). Esta prótese mantem a sua força radial e integridade durante 6-8 semanas após a sua colocação. A desintegração que se verifica, a partir desta data está completa por volta das 11-12 semanas e é acelerada por um baixo pH. A ideia original associada a este tipo de próteses é que a prótese rapidamente fique embebida na parede esofágica, tenha uma baixa taxa de migração e se dissolva lentamente, permitindo a resolução da estenose. Torna-se importante, neste contexto, a boa compatibilidade tecidular do material da prótese, de forma a reduzir o tecido hiperplásico, resultante da reactividade do organismo ao corpo estranho que é a prótese. O primeiro relato pertence a Saito *et al.* que em dois estudos consecutivos descreve a sua experiência com uma prótese fabricada manualmente, composta de monofilamentos de ácido poliláctico e colocada em doentes pós dissecção submucosa do esófago[104,105]. Existem 3 estudos na literatura com a prótese Ella®[106,107,108]. Um estudo prospectivo, com 21 doentes, refere uma taxa de sucesso clínico a longo prazo de 42.9%[106]. As principais complicações foram: dor intensa (14.3%), migração (9.5%), hemorragia (4.75%) e tecido hiperplásico clinicamente significativo (4.75%). Um estudo comparativo entre próteses plásticas e biodegradáveis refere uma taxa de sucesso clínico em 33% dos doentes[107]. As principais complicações foram: dor intensa (11%), hemorragia (2%) e tecido hiperplásico clinicamente significativo (11%). Um estudo recente, prospectivo, incluindo 10 doentes com estenoses pós anastomose esófago-gástrica, apresentou uma taxa de sucesso clínico a longo prazo de 70%[108]. Apenas se registaram 2 casos de hiperplasia clinicamente significativa e não existiram casos de migração ou dor intensa. Do que se disse as próteses biodegradáveis parecem um campo muito promissor e para além de estarem em estudo novas versões das próteses esofágicas (diferentes aberturas de malha, parcialmente cobertas), já existem próteses biliares para colocação por via trans-hepática.

Tabela 6. Características das próteses biodegradáveis

Marca	**Diâmetro (mm)**	**Comprimento (mm)**	**Diâmetro do sistema (mm)**	**Casa Comercial**
Ella	16	60, 80, 100	9.4	Królové
	18	60, 80, 100	9.4	
	23	60, 80, 100	9.4	
	25	60, 80, 100, 150	9.4	

Do exposto, parece evidente, que numa população onde as formas de tratamento disponíveis são muito limitadas, a colocação temporária de próteses se reveste de particular

interesse, estando por definir quais as melhores próteses e o tempo de colocação adequado às diversas formas de estenose esofágicas que se podem encontrar na prática clínica.

Próteses metálicas totalmente cobertas em condições biliares benignas

As condições biliares benignas incluem um conjunto de situações como as estenoses biliares, hemorragias, perfurações, fugas e cálculos.

As fugas biliares são situações que podem ocorrer após cirurgia do tracto biliar, em especial após a colecistectomia[109,110]. As fugas pós colecistectomia são habitualmente originárias do coto do cístico ou dos canais de Luschka. Porém, as fugas biliares podem ser mais complexas após lesões do hepático comum/via biliar principal ou após o transplante. O tratamento endoscópico baseado na colocação de próteses plásticas é considerado a primeira linha de tratamento, ainda que, ocasionalmente, não seja obtido um sucesso clínico em todos os casos[109,110]. As estenoses biliares benignas incluem as seguintes etiologias: lesões iatrogénicas pós-cirurgia, anastomoses, pancreatite crónica, colangite esclerosante e processos inflamatórios por coledocolitíase[111]. A coledocolitíase pode ser resolvida endoscopicamente através da Colangiopancreatografia Retrógrada Endoscópica (CPRE), procedimento associado a uma taxa de sucesso da ordem dos 95%[112]. Ocasionalmente, a utilização de próteses metálicas pode facilitar a remoção dos cálculos através da prótese (por exemplo em vias biliares com afilamentos do colédoco distal). A esfincterotomia endoscópica biliar (ETE) é um procedimento fundamental na terapêutica associada à CPRE. Este procedimento pode apresentar complicações como a hemorragia e a perfuração, que nem sempre são de fácil tratamento por métodos endoscópicos[113].

A CPRE, com colocação de próteses biliares de largo diâmetro é considerado o procedimento de rotina para o tratamento das diversas condições biliares benignas. Não obstante, as próteses plásticas estão associadas a alguns insucessos terapêuticos. Isto levou a uma procura de alternativas, nomeadamente a utilização de próteses metálicas, dispositivos de largo diâmetro e maior tempo de patência, como tratamento de recurso, após a falha da abordagem convencional. Uma vez que as próteses descobertas rapidamente ficam embebidas na parede biliar, a sua remoção torna-se difícil, o que limita a sua utilização[114]. De igual modo, as próteses parcialmente cobertas apresentam limitações, nomeadamente o facto da extremidade proximal destas próteses ser descoberta, e ter o potencial de ficar embebida na parede biliar, o que pode resultar no aparecimento, a longo prazo, de uma nova estenose, no local onde a prótese ficou aderente à via biliar[115].

Como consequência destas limitações, as próteses metálicas totalmente cobertas (Tabela 7), surgiram como uma opção no tratamento de recurso de várias condições biliares benignas, onde o tratamento endoscópico convencional com próteses plásticas se revestiu de insucesso. Um dos artigos desta dissertação avalia este problema, em especial no que diz respeito ao sucesso clínico, complicações e tempo de permanência das próteses na via biliar.

Tabela 7. Algumas das próteses metálicas totalmente cobertas para a via biliar

Marca	Diâmetro (mm)	Comprimento (mm)	Diâmetro do sistema (Fr)	Casa comercial
WallFlex	8	60, 80	8.5	Boston Scientific
	10	40, 60, 80	8.5	
Hanarostent	8	40, 60, 80, 100	8.5	MI Tech
	10	40, 60, 80, 100	8.5	
Niti-S	8	40-100, 120	8.5	Taewoong
	10	40-100, 120	8.5	Medical

a) Fugas biliares e prótese metálicas totalmente cobertas

A CPRE terapêutica recorrendo à ETE, colocação de próteses biliares plásticas de 10Fr ou a combinação de ambos é o tratamento de primeira linha para as fugas biliares. Embora não seja consensual a melhor abordagem terapêutica, existem trabalhos recentes que sugerem que a combinação dos dois métodos é a melhor opção no tratamento de fugas de alto débito[109,110]. O tratamento endoscópico é seguro, eficaz e com alta taxa de sucesso[116,117]. Apesar disso, existem relatos de fugas biliares refractárias necessitando de múltiplas intervenções e até de cirurgia[109,110]. No caso de fugas biliares simples, de baixo débito, como pequenas fugas do coto do cístico ou dos ductos de Luschka, o tratamento endoscópico apresenta uma taxa de sucesso muito elevado[109,110, 116,117]. A terapêutica endoscópica leva ao encerramento da fuga através da redução/eliminação do elevado gradiente trans-papilar; logo o mecanismo de encerramento é simplesmente mecânico. Contudo, num pequeno grupo de doentes com fugas mais complexas (fugas de alto débito do coto do cístico, fugas pós transplante, fugas pós colecistectomia parcial ou fugas do hepático comum/colédoco), o encerramento das fugas pode ser difícil, levando a um conjunto variado de procedimentos endoscópicos, ou mesmo implicando a cirurgia[114,118]. As fugas, resistentes à terapêutica convencional, designam-se por refractárias e podem ser, teoricamente, tratadas por próteses

metálicas totalmente cobertas. Devido ao seu largo diâmetro, estes dispositivos podem actuar por 2 mecanismos: a) redução ao máximo da pressão biliar; b) cobertura directa do local da fuga.

Baron *et al*[114]. foram os primeiros a relatar a utilização de próteses metálicas em fugas refractárias à terapêutica endoscópica convencional. Numa série de 3 doentes os autores utilizaram duas próteses parcialmente cobertas e uma totalmente coberta com um sucesso de 100%. Wang et *al.* avaliaram 13 doentes com fugas refractárias submetidas á colocação de próteses totalmente cobertas[119]. As próteses foram retiradas em apenas 11 doentes após um tempo mediano de 103 dias (intervalo, 67-493). Todos os doentes apresentaram encerramento das fugas, não obstante o procedimento ter sido associado a várias complicações: estenoses biliares de novo no local correspondente ao topo proximal da prótese, em 2 doentes, e que necessitaram de tratamento adicional; coledocolitíase em 10 dos 11 doentes; e ulcerações da via biliar após retirada das próteses em 5 doentes. Phillips *et al.* reportaram a sua experiência em 17 doentes com fugas biliares pós-transplante e que foram submetidos à colocação temporária de próteses totalmente cobertas para o tratamento das fugas[120]. As próteses foram retiradas ao fim de um tempo mediano de 102 dias (limites, 35-427). O tratamento foi eficaz em 94.1% dos casos (16/17 doentes), embora os autores refiram um elevado número de estenoses, clinicamente significativas, após a retirada das próteses (35% dos casos).

Estes dados parecem sugerir uma elevada eficácia das próteses no controlo de fugas refractárias, embora este procedimento esteja associado a complicações que limitam o seu uso. Uma das razões apontadas para a taxa de complicações é o excessivo tempo de permanência das próteses na via biliar, que poderá não ser justificável; ou seja as fugas poderiam ser tratadas com um menor tempo de permanência das próteses, o que hipoteticamente reduziria a taxa de complicações. Este assunto é estudado no artigo 6 desta dissertação, em que os bons resultados do trabalho abrem caminho a um estudo prospectivo sobre o tempo ideal de colocação das próteses.

b) Hemorragia pós-esfincterotomia e próteses metálicas totalmente cobertas

A hemorragia pós-ETE é uma complicação que pode ocorrer em 0.76-2% a 10-48% dos casos consoante a definição que é aplicada[121,122]. A principal abordagem terapêutica é o tratamento endoscópico que pode incluir injecção com epinefrina, endoclips, terapêutica térmica e compressão por balão, sejam estes tratamentos isolados ou em associação. Esta terapêutica está, habitualmente, associada à colocação de próteses plásticas de largo calibre

para permitir a drenagem biliar e ao mesmo tempo auxiliar no tamponamento do local da hemorragia. Porém, numa percentagem reduzida de casos, a hemorragia é refractária ao tratamento endoscópico e o seu controlo só é obtido por embolização angiográfica ou mesmo por cirurgia[121-124].

Num relato original Shah et *al.* trataram 5 doentes com hemorragia pós-ETE de difícil controlo e após falência de outras medidas terapêuticas incluindo embolização[123]. As próteses actuam por efeito mecânico, tamponando o local de hemorragia por compressão directa. Neste estudo observou-se sucesso clínico em todos os doentes. As próteses foram removidas em 3 doentes às 2,4 e 8 semanas e migraram em 2 doentes às 4 semanas. Num outro relato Itoi et al trataram 11 doentes com hemorragia pós-ETE de difícil controlo e obtiveram sucesso em todos os casos[124]. As próteses foram retiradas ao fim de um tempo médio de 8.2 dias (intervalo, 5-10) e não se registaram complicações.

Da escassa literatura disponível existe sugestão que a em situações de hemorragia de difícil controlo e após falência da terapêutica endoscópica habitual, o recurso a próteses metálicas totalmente cobertas pode constituir uma opção válida. Ficam por definir os tempos ideais de permanência da prótese na via biliar embora a literatura sugira que uma semana é suficiente. Este assunto é abordado no artigo 6 desta dissertação.

c) Perfurações pós-esfincterotomia e próteses metálicas totalmente cobertas

Outra complicação pós-ETE é a perfuração que pode ocorrer em 0.35% e 0.48-0.72% dos casos[113,125]. A terapêutica mais habitual para esta complicação é o tratamento conservador recorrendo a antibioterapia, dieta zero, soros e colocação de próteses plásticas. Apesar desta abordagem apresentar sucesso na grande maioria dos casos, o recurso à cirurgia é, ocasionalmente, necessário[113,125].

Na literatura existe um relato de Garcia-Cano *et al.* que trataram 2 perfurações com próteses cobertas, tendo retirado as próteses ao fim de um tempo médio de 96 dias, sem complicações[126]. Aparentemente o diâmetro e a força radial das próteses contribuem para a selagem da perfuração num mais curto espaço de tempo e com menor morbilidade. Na nossa dissertação incluímos um estudo (artigo 6) onde este problema é abordado.

Prótese metálicas auto-expansíveis na terapêutica paliativa da obstrução hilar maligna

A obstrução hilar maligna está associada a 3 etiologias distintas[127]: a) tumor primário das vias biliares (colangiocarcinoma); b) invasão local por tumores na vizinhança (vesícula,

pâncreas, estômago); c) envolvimento ganglionar por metástases de várias entidades (cólon, estômago, ovários, linfoma). A causa mais frequente de obstrução hilar é o colangiocarcinoma (CCA) e representa cerca de 3% dos tumores gastro-intestinais[128]. O CCA é o tumor primitivo dos colangiocitos, células epiteliais dos canais biliares. A localização mais comum do CCA é a região hilar, representando 60-70% dos casos, seguindo-se a porção distal do hepático comum em 20-30% dos casos e finalmente os ductos intra-hepáticos em 5-10% dos casos[129]. O CCA hilar foi pela primeira vez reconhecida como entidade clínica distinta em 1965, após o relato original de 13 casos por Klatskin[130]. O CCA é principalmente um tumor do idoso, com um pico de incidência na sétima década de vida e afectando predominantemente o sexo masculino[128,129]. Bismuth classificou as estenoses hilares malignas em 4 categorias, dependendo do envolvimento do hepático comum e do hilo (onde o Tipo I: envolvimento do hepático comum sem lesão da confluência; Tipo II: envolvimento da confluência sem lesão dos 2 hepáticos; Tipo III: envolvimento dos hepáticos direitos (IIIa) e esquerdo (IIIb) sem lesão nos ramos intra-hepáticos; Tipo IV: envolvimento da confluência, dos 2 hepáticos e de ramos destes[131]. Mais de 90% dos doentes apresentam-se com uma icterícia indolor. Habitualmente, os sintomas surgem tardiamente no curso da doença, determinando que, no momento do diagnóstico, cerca de 80-90% dos doentes tenham doença irressecável[132,133]. Por este motivo, o tratamento paliativo assume-se como principal objectivo terapêutico. A descompressão biliar com a consequente melhoria da icterícia e prurido contribui, adicionalmente, para melhorar a função hepática, para reduzir o risco de colangite e para uma melhoria da qualidade de vida ao diminuir a anorexia e perturbações do sono[134]. A drenagem endoscópica é preferível em relação à drenagem percutânea e à cirurgia, sendo considerada, no momento actual, a forma de tratamento a escolher[127,132-136].

a) Drenagem endoscópica da obstrução hilar maligna

A primeira descrição de uma drenagem endoscópica de carácter paliativo pertence a Nib Soehendra em 1979[11]. Na actualidade estão disponíveis dois tipos de próteses colocadas por via endoscópica: as próteses plásticas e as metálicas auto-expansíveis. A principal desvantagem das próteses plásticas é a sua elevada taxa de oclusão, que ocorre, habitualmente entre o 3º e o 4º mês após a sua colocação. As próteses metálicas auto-expansíveis biliares descritas, originalmente, em 1989[137,138] foram concebidas para oferecer um tempo de patência mais longo que as próteses plásticas. Existem poucos estudos comparativos entre próteses plásticas e metálicas no tratamento paliativo das obstruções hilares malignas. Wagner *et al* reportaram o único estudo prospectivo e randomizado disponível na literatura[139]. Vinte doentes com obstrução hilar maligna (Tipos II-IV) foram

randomizados para receber uma prótese plástica (n=9) ou uma prótese metálica (n=11), estas últimas colocadas por combinação de técnicas endoscópicas e percutâneas. Apesar das dimensões da amostra e da maior parte das próteses metálicas terem sido colocadas por via percutânea os autores observaram um maior tempo de patência, menor número de episódios de colangite, maior taxa de sucesso técnico, menor taxa de reintervenção, e menores custos associados aos procedimentos, nos doentes submetidos à colocação de uma prótese metálica. Um estudo avaliou prospectivamente os resultados clínicos, ao fim de 30 dias, da paliação endoscópica de 62 doentes com obstrução hilar maligna[140]. Os doentes foram submetidos a próteses plásticas (n=28) ou próteses metálicas (n=34). Os efeitos adversos foram classificados como: oclusão da prótese, colangite, migração e reintervenção. Recorrendo a um modelo multifactorial, de regressão logística, a colocação de uma prótese plástica esteve significativamente associada a um maior número de efeitos adversos a curto prazo (odds ratio: 6.32; 95% intervalo de confiança: 1.23-32.56), independentemente da classificação de Bismuth. Raju *et al.* apresentaram, recentemente, um trabalho retrospectivo onde compararam 100 doentes consecutivos, que foram submetidos à colocação de próteses plásticas (n=52) ou metálicas (n=48)[141]. Os principais objectivos do trabalho foram a avaliação da patência das próteses e a sobrevida. Os doentes foram divididos em grupos consoante a classificação de Bismuth, tendo sido seguidos até à morte, reintervenção ou durante um ano. A taxa de sucesso técnico foi elevada, em ambos os grupos (95.8% vs. 94.2% a favor das próteses metálicas). O grupo de doentes tratados com próteses metálicas apresentou uma patência significativamente maior das próteses (5.56 meses vs. 1.86 meses; $P < 0.001$), em comparação com as próteses plásticas, necessitando de menor número de reintervenções. Não houve diferenças entre os grupos na sobrevida e os autores concluíram que a patência das próteses metálicas é superior à das próteses plásticas em todos os grupos de Bismuth, embora o estudo não mostra uma clara comparação entre os diferentes tipos desta classificação.

Apesar de a literatura sugerir uma clara vantagem na utilização das próteses metálicas na paliação da obstrução maligna hilar, faltam estudos com elevado número de doentes em que as próteses plásticas sejam comparadas, num número variável de parâmetros, com as próteses plásticas em todas as classificações de Bismuth. O estudo 7 desta dissertação pretende contribuir para a clarificação desta temática.

Outro foco de discussão, assumindo a perspectiva de debate infindável, é a comparação entre a drenagem unilateral com a bilateral em doentes com envolvimento da confluência hilar. Só existe um estudo randomizado comparando estas duas abordagens, recorrendo a próteses plásticas[142]. Neste trabalho, 157 doentes consecutivos com obstrução

maligna hilar foram randomizados para colocação unilateral (n=79) ou bilateral (n=78). Na análise por intenção de tratar o grupo com colocação unilateral apresentou um maior sucesso técnico, menor taxa de complicações e menor taxa de colangites. Os autores concluíram que a tentativa de colocação bilateral, não só não apresentava vantagens, como poderia estar associada a uma maior taxa de complicações. Porém, este estudo deve ser encarado com reservas já que apresenta várias limitações: a) não refere as taxas de patência e de oclusão em ambos os grupos; b) não apresenta análise de grupos de Bismuth, tendo incluído um número elevado de doentes do tipo I, onde uma prótese é suficiente. Deviere *et al.,* utilizando duas ou mais próteses plásticas para obter uma drenagem completa biliar, referem que a utilização de duas ou mais próteses está associada a menores taxas de colangite precoce e tardia, bem como uma melhoria da sobrevida[143]. Um estudo retrospectivo recente analisou 46 doentes consecutivos com obstrução hilar maligna, submetidos a colocação unilateral (n=17) ou bilateral (n=29) de próteses metálicas[144]. Os autores não encontraram diferenças significativas no sucesso técnico (100% vs. 90%), no sucesso clínico (100% vs. 96%) e nas complicações tardias (65% vs. 54%). Os autores observaram que a patência cumulativa das próteses após colocação bilateral era significativamente superior à da colocação unilateral (488 dias vs. 210 dias, *P*=0.009), especialmente nos casos de CCA.

A colocação bilateral de próteses metálicas é tecnicamente difícil, mesmo para endoscopistas com experiência. Existem 3 técnicas distintas para esta colocação[144-150]: a) a técnica mais comum é designada por técnica de prótese através de prótese. Nesta abordagem uma prótese com malha constituída por células largas é colocada de um lado (preferencialmente o lado esquerdo). De seguida a segunda prótese é colocada contra-lateralmente através das malhas da primeira prótese[145,146]. Recentemente foram concebidas próteses de malha muito larga para facilitar esta técnica, e os resultados iniciais tem sido encorajadores[147,148]; b) uma segunda técnica consiste em, após colocação bilateral dos fios guia, introduzir uma prótese metálica e depois de estar em posição introduzir a segunda prótese no espaço entre a parede da via biliar e a primeira prótese parcialmente expandida. Alguns autores referem bons resultados com esta técnica[144,151,152]; c) recentemente foi desenvolvida um sistema de implantação com 6Fr de forma a permitir a colocação simultânea das duas próteses através do canal de um duodenoscópio terapêutico (4.2 mm). Existe um relato inicial, com elevada taxa de sucesso técnico e clínico recorrendo a esta técnica[149].

b) Reflexões sobre a drenagem endoscópica da obstrução maligna hilar

Do que foi dito parecem emergir dois aspectos fundamentais na discussão sobre a melhor abordagem endoscópica, em termos paliativos, da obstrução maligna hilar: a) parece haver vantagens no que diz respeito ao sucesso clínico e taxas de patência no uso de próteses metálicas em comparação com as próteses plásticas, embora não exista uma grande série comparando os dois dispositivos, que possa analisar sucessos técnico e clínico, complicações, patência, reintervenção e sobrevida.

O debate de colocação unilateral vs. bilateral está longe de ver o seu fim. Apesar de relatos recentes sugerirem um melhor tempo de patência e menor taxa de reintervenção após colocação bilateral de próteses metálicas, existe necessidade de maior evidência científica.

No estudo 7 desta dissertação observámos, numa larga população, diversas vantagens no uso de próteses metálicas em comparação com as próteses plásticas. Adicionalmente, encontrámos um maior tempo de patência e menor taxa de reintervenção após colocação bilateral de próteses metálicas em doentes com lesões de Bismuth tipo II. Este trabalho parece sugerir a realização de um estudo randomizado, multicêntrico, onde se possa comparar a colocação bilateral vs. unilateral de próteses metálicas em todas as classe de Bismuth, de forma a encontrar respostas para um debate com vinte anos.

OBJECTIVOS

OBJECTIVOS

Nas duas últimas décadas assistiu-se à disseminação do uso de próteses expansíveis, inicialmente metálicas e depois plásticas e biodegradáveis, em múltiplas doenças e condições benignas do tubo digestivo.

Nos primeiros anos utilizaram-se próteses esofágicas, seguindo-se as próteses biliares e posteriormente as entéricas (gastro-duodenais e colónicas). Finalmente as patologias benignas entraram no alvo terapêutico das próteses: no esófago, nas vias biliares ou em outros segmentos do tracto gastro-intestinal.

Subsistem, na actualidade, vários focos de controvérsia:

a) A colocação de próteses metálicas auto-expansíveis nas obstruções malignas gastro-duodenais permite a alimentação oral até à morte? É um procedimento com morbilidade apreciável? Doentes com uma sobrevida superior a 2 meses devem ser operados? Este evento está associado a que tipo de sobrevida?
b) A colocação de próteses metálicas como tratamento paliativo definitivo na obstrução maligna colo-rectal é eficaz durante o resto da vida dos doentes? É uma terapêutica tão eficaz como o uso de próteses metálicas na ponte para a cirurgia? Qual a necessidade da terapêutica cirúrgica após a colocação de uma prótese com intenção paliativa?
c) Qual a melhor abordagem de um doente com estenose refractária do esófago? Qual o valor da terapêutica temporária com próteses expansíveis e qual a prótese com mais eficácia (metálicas/plásticas/biodegradáveis)?
d) Justifica-se o uso da utilização temporária de próteses metálicas totalmente cobertas em condições benignas das vias biliares? Qual o período de tempo ideal para a sua utilização de forma a evitar as complicações descritas nos primeiros relatos da literatura?
e) Existe um debate infindável sobre a colocação unilateral e bilateral de próteses plásticas e metálicas no colangiocarcinoma hilar. Qual o melhor tratamento paliativo?

Esta dissertação é constituída por um conjunto de artigos que pretendem contribuir para a clarificação de várias questões associadas à colocação de próteses no tubo digestivo:

1) Papel das próteses metálicas auto-expansíveis na terapêutica paliativa de estenoses malignas gastro-duodenais, desde a sua colocação até à morte dos doentes (artigos 1 e 2).
2) Valor da utilização, a longo prazo, de próteses metálicas no tratamento paliativo de estenoses malignas colo-rectais (artigos 3 e 4).
3) Esclarecimento do papel de diferentes próteses expansíveis no tratamento de estenoses benignas do esófago, refractárias aos tratamentos convencionais (artigo 5).
4) Avaliação da importância, eficácia e tempo de colocação de próteses metálicas totalmente cobertas no tratamento de condições benignas das vias biliares (artigo 6).
5) Abordagem da importância e eficácia da colocação unilateral e bilateral de próteses plásticas e metálicas no tratamento do colangiocarcinomas hilar (artigo 7).

MÉTODOS

MÉTODOS

O detalhe específico dos métodos pode ser encontrado em cada artigo. Porém, existiram estratégias metodológicas que são importantes salientar:

1) Estudos retrospectivos (artigos 2,4,6,7): selecção de vários centros, onde o autor da tese trabalha ou colabora, de forma a obter uma casuística importante no panorama nacional e internacional. Após a selecção dos centros, recorreu-se a uma pesquisa exaustiva de diferentes bases de dados de doentes submetidos à colocação de próteses numa determinada patologia e num determinado espaço temporal. A identificação dos doentes levou à análise de múltiplas fontes de dados (processos clínicos, imagiológicos, relatórios médicos e de endoscopia, relatórios de seguimento e entrevistas telefónicas com doentes, familiares e médicos assistentes) de forma a obter, para cada doente, um número importante e variado de características. Desta forma foi possível constituir bases de dados completas e com casuísticas elevadas. Seguiu-se a análise estatística da base de dados levada a cabo por 2 estatistas, o que permitiu, para cada estudo, uma abordagem completa e uniforme.

2) Estudos prospectivos (artigos 1 e 5): após definição dos objectivos, local ou locais do estudo e realização dos tratamentos propostos, houve lugar ao seguimento detalhado dos doentes até ao fim do estudo (morte ou outro objectivo definido por data). Com os dados disponíveis elaborou-se uma base de dados que teve o tratamento estatístico adequado aos objectivos proposto permitindo a elaboração dos manuscritos.

3) Capítulo de livro (artigo 3) onde se faz uma revisão da metodologia e da literatura versando a importância e utilidade das próteses metálicas na obstrução maligna colo-rectal. Este capítulo apresenta os resultados de um estudo inicial, realizado de forma prospectiva e num único centro.

ARTIGOS

ARTIGO 1

Canena J, Liberato M, Romão C, Coutinho AP, Neves B, Guerreiro AS.

Utilização de próteses esofágicas metálicas expansíveis cobertas na paliação de estenoses malignas antro-pilóricas.

GE - J Port Gastrenterol 2005; 12:150-155

Artigo Original / Original Article

UTILIZAÇÃO DE PRÓTESES ESOFÁGICAS METÁLICAS EXPANSÍVEIS COBERTAS NA PALIAÇÃO DE ESTENOSES MALIGNAS ANTRO-PILÓRICAS

J. CANENA, M. LIBERATO, C. ROMÃO, A. P. COUTINHO, B. NEVES, A. S. GUERREIRO

Resumo

Introdução: O resultado da paliação de estenoses malignas antro-pilóricas (EMAP) com próteses metálicas é favorável, quando comparado com cirurgias de *bypass*, as quais apresentam morbilidade e mortalidade significativas. A experiência nesta área é ainda limitada, em especial o uso de próteses cobertas já que não existem próteses entéricas cobertas e as próteses esofágicas metálicas expansíveis cobertas (PEMEC) possuem, teoricamente, um cateter de aplicação curto. O recurso a próteses cobertas pode aumentar o tempo de paliação, e evitar a colocação de outra prótese em casos de sobrevivência mais prolongada.
Objectivos: Avaliar a possibilidade e a eficácia da paliação de EMAP com uma técnica uniforme recorrendo a PEMEC.
Material e Métodos: 10 doentes consecutivos (idade média 72,3, entre 68-77; 5 homens e 5 mulheres) com cancro gástrico avançado do antro e/ou piloro foram submetidos à colocação endoscópica de PEMEC. As indicações foram: tumor inoperável com metástases à distância em 9 doentes e recusa da cirurgia em um doente. Recorremos, em todos os casos, a PEMEC de nitinol com o cateter de aplicação original (95 cm). Todas as estenoses malignas foram dilatadas com balão TTS antes da aplicação e sempre que necessário recorreu-se a compressão abdominal para o avanço (sob controlo fluoroscópico) do cateter de aplicação. Em todos os casos procedeu-se ao seguimento dos doentes avaliando a duração da permeabilidade da prótese (por endoscopia), a tolerância alimentar e as complicações.
Resultados: A colocação da PEMEC foi possível em todos os casos. Registou-se franca melhoria dos sintomas de estase em todos os doentes com tolerância de dieta líquida/pastosa. Não se registaram casos de migrações e/ou invasão tumoral das próteses. Todos os doentes morreram durante o seu seguimento (média de sobrevivência: 8,9 meses, entre 2-23). Durante a colocação das próteses apenas houve a registar pequena hemorragia auto-controlada em 1 caso.
Conclusões: O recurso a PEMEC para a paliação de EMAP é possível do ponto de vista técnico. Este procedimento oferece boa paliação sem complicações *major*. O recurso a próteses cobertas oferece uma longa permeabilidade, evitando novos procedimentos, mesmo em casos de longa sobrevida (23 meses num doente).

Summary

The outcome of stenting gastric outlet malignant strictures (GOMS) is favourable when compared with bypass surgery which has significant morbidity and mortality. However, experience in this area is limited and covered stents are almost never used because of the non-existence of enteral covered stents and because covered oesophageal stents have, theoretically, a short delivery catheter length. Furthermore using covered stents could increase the time of lumen permeability avoiding further stenting.
Aim: To investigate the feasibility and efficacy of stenting GOMS with a uniform technique using self-expandable oesophageal covered metal stents.
Method: Ten consecutive patients (mean age 72.3, age range 68-77; 5 men and 5 women) with advanced gastric carcinoma of the antrum and/or pylorus underwent endoscopic placement of expandable metal stents. The indication for stenting was extensive tumour growth with presence of distant metastasis in 9 patients and refusal of surgical operation in one. The *Ultraflex* oesophageal covered stent with original delivery catheter (95 cm) was used in all cases. All malignant strictures were dilated with TTS balloon before stenting. Abdominal compression was used to help advance the delivery system when necessary. Complications and clinical outcomes were assessed in each patient during follow-up, which included repeat endoscopies to assess stent permeability.
Results: Stent placement was successful in all patients. Symptoms improved in all patients with tolerance of liquid and soft diets. There were no migrations, fracture or tumour overgrowth during survival period in all cases. All patients died during follow-up (mean survival 8.9 months, range 2-23). During stenting only minor bleeding occurred during one procedure: was registered without the need of blood transfusions.
Conclusion: Using covered oesophageal stents for GOMS is technically feasible. This procedure offers good palliation with no major complications. The use of covered stents offers long life permeability, avoiding further stenting even in long time survival rate (23 months in one patient).

GE - J Port Gastrenterol 2005, 12: 150-155

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Recebido para publicação: 07/12/2004
Aceite para publicação: 08/04/2005

INTRODUÇÃO

O cancro gástrico avançado pode complicar-se de estenose antro-pilórica que causa, frequentemente, dor abdominal, náuseas, vómitos e, em última análise, intolerância alimentar e malnutrição. Estes doentes são, habitualmente, maus candidatos para cirurgias de ressecção devido à existência de doença avançada (localmente e/ou à distância) como também ao estado de desnutrição apresentado. A abordagem convencional destas situações era, até à década de 90 do século XX, a cirurgia de derivação gastroentérica (aberta ou laparoscópica) cujos resultados não são os mais animadores em termos de morbilidade e mortalidade (1,2). A utilização de próteses metálicas por via peroral, tal como descrito inicialmente (3), parece ser mais rápida e com maior sucesso que as modalidades cirúrgicas (4,5). Contudo, este procedimento era geralmente considerado de difícil execução técnica (6,7), já que as próteses utilizadas eram habitualmente concebidas para o esófago, tendo catéteres de implantação excessivamente curtos.
Mais recentemente, a disponibilidade de próteses entéricas colocadas através do canal de trabalho do endoscópio tornou o procedimento mais fácil (8,9). Porém, o facto das próteses não serem cobertas têm-se reflectido no relato de uma relativamente alta incidência de reobstrução por invasão tumoral das próteses (10,11).
Neste trabalho, apresentamos os nossos resultados prospectivos da paliação endoscópica de estenoses malignas antro-pilóricas com uma prótese metálica auto-expansível coberta, concebida originalmente para o esófago, através de uma técnica uniforme e sem modificação das características originais da prótese.

MATERIAL E MÉTODOS

População Estudada

O estudo englobou 10 doentes consecutivos (entre Dezembro de 1999 e Outubro de 2002), 5 homens e 5 mulheres (idade média 72,3 anos, entre 68-73) com adenocarcinoma gástrico (7 de tipo intestinal e 3 de tipo difuso) de localização predominante antro-pilórica. Todos os doentes tinham vómitos de estase e intolerância alimentar, mesmo para líquidos. Nove doentes tinham um tumor maligno considerado irressecável devido a doença localmente avançada e/ou metástases à distância. Um doente, potencialmente operável, recusou cirurgia preferindo uma abordagem paliativa.
Após a colocação da prótese todos os doentes foram seguidos de forma a avaliar as complicações precoces e tardias, a retoma e tipo de nutrição entérica, permeabilidade da prótese (através de endoscopia digestiva alta se necessário) e sobrevivência.
Foi obtido o consentimento informado em todos os doentes antes do procedimento endoscópico.

Colocação da Prótese

Todos os procedimentos foram realizados sob sedação inconsciente com midazolam e propofol. Após acesso endoscópico à lesão, a sua parte proximal (antro-pilórica) foi marcada com um *clip* hemostático (Figura 1) utilizando um aplicador reutilizável (*Olympus Co*, Tokyo). Após esta manobra foi avançado um catéter radiopaco de duplo canal (*Boston Scientific Co*, USA) através da estenose, injectando-se contraste, sob controlo fluoroscópico, para avaliar a sua extensão. O comprimento das estenoses foi sempre avaliado pelo tamanho do catéter na estenose e nunca pelo comprimento do endoscópio. Em seguida avançou-se pelo catéter um fio guia de extremidade hidrofílica 0.035 de tipo *jagwire* (*Boston Scientific Co*, USA), de forma a franquear a estenose, e cuja extremidade distal ficou habitualmente na terceira porção do duodeno. Sobre o fio guia todas as estenoses foram dilatadas com balão hidrostático TTS (*Boston Scientific Co*, USA) até 12 mm de diâmetro (Figura 2). Sempre que possível a lesão era ultrapassada com o endoscópio de forma a marcar com novo *clip* a transição bulbo/D2 que se pretendia ser a parte distal de colocação da prótese e de forma a evitar que esta ficasse angulada na transição para D2. Esta abordagem foi conseguida em todos os doentes. Após dilatação o fio guia foi trocado por outro, de maior consistência, 0.035 de tipo *Schneider* (*Boston Scientific Co*, USA). A escolha deste fio resulta da sua consistência e estabilidade necessárias ao avanço da prótese no estômago. Uma manobra fundamental, foi a colocação o mais distal possível do fio guia (3ª/4ª porção do duodeno).

Figura 1 - Marcação do antro gástrico com *clip* hemostático.

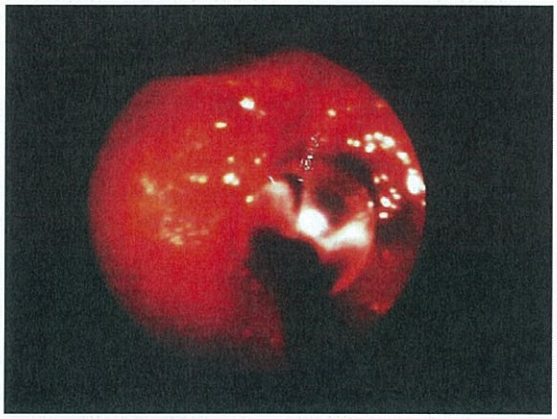

Figura 2 - Dilatação de estenose pilórica maligna com balão hidrostático.

Depois do endoscópio ser retirado (lentamente de forma a evitar a angulação e excessivo enrolamento do fio guia no fórnix gástrico) avançou-se sob o novo fio guia a prótese seleccionada de acordo com a extensão da lesão. Em todos os doentes foi utilizada uma prótese esofágica metálica auto-expansível de nitinol de libertação distal, coberta centralmente, com as duas extremidades descobertas, numa extensão de 1,5 cm, de tipo *Ultraflex* (*Boston Scientific Co*, USA) com cateter de implantação original com 95 cm de comprimento e com 18 mm de diâmetro de corpo. A extermidade distal da prótese ficava na porção distal do bulbo e a proximal (no estômago) com 2-3 cm de margem de segurança. Com esta abordagem foram utilizadas 8 próteses de 10 cm (7 cm de cobertura) e 2 próteses de 12 cm (9 cm de cobertura). A prótese foi avançada sobre o fio guia com controlo fluoroscópico (Figura 3), com compressão gástrica e mobilização do doente, sempre que necessário, de forma a evitar a formação de ansa no fórnix gástrico. A mobilização do doente mais utilizada foi o recurso ao decúbito dorsal com compressão do fórnix e corpo gástrico. Esta manobra foi o momento crucial do exame, implicando um lento avanço da prótese associada a uma cuidadosa retirada do fio guia. Esta abordagem foi utilizada em todos os doentes. Em quatro colocações foi necessário reposicionar o fio guia, iniciando o avanço da prótese sobre o guia desde o início. Após colocação da prótese em posição esta foi libertada lentamente, de forma a evitar posicionamentos inadequados e/ou migração para o duodeno. Logo após a expansão da prótese foi feito controlo endoscópico (Figura 4) e injecção de contraste de modo a confirmar o seu correcto posicionamento e a sua permeabilidade.

Os doentes iniciaram dieta líquida 6 horas após a colocação da prótese, sendo instruídos para recorrerem a dieta liquída durante 48 horas após a colocação da prótese e depois dieta mole e pastosa, recorrendo a 4-6 refeições diárias em pequena quantidade. Todos os doentes foram aconselhados a realizarem um jantar de dimensões reduzidas, seguido, se possível, de um jejum nocturno de 8-9 horas. Todos os doentes foram seguidos mensalmente até ao seu falecimento como detalhado anteriormente.

RESULTADOS

Antes da colocação da prótese todos os doentes tinham intolerância alimentar e vómitos de estase. O sucesso técnico foi obtido em todos os doentes, sendo apenas necessária uma prótese nos dez casos. Todos os doentes iniciaram a ingestão de uma dieta líquida nas primeiras 24 horas, aumentando a consistência da dieta durantes os 3-4 dias seguintes à colocação da prótese. No final da primeira semana todos os doentes toleravam bem dieta líquida e mole/pastosa. Durante o período de vida 4 doentes foram internados por vómitos de estase. Após EDA para confirmar a permeabilidade da prótese a abordagem seguida foi dieta 0 durante 48 horas com recurso a eritromicina endovenosa como procinético. Findo este

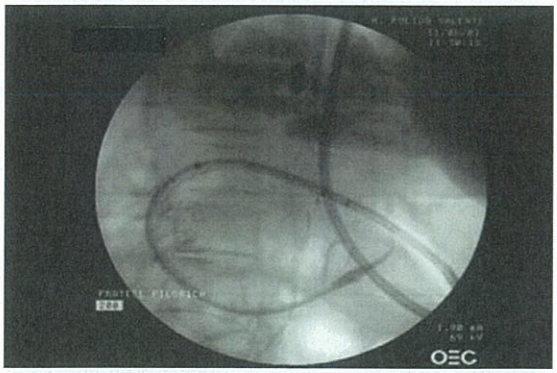

Figura 3 - Avanço do cateter de implantação da prótese sobre fio guia com controlo fluoroscópico.

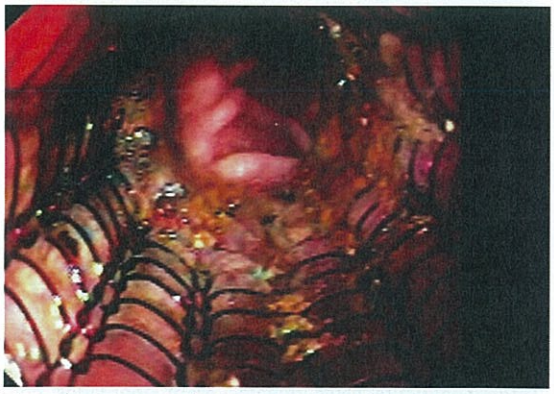

Figura 4 - Prótese totalmente expandida a nível pilórico.

Figura 5a - Prótese pilórica ao fim de 23 meses de implantação, totalmente adaptada ao piloro.

Figura 5b - Interior da prótese, permeável e terminando no início de D2.

período realizou-se nova endoscopia digestiva alta (EDA) para confirmar o esvaziamento gástrico, instituindo-se uma dieta de consistência progressiva tal como após a colocação da prótese. Esta abordagem permitiu a resolução do problema em todos os casos. Um dos doentes teve dois internamentos pelo mesmo motivo. Não se registaram complicações imediatas/precoces do procedimento não existindo história de hemorragia, perfuração e migração da prótese. Não houve nenhum caso de dor abdominal de novo ou agravamento da dor abdominal previamente existente. Todos os dez doentes estavam internados, pela sua situação clínica de intolerância alimentar. Após a colocação da prótese todos tiveram alta entre o 3º e o 4º dia.

Durante o período de seguimento não se registaram casos de migração e/ou obstrução da prótese implantada, o que foi verificado, quer pela clínica quer por 4 casos em que os doentes desenvolveram transitoriamente vómitos, tendo sido feita EDA para despiste de disfunção da prótese (como explicitado anteriormente). O tempo médio de sobrevivência foi de 8,9 meses (2-23 meses). O doente que apresentou maior sobrevivência foi o que recusou a cirurgia. Realizou EDA cerca de 15 dias antes do falecimento, tendo-se verificado a boa permeabilidade da prótese e o seu correcto posicionamento (Figuras 5a e 5b).

DISCUSSÃO

A obstrução gástrica pode ser causada por uma variedade de tumores como o cancro pancreático, duodenal, metástases de outras neoplasias e pelo próprio cancro gástrico (10,11), situação bastante frequente no nosso país. Este tipo de obstrução ocorre, mais habitualmente, num estadio avançado da doença, em que a intolerância alimentar está frequentemente associada a uma situação de malnutrição.

Tradicionalmente estes doentes eram abordados com cirurgia paliativa do tipo gastroenterostomia por via aberta ou laparoscópica (1,2,4,5). Contudo, várias séries referiam mortalidade e morbilidade apreciáveis que em alguns relatos atingiam os 30 e 15% respectivamente (12). Por outro lado, a abordagem cirúrgica associa-se a tempos de hospitalização prolongados, a disfunção gástrica pós cirúrgica importante (por esvaziamento deficiente) e a custos económicos não desprezíveis (1,2,4,5,12).

Na década de 90 do século XX, a partir do relato inicial de Truong et al. (3), surgiu no arsenal clínico a colocação de próteses metálicas auto-expansíveis para a paliação da obstrução gástrica maligna (7-9,10,11). Esta abordagem permitiria a rápida descompressão gástrica, restaurando precocemente e com sucesso a alimentação oral, com baixa morbilidade (6-11). Nos últimos anos existem vários relatos de paliação de obstrução gástrica por estenoses malignas de várias etiologias, sendo as localizações pancreática e gástrica as mais frequentes (6-11). Os trabalhos melhor documentados variam desde 8 a 63 doentes (6-11,13-15), referindo um sucesso técnico invariavelmente superior a 90% e um sucesso clínico (tolerância a dieta pelo menos líquida/pastosa) entre 78-100%. A grande generalidade dos estudos refere a utilização de próteses entéricas descobertas colocadas através do endoscópio (7-11) de tipo *Wallstent* (*Boston Scientific Co*, USA), com valores de oclusão da prótese por crescimento intra-tumoral entre os 11,7% (11) e os 20% (10). Devido a estas, relativamente elevadas, taxas de oclusão existem relatos na literatura de colocação de próteses cobertas, concebidas para o esófago, após modificação do cateter de implantação de forma a torná-lo mais longo (6,7,13,14). Dois trabalhos merecem especial referência. O primeiro (6) recorreu a próteses do tipo *Coil* (*InStent, Edeen Prairie,* Minnesota, USA), tendo sido tratados 29 doentes com uma taxa de sucesso técnico de 89,7% (26 doentes). O sucesso clínico foi obtido em 96.3% destes casos. Quanto às complicações detectaram-se 11,1% situações de obstrução e 7,0% de casos de migração das próteses. O segundo relato (14), com 28 doentes, recorreu a próteses do tipo *Z-stent* (5 doentes) e *Ultraflex* (23 doentes), cujo sistema de implantação foi aumentado. Foi obtido sucesso técnico e clínico em todos os casos. Apenas se registaram migrações no grupo das próteses do tipo *Z-stent*. No grupo de próteses do tipo *Ultraflex* apenas se detectou um caso de obstrução (5,5%).

Estes relatos, no global, criam a ideia de que as próteses cobertas não teriam uma maior taxa de migração e tendencialmente apresentariam um menor número de situações de oclusão.

Nós adoptamos estas linhas de orientação e através de uma técnica desenvolvida e aperfeiçoada no nosso cen-

tro conseguimos a colocação de próteses concebidas originalmente para a neoplasia esófago-cárdica do tipo *Ultraflex*. Estas próteses foram escolhidas devido à sua flexibilidade, força radial e ao facto das suas extremidades serem descobertas, diminuindo a probabilidade de migração. Através da compressão abdominal e da mobilização do doente foi possível avançar a prótese até ao local da estenose. A dilatação prévia da estenose maligna permitiu, não só, a mais fácil passagem da extremidade distal da prótese (a de maior calibre) como também ultrapassar a estenose e marcar a transição bulbo/D2 com um *clip*. Isto evitou que fossem colocadas próteses em D2 prevenindo a possibilidade de compressão da papila, causadora de eventuais pancreatites agudas ou mesmo oclusão biliar, tal como descrito na literatura, ainda que a parte terminal da prótese, descoberta, tornasse isso pouco provável.

Dois relatos recentes (4,5) pretendem comparar a abordagem cirúrgica com a paliação endoscópica em estenoses malignas antro-pilóricas. O primeiro (5), proveniente de Itália, avaliou a utilização da cirurgia convencional *versus* a utilização de próteses metálicas. Os autores referem resultados semelhantes em termos de morbilidade, mortalidade e sucesso clínico aos 3 meses. Contudo o grupo que beneficiou da paliação endoscópica apresentou um mais rápido restablecimento do início da alimentação e um menor tempo médio de hospitalização. Um outro estudo (4) comparou a cirurgia de derivação convencional e laparoscópica com a colocação de próteses metálicas. Os autores referem uma significativa vantagem no grupo das próteses metálicas, em termos de complicações, precocidade da alimentação e tempo de internamento. No nosso estudo todos os doentes tiveram uma alta precoce (entre 72 a 96 horas) após a colocação da prótese.

Em resumo podemos dizer que a colocação de próteses metálicas auto-expansíveis é a abordagem mais adequada na paliação da obstrução maligna antro-pilórica e que deve ser sempre considerada como a primeira alternativa, quando a cirurgia de ressecção não está indicada. Por outro lado e embora isso seja discutível, o nosso relato e outros da literatura (6,7,13,14) parecem sugerir que a colocação de próteses metálicas cobertas pode ser vantajosa, não aumentado a frequência da migração e parecendo ter uma menor taxa de oclusão (repare-se que na nossa série um doente com elevada sobrevivência não apresentou oclusão da prótese). Assim, a nossa experiência demonstra que é técnicamente possível a colocação de prótese coberta de tipo *Ultraflex* no piloro, sem ser obrigatoriamente necessário aumentar o cateter de implantação, ainda que este procedimento seja moroso e implique exposição fluoroscópica importante. Contudo, nem sempre isso é tecnicamente possível, particularmente em doentes com estômagos muito dilatados ou com marcada invasão do antro gástrico. Neste caso optamos por colocar uma prótese metálica expansível através do endoscópio, tendo já uma série razoável (dados não publicados) e que é bastante mais fácil do ponto de vista técnico.

Do exposto, compreende-se, facilmente, a implantação no mercado de três próteses metálicas expansíveis cobertas com cateter de implantação através do endoscópio: duas entéricas: *Song Stent* (Stentech, Seoul, Coreia do Sul) e a *Hanarostent* (*M.I. Tech*, Seoul, Coreia do Sul) e uma concebida especialmente para o piloro (*NITI-S, Taewoong Medical Co.*, Lda, Seoul, Coreia do Sul), esta com as extremidades descobertas de forma a diminuir o risco de migração. Todas estas próteses têm diâmetros muito adequados à função (18 mm). Em Portugal apenas estão disponíveis as duas últimas, tendo a sua introdução no mercado uma data muito recente. Os dados da literatura com estas próteses são limitados, resumindo-se praticamente a pequenas séries, efectuadas por radiologistas de intervenção (16-19), com alguns doentes operados e localização variada da estenoses malignas (estômago, duodeno e anastomoses), e com seguimentos curtos em alguns estudos. Os resultados são por isso de difícil interpretação embora num dos estudos (19) houvesse uma interessante comparação, em 16 doentes, entre 3 tipos de próteses: totalmente coberta, descoberta e apenas com as extremidades descobertas. Este último tipo de próteses apresentou uma taxa de 100% de sucesso técnico e clínico, não se registando obstruções e/ou migrações durante todo o seguimento (até ao falecimento de todos os doentes).

Em resumo, podemos dizer que a colocação de próteses esofágicas cobertas, sem mudança do cateter de implantação é tecnicamente possível, havendo sugestão, consubstanciada por outros trabalhos que o recurso a próteses cobertas neste tipo de paliação é a melhor abordagem Seria interessante a realização de estudos randomizados entre prótese cobertas e descobertas, ainda que o pouco tempo de sobrevivência dos doentes possa, eventualmente, não colocar em evidência a vantagem das próteses cobertas em todas as situações.

Como comentário final e numa perspectiva pessoal parece-me que a colocação transendoscópica de uma prótese coberta será a abordagem ideal. O nosso estudo, realizado antes de haver em Portugal a disponibilidade de próteses entéricas cobertas, foi feito com duas finalidades: por um lado dismistificar a teórica impossibilidade técnica de colocar uma prótese *Ultraflex* coberta no piloro e associadamente criar evidência para a escolha preferencial de próteses cobertas nas EMAP. A utilização da nossa abordagem deverá ser de recurso quando um centro de endoscopia não tiver possibilidades de

aquisição das próteses cobertas e/ou impossibilidade de as colocar por via transendoscópica.

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BIBLIOGRAFIA

1. Ouchi K, Sugawara T, Ono H, Fujiya T, Kamiyama Y, Kakugawa Y, et al. Therapeutic significance of palliative operations for gastric cancer for survival and quality of life. J Surg Oncol 1998; 69: 41-4.
2. Smith J, Brennan MF. Surgical treatment of gastric cancer: proxi mal, mid and distal stomach. Surg Clin North Am. 1992; 72: 381-99.
3. Truong S, Bohndorf V, Geller H, Schumpelick V, Gunther RW. Self expanding metal stent for palliation of malignant gastric outlet obstruction. Endoscopy 1992; 24: 433-5.
4. Mittal A, Windsor J, Woodfield J, Casey P, Lane M. Matched study of three methods for palliation of malignant pyloroduodenal obstruction. Br J Surg 2004; 91: 205-9.
5. Fiori E, Lamazza A, Volpino P, Burza A, Paparelli C, Cavallaro G et al. Palliative management of malignant antro-pyloric strictures.Gastroenterostomy vs. endoscopic stenting. A randomized prospectiv trial. Anticancer Res 2004; 24: 269-71.
6. Kim JH, Yoo BM, Lee KJ, Hahm KB, Cho SW, Park JJ, et al. Self-expanding coil stent with a long delivery system for palliation of unresectable malignant gastric outlet obstruction: a prospective study. Endsocopy 2001; 33: 838-42.
7. de Baere T, Harry G, Ducreux M, Elias D, Briquet R, Kuoch V, et al. Self-expanding metallic stents as palliative treatment of malignant gastroduodenal stenosis.. Am J Roentgenol 1997; 169: 1079-83.
8. Soetikno RM, Lichtenstein DR, Vandervoort J, Wong RC, Roston AD, Slivka A, et al. Palliation of malignant gastric outlet obstruction using an endoscopically placed Wallstent. Gastrointest Endosc 1998; 47: 267-70.
9. Kim JH, Yoo BM, Lee KJ et al. Through-the-scope stent for the palliation of malignant stenoses of upper gastrointestinal tract beyond the esophagus: long term results. Gastrointestin Endosc 2000; 51: AB222.
10. Nassif T, Prat F, Meduri B, Fritsch J, Choury AD, Dumont JL, et al. Endoscopic palliation of malignant gastric outlet obstruction using self-expandable metallic stents: results of a multicenter study. Endoscopy 2003; 35: 483-9.
11. Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. Am J Gastroenterol 2002; 97: 72-8.
12. Lillemoe KD, Cameron JL, Hardacre JM, Sohn TA, Sauter PK, Coleman J, et al. Is prophylatic gastrojejunostomy indicated for periampullary cancer? A prospective randomized trial. Ann Surg 1999; 230: 322-8.
13. Venu RP, Pastika BJ, Kini M, Chua D, Christian R, Schlais J, et al. Self-expanding metal stents for malignant gastric outlet obstruction: a modified technique. Endoscopy 1998: 30: 553-8.
14. Maetani I, Tada T, Shimura J, Ukita T, Inoue H, Igarashi Y, et al. Technical modifications and strategies for stenting gastric outlet stictures using esophageal endoprostheses. Endoscopy 2002; 34: 402-6.
15. Dumas R, Demarquay JF, Caroli-Bosc FX, Paolini O, Guenenna D, Peten EP, et al. Palliative endoscopic treatment of malignant duodenal stenosis by metal prosthesis. Gastroenterol Clin Biol 2000; 24: 714-8.
16. Lee JM, Han YM, Kim CS, Lee SY, Lee ST, Yang DH. Fluoroscopic-guided covered metallic stent placement for gastric outlet obstruction and post-operative gastroenterostomy anastomotic stricture. Clin Radiol 2001; 56: 560-7.
17. Jeong JY, Han JK, Kim AY, Lee KH, Lee JY, Kang JW, et al. Fluoroscopically guided placement of a covered self-expandable metallic stent for malignant antroduodenal obstructions: preliminary results in 18 patients. AJR Am J Roentgenol 2002; 178: 847-52.
18. Jeong JY, Kim YJ, Han JK, Lee JM, Lee KH, Choi BI, et al. Palliation of anastomotic obstructions in recurrent gastric carcinoma with the use of covered metallic stents: clinical results in 25 patients. Surgery 2004; 135; 171-7
19. Lopera JE, Alvarez O, Castano R, Castaneda-Zuniga W. Inicial experience with Song's covered duodenal stent in the treatment of malignant gastroduodenal obstruction. J Vasc Interv Radiol 2001; 12: 1297-303

ARTIGO 2

Canena JM, Lagos AC, Marques IN, Patrocínio SD, Tomé MG, Liberato MA, Romão CM, Coutinho AP, Veiga PM, Neves BC, Além HD, Gonçalves JA.

Oral intake throughout the patients' lives after palliative metallic stent placement for malignant gastroduodenal obstruction: A retrospective multicentre study.

Eur J Gastroenterol Hepatol 2012 April 13; [Epub ahead of print] DOI: 10.1097/MEG.0b013e328353d9d3

Oral intake throughout the patients' lives after palliative metallic stent placement for malignant gastroduodenal obstruction: a retrospective multicentre study

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Objectives Patients with inoperable malignant gastric outlet obstruction (GOO) have been managed with self-expandable metal stents to improve oral intake. Recent studies have shown conflicting results on the capacity of self-expandable metal stents to restore food intake in the long term. This study evaluated the clinical effectiveness of enteral stent placement for GOO throughout the patients' lives.

Methods This was a multicentre, retrospective study with a long-term follow-up of 74 patients who underwent enteral stenting for symptomatic GOO. Data were collected to analyse improvements in oral intake for the patients' entire lives as assessed by the GOO scoring system (GOOSS), technical success, stent patency, complications, the need for reintervention, survival and the prognostic factors associated with stent patency.

Results Technical and clinical success was achieved in 100 and 97.2% of the patients, respectively. A total of 71/74 patients (95.9%) continued oral intake for the rest of their lives and 58/74 patients (78.4%) needed no further intervention until death. Solid food intake (GOOSS 2–3) continued until death in 47/74 patients (63.5%). The GOOSS score improved ($P<0.001$) during the follow-up compared with the baseline. The median survival and the mean stent patency were 8 and 76.6 weeks, respectively. The complication rate was 18.9%. Malignant stent reobstruction was observed in 7/74 patients (9.5%). A Cox multivariate analysis showed that duodenal location of the obstruction was the only independent factor associated with stent patency (hazard ratio=5.28; 95% confidence interval=1.14–24.45; $P=0.033$).

Conclusion Enteral stenting in patients with unresectable GOO is safe and clinically effective. Ninety-five per cent of patients are able to resume oral intake for the rest of their lives, and the great majority remain free from further intervention. In approximately two-thirds of patients, solid food intake continues until death. *Eur J Gastroenterol Hepatol* 00:000–000 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Gastroenterology & Hepatology 2012, 00:000–000

Keywords: endoscopic palliation, enteral stenting, gastric outlet obstruction, gastric outlet obstruction scoring system, self-expanding metal stent

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Received 22 January 2012 Accepted 19 March 2012

Introduction

Malignant gastric outlet obstruction (GOO) can occur as a late complication of unresectable gastric and periampullary cancers [1–4]. This advanced-stage disease event is associated with severe nausea, vomiting, intolerance to oral feeding and abdominal pain, resulting in a progressive deterioration in the quality of life among these patients, who have limited survival [1,3,4]. Palliation of symptoms is the primary aim in these patients [4,5]. Traditionally, GOO was managed by surgical gastrojejunostomy [3,4]. However, most of the patients tend to be poor surgical candidates for this procedure because of advanced disease and underlying malnutrition [1,4]. Furthermore, surgery is associated with significant morbidity and mortality, delayed gastric emptying and prolonged hospital stays [3,4,6,7].

First reported by Truong *et al.* [8], self-expandable metal stents (SEMS) have been increasingly used as a safe, minimally invasive, nonsurgical, palliative treatment for malignant GOO [1–7,9–13]. A large systematic review of patients undergoing SEMS placement for malignant GOO indicated high levels of technical and clinical success rates and an acceptable complication rate [9]. A recent meta-analysis comparing endoscopic stenting with surgical gastroenterostomy showed that stenting was associated with better outcomes, namely, less morbidity, shorter hospital stays and a shorter recovery time [14]. However, few studies followed patients for their entire remaining lives after stent placement, and there are conflicting results on the long-term clinical effectiveness of enteral stenting [4,15]. One additional conflicting

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DOI: 10.1097/MEG.0b013e328353d9d3

issue is the identification of other factors associated with clinical outcomes. For example, chemotherapy after enteral stent insertion has been suggested by some studies [2,11] and denied by others [3] as an independent factor associated with prolongation of oral intake and/or increased stent patency.

This study evaluated the improvement in the ability to tolerate oral intake for the duration of the patients' lives as assessed by the GOO scoring system (GOOSS), the technical success rate, stent patency, complications, the need for reinterventions, survival and the prognostic factors associated with stent patency after the placement of a self-expanding metallic stent in patients with malignant gastroduodenal obstruction.

Methods

Patients and setting

This was a multicentre, single-arm, retrospective clinical study with a long-term follow-up. A dedicated, prospective, computerized endoscopy database was retrospectively reviewed to identify all of the consecutive patients who had undergone enteral stent placement for symptomatic malignant GOO between November 2005 and August 2011. The following criteria were used for inclusion in this study: (a) symptomatic pyloroduodenal obstruction as assessed by a GOOSS score of 0 or 1, (b) histologically confirmed malignancy, (c) inoperable disease on the basis of the presence of advanced/metastatic disease or medical comorbidity and (d) death at the time of data collection. The exclusion criteria were as follows: (a) evidence of other obstructions in the gastrointestinal tract, (b) previous gastric, duodenal or ampullary surgery and (c) previous stent placement or palliative surgery for the same condition.

The data were collected from a variety of sources, including hospital records, patient discharge letters, clinical notes, radiology reports, endoscopic procedure reports, follow-up clinic visits, our prospective database and telephone interviews with treating physicians or family during follow-up or at the time of manuscript preparation. The data collected included patient demographics, type of malignancy, location of stricture, technical success, GOOSS score (at baseline, after stenting and during follow-up), complications, reinterventions, chemotherapy, survival and the WHO performance status score (where 0 = normal activity, 1 = symptomatic but ambulatory, 2 = in bed less than 50% of the time, 3 = in bed more than 50% of the time and 4 = 100% bed-bound or chair-bound). This study was carried out at four institutions (Pulido Valente Hospital, Faculty of Medical Sciences, Lisbon, Portugal; Cuf Infanto Santo Hospital, Lisbon, Portugal; Centro Hospitalar do Barreiro-Montijo, Barreiro, Portugal; and José Joaquim Fernandes Hospital, Beja, Portugal). All patients provided informed written consent before their procedures. Each Ethics Committee involved approved this retrospective study.

Outcomes and definitions

The primary outcome was an improvement in the ability to tolerate an oral diet for the entire remaining duration of the patient's life after stent placement (as assessed by the GOOSS score). The secondary outcomes included technical success rates, clinical success rates (defined as relief of obstructing symptoms, improvement in oral intake and improvement in the GOOSS score 5 days after intervention), stent patency, survival, complications, the need for reintervention and the prognostic factors associated with stent patency. The severity of GOO symptoms (defined as early satiety, nausea and vomiting) was assessed using a previously described scoring system (GOOSS), where 0 = no oral intake, 1 = liquids only, 2 = soft solids and 3 = low residue or full diet [1]. Technical success was defined as deployment of the stent across the stricture, with patency visualized both fluoroscopically and endoscopically. Stent patency was defined as the period between stent placement and the recurrence of obstructive symptoms caused by stent obstruction (tumour overgrowth or ingrowth) or migration. Complications were defined as any adverse event related to stent placement. Complications were also categorized as major (severe events such as perforations or haemorrhage requiring transfusion) and minor (non-life-threatening, such as migration, mild bleeding, malignant restenosis or food impaction). Stent migration was considered if the stent moved from its initial position and was unable to cover the entire stenosis. Reintervention was defined as any procedure performed after the initial stent placement, including endoscopic resolution of food impaction, the placement of a new stent because of malignant stent restenosis, endoscopic resolution of haemorrhage or surgery.

Intervention and stents

The details of the stent placement procedures have been described elsewhere [10,16–18]. Briefly, all procedures were performed with patients in the left lateral position under sedation with propofol administered by an anaesthesiologist. The stricture was negotiated with a triple-lumen biliary catheter and a biliary guidewire under endoscopic and fluoroscopic guidance. The length of the stricture was assessed either endoscopically or fluoroscopically after the injection of contrast media. Passage of the endoscope through the stricture was not attempted unless required for biliary stenting before enteral stent placement. Balloon dilatation of the stricture was not routinely performed because of the risk of perforation and because it is associated with increased migration rates after stent deployment. The stent delivery system was advanced through the working channel (> 3.8 mm) of a therapeutic endoscope, and the stent was deployed under endoscopic and fluoroscopic control. Special care was taken to place the stent at least 1–2 cm proximal to the duodenal ampulla in cases where the stricture did not involve the papilla of Vater to allow future biliary access

after enteral stenting, if needed. Biliary involvement was assessed in all cases before the placement of an enteral stent. Prophylactic biliary stenting was not performed before enteral stenting. Patients with a plastic biliary stent had their stents replaced by a metal biliary stent, irrespective of its patency. Patients with laboratory evidence of concurrent biliary obstruction underwent biliary drainage by insertion of a biliary metal stent at the same time as enteral stent placement. When the stricture involved the papilla and endoscopic biliary stenting was impossible, a percutaneous transhepatic approach was performed immediately before enteral stenting. If biliary obstruction developed after enteral stent placement and the stent was covering the biliary papilla, an intervention was undertaken using a percutaneous transhepatic approach or endoscopically through the mesh of the stent. Patients were instructed to resume oral intake of liquids the day after the procedure. The diet was advanced gradually to a soft diet and then a low-residue diet if the patient tolerated the diet and obstructive symptoms did not recur.

The duodenal stent used in this study was the Duodenal WallFlex stent (Boston Scientific, Natick, Massachusetts, USA). This stent is an uncovered stent made of nitinol that has a flare at the proximal end to minimize the risk of migration and has looped ends to reduce the risk of mucosal injury. The stent is preloaded in a 10-Fr delivery system and has a 22 mm mid-body diameter and a 27 mm diameter at the flared proximal end. After complete expansion, the WallFlex stent can undergo shortening by up to 45%. The stent is available in lengths of 60, 90 or 120 mm and is CE approved.

Follow-up

Follow-up continued from stent insertion to the death of the patient. The diet was periodically assessed during follow-up, and endoscopic evaluation of stent patency was performed if obstructive symptoms recurred. Follow-up was obtained by reviewing clinical notes provided by regular clinic visits after stent placement or the treating physician reports, data from our prospective database and structured telephone interviews with the treating physician or family during follow-up or at the time of manuscript preparation. Patients with incomplete follow-up were excluded from the study. All of the patients were dead at the time of manuscript preparation.

Statistical analysis

The intention-to-treat method was used in all analyses. The GOOSS scores, taken at baseline, at 5 days and during follow-up, were compared using the Friedman test. Multiple comparisons were performed with the Wilcoxon signed-rank test using the Bonferroni correction. Cumulative stent patency and cumulative patient survival were calculated using the Kaplan–Meier method. For the calculation of the stent patency period, death before stent dysfunction was considered a censored observation. Multivariate Cox proportional hazard models with forward stepwise selection were used to evaluate the independent prognostic factors potentially associated with stent patency. Age, sex, site of lesion (peripyloric/duodenum), source of malignancy (gastric cancer/pancreatic cancer/other malignancy), chemotherapy after stent placement and the WHO score were the variables included in the analysis. All reported P values were for a two-sided test, and a P value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using Statistical Package for the Social Sciences 18 (SPSS; IBM Corporation, New York, New York, USA).

Results

Patients

In total, 74 patients (42 men and 32 women), mean age 75.0 years (range: 35–99 years), were enroled in the study. The patient demographics and clinical characteristics are summarized in Table 1.

Stent placement and clinical success

Stent deployment was technically successful in all patients. Clinical success was achieved in 72/74 patients (97.2%). The remaining two patients with successful stent placement showed no improvement in their GOOSS scores and showed no improvement in oral intake. These patients had no evidence of other obstructions in the gastrointestinal tract and they were considered to have a motility dysfunction. They underwent surgical gastroenterostomy, and they were able to resume oral intake. The food intake scores (GOOSS) before and 5 days after stent placement are shown in Tables 1 and 2 and in Figs 1 and 2. Before

Table 1 Patient characteristics

Patients, *n*	74
Sex	
Male, *n* (%)	42 (56.8)
Female, *n* (%)	32 (43.2)
Age (years), mean±SD (range)	75.0±11.8 (35–99)
Source of malignancy	
Gastric cancer, *n* (%)	49 (66.2)
Pancreatic cancer, *n* (%)	19 (25.6)
Cancer of the ampulla of Vater, *n* (%)	2 (2.7)
Duodenal cancer, *n* (%)	2 (2.7)
Gallbladder cancer, *n* (%)	1 (1.4)
Hilar cholangiocarcinoma, *n* (%)	1 (1.4)
Location of stricture	
Peripyloric region, *n* (%)	49 (66.2)
Duodenum alone, *n* (%)	25 (33.8)
GOOSS score at baseline, mean±SD	0.23±0.42
0, no oral intake, *n* (%)	57 (77.0)
1, liquids only, *n* (%)	17 (23.0)
Chemotherapy after stent placement	
Yes, *n* (%)	24 (32.4)
No, *n* (%)	50 (67.6)
WHO performance score, mean±SD	2.37±0.88
WHO 0, fully active, *n* (%)	0 (0)
WHO 1, symptoms but ambulatory, *n* (%)	15 (20.3)
WHO 2, in bed less than 50% of time, *n* (%)	22 (29.7)
WHO 3, in bed more than 50% of time, *n* (%)	32 (43.2)
WHO 4, 100% bed or chair bound	5 (6.8)

GOOSS, gastric outlet obstruction scoring system.

stent placement, 57/74 patients (77.0%) had no oral intake (GOOSS score 0), and 17/74 patients (23.0%) were only tolerating liquids (GOOSS score 1) but had major complaints of GOO (nausea and/or early satiety and/or vomiting). The two patients without clinical success had an initial GOOSS score of 1, and they maintained this score after stenting without an improvement in GOO symptoms. Five days after stent placement, the GOOSS score improved by 1 point in 33 patients (44.6%), by 2 points in 37 patients (50%) and by 3 points in two patients (2.7%). Resumption of solid food intake (GOOSS 2–3) was achieved by 53/74 patients (71.6%) within 5 days of enteral stenting. After comparing the mean GOOSS score at baseline (0.23±042) and 5 days after SEMS placement (1.76±0.52), a statistically significant improvement was found ($P < 0.001$).

Duration of oral intake

In total, 71/74 patients (95.9%) who underwent enteral stent placement were able to tolerate an oral diet (Table 2, Figs 2 and 3) for the rest of their lives. During follow-up, 6/53 patients (11.3%) who resumed solid food intake within 5 days of enteral stenting had a decreased GOOSS score and could only tolerate liquids. Solid food intake continued until death in 47/74 patients (63.5%). A comparison of the mean GOOSS score at baseline (0.23±042) with the mean GOOSS score during follow-up (1.64±0.48) showed a statistically significant improvement ($P < 0.001$).

Table 2 Outcomes after enteral stent placement in 74 patients with malignant gastric outlet obstruction

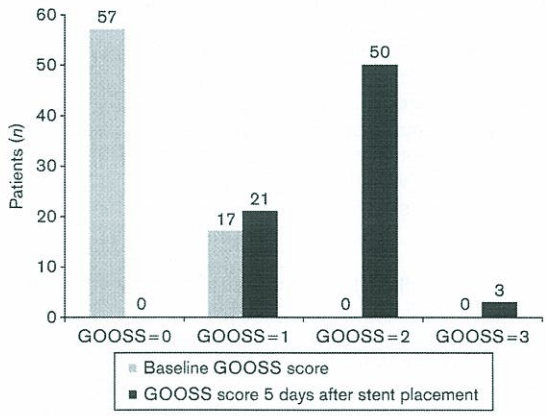
Technical success, *n*/total (%)	74/74 (100)
Clinical success, *n*/total (%)	72/74 (97.2)
Patients with oral intake until death, *n*/total (%)	71/74 (95.9)
Patients with oral intake until death without further intervention, *n*/total (%)	58/74 (78.4)
Patients with solid food intake (GOOSS 2–3) until death, *n*/total (%)	47/74 (63.5)
GOOSS score 5 days after stent placement, mean±SD	1.76±0.52
GOOSS score during follow-up, mean±SD	1.64±0.48

GOOSS, gastric outlet obstruction scoring system.

Complications and reinterventions

A total of 14/74 patients (18.9%) experienced complications after enteral stenting (Table 3). No severe complications were observed. Minor complications were stent obstruction by tumour overgrowth or ingrowth, self-limited mild bleeding, food impaction and cholangitis. Malignant restenosis was observed in seven patients. Stent obstruction was observed at 3, 12, 12, 14, 16, 20 and 32 weeks after stent placement (median time to occlusion: 14 weeks). One patient underwent gastrojejunostomy, and in the remaining six patients, stent obstruction was successfully managed by placing another stent that allowed the patients to resume oral intake. Three of these six patients maintained oral intake until death, and the remaining three developed malignant stent reobstruction at 11, 26 and 56 weeks after the second stent placement. They were treated successfully by a third enteral stent and resumed oral food intake for the rest of their lives. Food impaction was observed in five patients, and all cases of food impaction were successfully managed by endoscopic intervention. One patient had haematemesis and melena that stopped within 24 h without further intervention. One patient developed jaundice and cholangitis as a result of stent occlusion of the ampulla of Vater, and he underwent successful percutaneous insertion of a biliary SEMS. No case of stent migration was encountered, and there was no procedure-related mortality. In total, 58/74 patients

Fig. 1



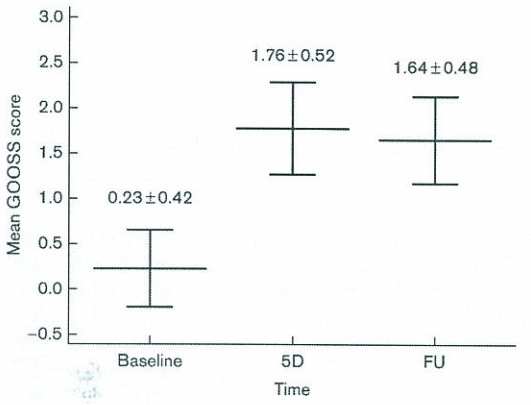
Bar graph, showing the evolution of the gastric outlet obstruction scoring system (GOOSS) score from baseline to 5 days after enteral stenting.

(78.4%) who underwent enteral stent placement for malignant GOO maintained food intake until death without further intervention.

Biliary involvement

Malignant biliary obstruction developed in association with GOO in 14/74 patients (18.9%). Nine patients had pancreatic cancer, two had cancer of the ampulla of Vater, one had gallbladder cancer, one had hilar cholangiocarcinoma and one had gastric cancer. Biliary involvement developed before GOO in eight patients (10.4%), concomitantly in four patients (5.4%) and was observed in two patients (2.7%) after enteral stent placement. Endoscopic palliation with endoscopic retrograde cholangiopancreatography was attempted in all cases. Endoscopic retrograde cholangiopancreatography was successful in the placement of a biliary SEMS in 13/14 patients (92.9%). In one patient with severe duodenal malignant involvement, access to the common bile duct was impossible because the papilla was covered by the mesh of a previously placed enteral stent. This patient underwent successful percutaneous insertion of a biliary SEMS.

Fig. 2

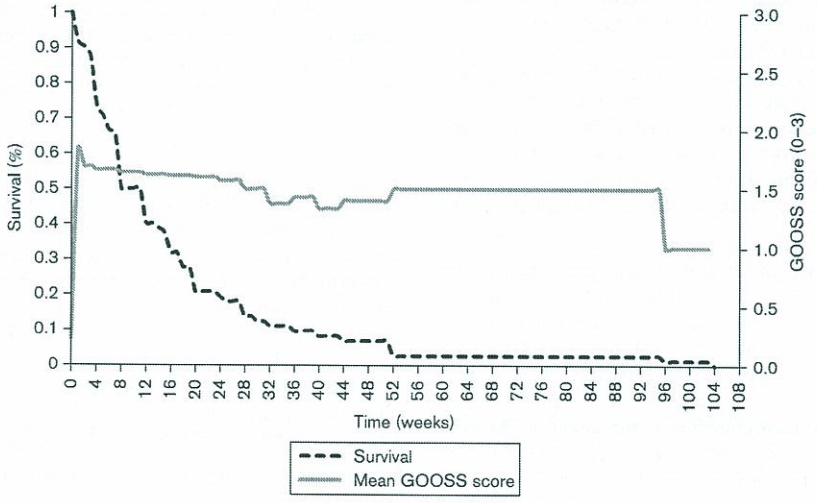


Multiple variables graph, with the mean gastric outlet obstruction scoring system (GOOSS) score at baseline, 5 days within stent placement (5D) and during follow-up (FU). Bars represent the SD.

Survival, stent patency and prognostic factors for stent patency

All of the patients died before the retrospective analysis. The median and mean survival periods were 8.0 (range: 1–104) [95% confidence interval (CI) 5.69–10.31] and 16.4 weeks (95% CI 5.69–10.31) (Fig. 4), respectively. Cessation of stent patency occurred in 7/74 patients (9.5%) as a result of malignant stent obstruction (tumour overgrowth or ingrowth). The mean stent patency was 76.6 weeks (95% CI 55.74–97.36; Fig. 5). The Kaplan–Meier method did not estimate the median stent patency because more than 50% of observations were censored early in the analysis. Multivariate Cox regression analysis showed that the site of the lesion, namely duodenal obstruction, was the only independent prognostic factor associated with stent patency (hazard ratio = 5.28; 95% CI = 1.14–24.45; $P = 0.033$).

Fig. 3



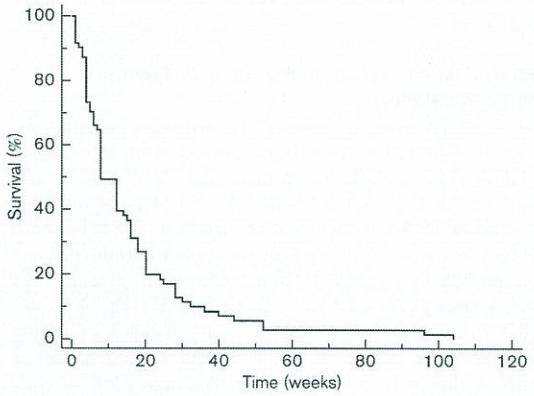
The mean gastric outlet scoring system (GOOSS) score from stent placement until the death of all patients.

Table 3 Complications and management

Complications	*N* (%)	Management (*n*)
Stent obstruction (tumour ingrowth/overgrowth)	7/74 (9.5)	Subsequent enteral stent insertion (6) Surgery (1)
Food impaction	5/74 (6.8)	Endoscopic removal (5)
Haemorrhage	1/74 (1.4)	No intervention
Cholangitis	1/74 (1.4)	PTDB (1)
Total	14/74 (18.9)	–

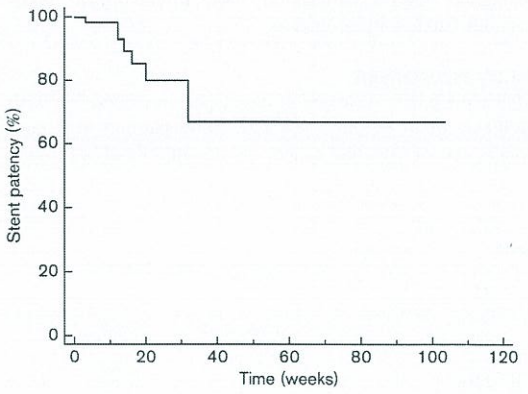
PTDB, percutaneous transhepatic biliary drainage.

Fig. 4



Kaplan–Meier analysis showing cumulative survival.

Fig. 5



Kaplan–Meier curves of cumulative stent patency.

Discussion

According to the findings of this retrospective, single-arm, multicentre study, enteral stenting in inoperable patients with malignant symptomatic GOO resulted in an improvement in oral intake in 71/74 patients (95.9%) for the rest of their lives. Approximately 80% of the patients maintained oral intake without further intervention until death. The procedure is associated with acceptable morbidity and acceptable need for reintervention. Duodenal location of the obstruction was the only independent factor associated with a decrease in stent patency.

Malignant GOO is associated with a poor quality of life in patients with low nutritional status and limited life expectancy. Palliation of obstructive symptoms and resumption of oral intake is essential to reduce morbidity and improve the quality of life [2,3,6,19]. Although both open and laparoscopic palliative gastrojejunostomies have been used as the standard approach, enteral stenting as a minimally invasive technique for the treatment of GOO has been increasingly used in recent years [1–7,11–15,18–21] (Table 4). Three randomized trials have compared enteral stenting with surgery [15,22,23]. One study showed that enteral stenting offered better outcomes in terms of operative time, restoration of oral intake and the median length of hospital stay but showed similar results in terms of morbidity, mortality, delayed gastric emptying and clinical outcomes at the 3-month follow-up [22]. In another study, duodenal stenting was associated with shorter hospital stays, fewer complications and a greater improvement in physical health when compared with surgery [23]. However, a recent trial suggests that despite slow initial symptom improvement, surgery was associated with better long-term results and therefore should be the treatment of choice in patients with an expected survival of 2 months or longer [15]. The same authors, in another journal, pointed to the WHO score as a predictor of survival that could help to decide which palliative treatment should be performed in patients with malignant GOO [24]. However, the results of this recent and very well-conducted randomized trial should be interpreted with caution. The median survival in the stent group (21 patients) was 56 days, and few patients were still alive by the cut-off time of 60 days, making it difficult to confidently state that after 2 months, stenting is associated with increasingly compromised food intake.

Malignant GOO is frequently a preterminal event in patients with a relatively short expected survival. In our study, the median survival was 8 weeks (56 days), which was not inconsistent with the often short median survival reported in other studies, ranging from 49 to 121 days [2–5,7,11–13,18–21] (Table 4). In the systematic review of Dormann *et al.* [9] the mean survival time was 12.1 weeks, whereas in our study, it was 16.6 weeks. All patients in this study were followed until death, and even though our population had a short survival time, this is an expected outcome in patients with malignant GOO.

In this study, technical success was achieved in 100% of the patients, similar to previous studies reporting a technical success rate ranging from 91 to 100% [2–5,7,11–13,18–21] (Table 4). In previous clinical studies, the rate of

Table 4 Case series evaluating the outcomes of self-expandable metallic stents for malignant gastric outlet obstruction

References	Patients (*n*)	Technical success (%)	Clinical success (%)	Survival (time)	Stent patency	Complication rate (%)
Kim *et al.* [2]	213	94	94	99 days (median)	270 days (median)	21
Piesman *et al.* [3]	43	100	NA	49 days (median)	NA	23
van Hooft *et al.* [4]	51	98	84	62 days (median)	307 days (median)	NA
Havemann *et al.* [5]	45	91	77.7	121 days (mean)	NA	NA
Nassif *et al.* [7]	63	95.3	92.1	7 weeks (median)	5.5 weeks (median)	30
Telford *et al.* [11]	176	98.3	NA	97 days (median)	146 days (median)	9
Costamagna *et al.* [12]	202	98	91	94 days (median)	NA	20.3
Lopes *et al.* [13]	44	100	NA	17 weeks (median)	NA	27.5
Grabber *et al.* [18]	51	98	84	71.5 days (median)	NA	21.5
Maetani *et al.* [19]	37	97	94.4	118 days (median)	NA	16.2
Garcia-Cano *et al.* [20]	23	100	92.5	104 days (mean)	NA	NA
Holt *et al.* [21]	28	92.9	85.7	51 days (median)	NA	NA

resumption of oral intake after enteral placement has ranged from 97.2 to 84% [2,4,5,7,18–21] (Table 4). In the present study, we observed high levels of clinical success and during follow-up, only 11.3% of the patients who resumed solid food intake within 5 days of enteral stenting showed a decrease in the GOOSS score, allowing solid food intake to continue until death in approximately two-thirds of the patients. Decreased oral intake near the end of life may represent the burden of disease instead of stent function itself. In the present study, there was a large difference between the mean survival (16.6 weeks) and the mean stent patency (76.6 weeks), suggesting that enteral stenting is able to provide oral intake for the majority of the patients until death. Furthermore, among the limited number of patients in whom cessation of oral intake was caused by stent obstruction, almost all were able to regain oral intake by the placement of another stent.

Few studies have addressed oral intake from stent placement until death, as the majority of reports have either limited follow-up or a significant number of patients lost to follow-up. A prospective multicentre cohort study assessed improvements in the GOOSS score during follow-up until death [4]. Although detailed information was not provided, the mean GOOSS score improved significantly when comparing the baseline values with the score during follow-up, and the majority of the patients remained on an oral diet until death. In a previous prospective study with 43 patients, 48% of the patients remained on solid food until death or the last follow-up [3]. Taken together, the results of these studies and this study provide evidence that unresectable symptomatic malignant GOO is associated with short expected survival, that oral intake can be restored with enteral stenting and that oral intake can be maintained until death for the great majority of the patients.

Enteral stenting in malignant GOO is safe. Three recent studies have reported experiences using the Duodenal WallFlex stent [3,4,6]. In a prospective study with 51 patients, no major complications were observed, and stent dysfunction was proved in seven patients (14%) after a median time of 121 days [4]. Piesman *et al.* [3] conducted a multicentre prospective study with 43 patients and reported a complication rate of 23%. Stent occlusion was observed in 9% of patients and perforation in 5% of patients. A systematic review (using different types of stents) reported the outcomes of 606 patients. Severe complications (bleeding and perforation) were observed in 1.2% of patients and stent obstruction occurred in 18% of patients [9].

In this study, severe complications and procedure-related mortality were not observed. Migration was also not found in our series, a result that is consistent with the three previous studies using the WallFlex stent [3,4,6], where only one migration was reported [3]. In this study, the low stent migration rate could be explained partly by the stent design (with a proximal large-diameter flare) and by the fact that stricture dilatation before stent deployment was not performed. The most frequently noted complication in this study was stent obstruction, occurring in 9.5% of patients and observed after a median time of 14 weeks (98 days). This median time to occlusion compares with the report of van Hooft *et al.* [4] (121 days), implying that malignant stent restenosis is a late complication. In the present study, six patients were treated successfully with a second stent and three patients with a third stent with prompt resumption of oral intake. The repeat stenting increased the median time to occlusion from 14 weeks (98 days) to 21 weeks (147 days), allowing almost all patients to continue oral intake for the rest of their lives with enteral stenting. This observation suggests that subsequent enteral stent insertion is efficacious and increases the duration of oral intake, as reported previously by others [11]. The remaining patient with stent occlusion declined further stenting and request for surgery because he decided to spend his final days in a country where endoscopic expertise was not available.

Covered stents were designed to prevent stent obstruction. However, previous studies have reported a high migration rate (17–26%), limiting their routine use [25–27]. Two recent studies have addressed the outcomes of covered stents. A retrospective study of 60 patients compared the performance of uncovered stents ($n = 31$) with covered devices ($n = 29$) and found no differences between technical and clinical success rates, migration rate or reobstruction rate [28]. However, covered stents were associated with a more frequent

need for repeat interventions. A recent randomized trial evaluated the clinical effectiveness of covered versus uncovered stents [29]. The authors concluded that the 8-week patency in the two groups was similar. Thus, until more data are available, there is no clear advantage for using covered stents in malignant GOO.

In this study, biliary involvement was observed in 14/74 patients (18.9%), which is a lower rate than that reported by Adler and Baron [1] or that reported in the previously cited systematic review, where 61% of the patients receiving a duodenal stent needed biliary drainage [9]. One explanation for this could be that in these reports, pancreatic cancer was the most common diagnosis, whereas in our study, gastric cancer was the major cause of GOO (66.2% of the patients); biliary involvement is less frequent in gastric cancer than in pancreatic cancer. The majority of the patients developed biliary problems before or concomitantly with GOO, which is consistent with the literature [4,6,7,9]. When biliary involvement was observed concomitantly with GOO, balloon dilatation of the stricture was not performed, and special care was taken to avoid covering the ampulla of Vater with the enteral stent. Three to 4 days after enteral stenting, the papilla was reached through the previously placed enteral stent.

There is a continuing debate on whether prophylactic biliary drainage should be undertaken in patients with no signs of obstruction and in cases where duodenal stenting is expected to cover the papilla. Some authors advocate that prophylactic biliary stenting should not be performed because biliary obstruction after duodenal stent placement is a rare event (approximately 1–3%) and could always be managed by the percutaneous route or through the mesh of a duodenal stent placed across the papilla [4,6,9]. Recently, Mutignani *et al.* [30] reported a high success rate (86%) in biliary stenting through the mesh of a duodenal SEMS. However, these results are from a single expert centre, and the role of prophylactic biliary stenting is still debatable. In this study, biliary involvement was observed in two patients (2.7%) after enteral stent placement (in the two cases, the duodenal stent covered the papilla). One patient was managed by the percutaneous route, and in the other patient, biliary cannulation was achieved through the meshes of the duodenal stent.

Duodenal stricture location was independently associated with a higher risk of stent obstruction. Two previous studies have evaluated whether certain factors influence the outcomes of enteral stenting [2,11]. In a study by Telford *et al.* [11], chemotherapy after stent insertion was associated with increased oral intake. In the study of Telford *et al.*, the WHO performance status score, which may represent an important confounding factor, was not included in the analysis. In a prospective evaluation of 213 patients, chemotherapy after enteral stenting was also the only factor associated with an increase in stent patency [2]. However, an American clinical trial using the WallFlex stent reported that chemotherapy after stent placement had no effect on the maintenance of either a GOOSS increase of at least 1 or a GOOSS of 2–3 [3]. In our study, patient sex, age, source of malignancy, chemotherapy after stent placement and the WHO score were not associated with stent patency. This is the first report suggesting that the location of a malignant stricture in the duodenum is associated with a higher risk of obstruction, and this should be confirmed in additional prospective studies.

The present study has several limitations. First, this was a retrospective study, limiting the number of included patients because some of the identified consecutive patients had incomplete data and were excluded from the analysis. Our data may therefore have been subject to selection bias. Another potential weakness is the single-arm design without comparison with other available treatments, namely surgical gastroenterostomy. Finally, although this study was performed in two tertiary referral centres and two community hospitals, stenting was performed by very experienced endoscopists, and we cannot exclude the possibility of obtaining a poorer outcome in community hospitals with less experienced endoscopists. The strengths of our study are the design, which provided long-term follow-up until death for all patients, and the relatively large sample size.

Conclusion

Our data suggest that although our population had a limited median survival, enteral stent placement in patients with inoperable malignant GOO is safe and clinically effective; more than 90% of patients are able to restore their eating ability for the rest of their lives. The procedure is associated with early resumption of food intake, and the great majority of the patients (75%) remained on an oral diet without further intervention until death. Approximately two-thirds of the patients maintained solid food intake during their lives. The rate of malignant stent obstruction is low, and it can be successfully managed by subsequent enteral stent insertion. In addition, duodenal lesions are associated with a higher risk of malignant stent reobstruction.

Acknowledgements

Conflicts of interest

Jorge Canena is a consultant for Boston Scientific but did not receive any financial arrangements for this research, nor any assistance with manuscript preparation. For the remaining authors there are no conflicts of interest.

References

1 Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. *Am J Gastroenterol* 2002; **97**:72–78.

2 Kim JH, Song HY, Shin JH, Choi E, Kim TW, Jung HY, *et al.* Metallic stent placement in the palliative treatment of malignant gastroduodenal obstructions: prospective evaluation of results and factors influencing outcome in 213 patients. *Gastrointest Endosc* 2007; **66**: 256–264.

3 Piesman M, Kozarek RA, Brandabur JJ, Pleskow DK, Chuttani R, Eysselein VE, *et al.* Improved oral intake after palliative duodenal stenting for malignant obstruction: a prospective multicenter clinical trial. *Am J Gastroenterol* 2009; **104**:2404–2411.

4 van Hooft JE, Uitdehaag MJ, Bruno MJ, Timmer R, Siersema P, Dijkgraaf MG, *et al.* Efficacy and safety of the new WallFlex enteral stent in palliative treatment of malignant gastric outlet obstruction (DUOFLEX study): a prospective multicenter study. *Gastrointest Endosc* 2009; **69**:1059–1066.

5 Havemann MC, Adamsen S, Wøjdemann M. Malignant gastric outlet obstruction managed by endoscopic stenting: a prospective single-centre study. *Scand J Gastroenterol* 2009; **44**:248–251.

6 van Hooft J, Mutignani M, Repici A, Hessmann H, Neuhaus H, Fockens P. First data on the palliative treatment of patients with malignant gastric outlet obstruction using the WallFlex enteral stent: a retrospective multicenter study. *Endoscopy* 2007; **39**:434–439.

7 Nassif T, Prat F, Meduri B, Fritsch J, Choury AD, Dumont JL, *et al.* Endoscopic palliation of malignant gastric outlet obstruction using self-expandable metallic stents: results of a multicenter study. *Endoscopy* 2003; **35**:483–489.

8 Truong S, Bohndorf V, Geller H, Schumpëlick V, Günther RW. Self-expanding metal stents for palliation of malignant gastric outlet obstruction. *Endoscopy* 1992; **24**:433–435.

9 Dormann A, Meisner S, Verin N, Lang AW. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. *Endoscopy* 2004; **36**:543–550.

10 Laasch H-U, Martin DF, Maetani I. Enteral stents in the gastric outlet and duodenum. *Endoscopy* 2005; **37**:74–81.

11 Telford JJ, Carr-Locke DL, Baron TH, Tringali A, Parsons WG, Gabbrielli A, *et al.* Palliation of patients with malignant outlet obstruction with the enteral Wallstent: outcomes from a multicenter study. *Gastrointest Endosc* 2004; **60**:916–920.

12 Costamagna G, Tringali A, Spicak J, Mutignani M, Shaw J, Roy A, *et al.* Treatment of malignant gastroduodenal obstruction with a nitinol self-expanding metal stent: an international prospective multicentre registry. *Dig Liver Dis* 2012; **44**:37–43.

13 Lopes CV, Pesenti C, Bories E, Caillol F, Giovannini M. Self-expandable metallic stents for palliative treatment of digestive cancer. *J Clin Gastroenterol* 2008; **42**:991–996.

14 Hosono S, Ohtani H, Arimoto Y, Kanamiya Y. Endoscopic stenting versus surgical gastroenterostomy for palliation of malignant gastroduodenal obstruction: a meta-analysis. *J Gastroenterol* 2007; **42**:283–290.

15 Jeurnink AM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz P, Vleggaar FP, *et al.* Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc* 2010; **71**:490–499.

16 Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. *N Engl J Med* 2001; **344**: 1681–1687.

17 Baron TH, Harewood GC. Enteral self-expandable stents. *Gastrointest Endosc* 2003; **58**:421–433.

18 Grabber I, Dumas R, Filoche B, Boyer J, Coumaros D, Lamouliatte H, *et al.* The efficacy and safety of duodenal stenting: a prospective multicenter study. *Endoscopy* 2007; **39**:784–787.

19 Maetani I, Isayama H, Mizumoto Y. Palliation in patients with malignant gastric outlet obstruction with a newly designed enteral stent: a multicenter study. *Gastrointest Endosc* 2007; **66**: 355–360.

20 Garcia-Cano J, Sanchez-Manjavacas N, Chicano MV, Ayllón CJ, Fernández RM, Ruiz CG, *et al.* Palliative management of malignant gastric outlet obstruction with endoscopically inserted self-expanding metal stents. *Rev Esp Enferm Dig* 2008; **100**:320–326.

21 Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metal stents: the treatment of choice? *Gastrointest Endosc* 2004; **60**:1010–1017.

22 Fiori E, Lamazza A, Volpino P, Burza A, Paparelli C, Cavallaro G, *et al.* Palliative management of malignant antro-pyloric strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. *Anticancer Res* 2004; **24**:269–271.

23 Mehta S, Hindmarsh A, Cheong E, Cockburn J, Saada J, Tighe R, *et al.* Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. *Surg Endosc* 2006; **20**:239–242.

24 Jeurnink SM, Steyerberg EW, Vleggaar FP, van Eijck CH, van Hooft JE, Scwartz MP, *et al.* Predictors of survival in patients with malignant gastric outlet obstruction: a patient-oriented decision approach for palliative treatment. *Dig Dis Sci* 2011; **43**:548–552.

25 Jeong JY, Han JK, Kim AY, Lee KH, Lee JY, Kang JW, *et al.* Fluoroscopically guided placement of a covered self-expandable metallic stent for malignant antroduodenal obstructions. *Am J Roentgenol* 2002; **178**: 847–852.

26 Jung JS, Song HY, Kang SG, Huh JD, Park SJ, Koo JY, *et al.* Malignant gastroduodenal obstructions: treatment by means of a covered expandable metallic stent-initial experience. *Radiology* 2000; **216**:758–763.

27 Park KB, Do YS, Kang WK, Choo SW, Han YH, Suh SW, *et al.* Malignant obstruction of gastric outlet and duodenum: palliation with flexible covered metallic stents. *Radiology* 2000; **216**:758–763.

28 Maetani I, Ukita T, Tada T, Shigoka H, Omuta S, Endo T. Metallic stents for gastric outlet obstruction: reintervention rate is lower with uncovered versus covered stents, despite similar outcomes. *Gastrointest Endosc* 2009; **69**:806–812.

29 Kim CG, Choi IL, Lee JY, Cho SJ, Park SR, Lee JH, *et al.* Covered versus uncovered self-expandable metallic stent placement for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study. *Gastrointest Endosc* 2010; **72**:25–32.

30 Mutignani M, Tringali A, Shah SG, Perri V, Familiari P, Lacopini F, *et al.* Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. *Endoscopy* 2007; **39**:440–447.

ARTIGO 3

Liberato MA, Canena J.

Obstrução Colônica Aguda.

In: Costa Junior AB, eds, Endoscopia Digestiva de Urgência. Edições Livraria Santos Editora Ltda, Brasil, 2009: capítulo 24, pp 261-271

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Capítulo 24

Obstrução Colônica Aguda

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O PROBLEMA

A principal causa de obstrução colónica aguda é o cancro colo-rectal[1], sendo esta entidade uma das neoplasias com maior incidência no mundo ocidental[2]. A sua incidência e mortalidade apresentam uma distribuição a nível mundial muito variável, embora os países industrializados, com excepção do Japão, sejam aqueles que apresentam maior incidência desta doença[2]. Calcula-se que existam 300000 novos casos de cancro colo-rectal diagnosticados, por ano, no mundo ocidental, com mortalidade anual de cerca de 50% [2]. Nos Estados Unidos o cancro colo-rectal é a quarta neoplasia mais frequente e a segunda causa de mortalidade por doenças do foro oncológico.[2]

A oclusão intestinal é uma complicação frequente do tumor maligno colo-rectal, podendo ocorrer em 8-25% dos casos durante a sua evolução[3], estimando-se que 10-30% dos doentes tem, como forma de manifestação inicial, sintomas obstructivos [3]. Os doentes com sub ou oclusão colónica total apresentam-se, habitualmente, num estadio mais avançado da doença[3]. A terapêutica habitual é a cirurgia de urgência, associada a taxas de mortalidade e morbilidade não desprezíveis [4]. A intervenção cirurgica é habitualmente realizada em duas etapas, com uma colostomia temporária de inicio, que em muitas situações se torna definitiva, criando um impacto negativo na qualidade de vida [5]. Com o desenvolvimento da endoscopia de intervenção foram utilizados um número variável de tratamentos endoscópicos para a obstrução colónica: dilatação com balão hidrostático 6; fotoablação com laser Nd:Yag [7]; electrocoagulação [8] e terapêutica fotodinâmica [7]. Todas estas modalidades são relativamente eficazes no alívio da obstrução intestinal, mas acabam por ser limitadas pela necessidade de tratamentos repetidos e por uma taxa não negligenciável de complicações [6,7,8]. Para agravar a situação, após múltiplas sessões, a necessidade de recurso à colostomia é frequente.[9] O aparecimento de uma

terapêutica endoscópica eficaz, com baixa morbilidade e mortalidade, em alternativa à cirurgia de urgência surgiu com as próteses metálicas auto-expansíveis (PAME). Estas resolvem a obstrução aguda, permitindo uma cirurgia posterior e nos doentes sem perspectiva cirurgica constituem terapêutica paliativa definitiva.[10,11]

A utilização de PMAE na obstrução do cólon foi originalmente descrita por Dohmoto em 1991.[12] Desde essa altura, a melhoria técnica nos sistemas de aplicação mais finos e manobráveis, associados a próteses de maior flexibilidade e maior diâmetros, aumentaram a popularidade desta técnica, como ponte para cirurgia, e na paliação definitiva da obstrução colónica nos estadios avançado da doença.[11,13,14,15,16]

ABORDAGEM ENDOSCÓPICA

Perante a suspeita clínica de uma oclusão intestinal, existe uma investigação rápida: raio X simples do abdómen em pé, avaliação analítica e tomografia computorizada para uma mais correcta localização do local de oclusão. Os doentes são submetidos a entubação nasogástrica, reequilíbrio hidroelectrolítico e antibioterapia de largo espectro. Devido à existência de obstrução colónica total ou subtotal a preparação consiste, em dois a quatro enemas de limpeza, de acordo com a provável localização da obstrução.

Os exames são feitos com controlo endoscópico e fluoroscópico em sala apropriada e recomenda-se a sedação ministrada por anestesista.

Existem dois tipos de próteses (Fig. 24.1): 1) as que tem um catéter de implantação com diâmetro que não permite a passagem da prótese através do canal de trabalho do colonoscópio e que, habitualmente, são apenas colocadas em lesões do recto e cólon sigmoideu. Esta modalidade designa-se por colocação não TTS ("trough-the-scope"); 2) próteses cujo catéter de implantação (8-10 French) permite a passagem através do canal do colonoscópio, tornando possível a colocação em qualquer local do cólon onde exista a obstrução. Esta técnica designa-se por colocação TTS. O doente é colocado em decúbito lateral esquerdo, no início da terapêutica; por vezes os doentes são mudados para decúbito dorsal, durante o procedimento, para uma velhor visualização anatómica, sob controlo fluoroscópico.

Colocação não TTS: depois da visualização endoscópica da lesão, é indispensável a marcação da margem proximal (em relação ao colonoscópio) do tumor para uma correcta visualização fluoroscópica. Existem várias formas de marcação: injecção sub-mucosa de produtos radio-opacos como o lipiodol; marcação externa com peças metálicas aderentes à pele do doente, e a mais segura e fácil que é a marcação das margens do tumor com um clip hemostático. Em seguida a estenose deve ser canulada com um catéter, como os utilizados na CPRE, de perferência de triplo lúmen, que permita a injecção de contraste ao mesmo tempo que é possível avançar um fio guia sobre o catéter. A injecção de contaste hidro-solúvel permite definir a anatomia e o comprimento da estenose. Após a injecção introduz-se um fio guia de extremidade hidrofílica ou então totalmente hidrofílico, de forma a ultrapassar a estenose, evitando fios pouco flexíveis, que aumentam o risco de perforação.[11,13,14] Após o fio ultrapassar a estenose, o catéter é avançado sobre o guia, através da lesão, sob controlo fluoroscópico. A injecção de contraste permite verificar o limite superior do tumor e definir a anatomia do cólon a montante da obstrução. É recomendável colocar o guia, pelos menos 20-30 cm para além da estenose. Com o

Figuras 24.1A e B Algumas próteses colónicas metálicas auto-expansíveis disponíveis no mercado

Modelo	Diâmetro do catéter (French)	Diâmetro da prótese (mm)	Comprimentos (mm)	Fabricante
Wallflex	10	22 e 25	60-90-120	Boston Scientific
Bonastent	10	20*-22*-24	70*-80-100-140	Life Partners
Hanarostent	10.2/8*	22/24*/28/32*	60*-80-90*-110-140-170	M.I.Tech

Fig. 24.1A Modalidades TTS ("trough the scope") *versão coberta.

Modelo	Diâmetro do catéter (French)	Diâmetro da prótese (mm)	Comprimentos (mm)	Fabricante
Ultraflex precision	16	25	90	Boston Scientific
Ella	13	22-25-30	de 22 a 136	Ella

Fig. 24.1B Modalidade não TTS ("trough the scope").

catéter a montante da obstrução o fio deve ser mudado para um guia mais rígido, para melhor estabilidade na colocação da prótese, precaução muito útil em especial nas estenoses longas, anguladas e tortuosas. A estenose deve ser medida durante a retirada do catéter. Após a saída do colonoscópio e com o fio em posição, a prótese é montada sobre o guia e avançada sob controlo fluoroscópico até à zona de obstrução. O colonoscópio é introduzido ao lado do catéter da prótese, até ao tumor, permitindo um controlo fluoro e endoscópico durante a libertação da prótese. Quando esta é totalmente libertada deve ser injectado contraste através da mesma para assegurar a sua patência. Este tipo de técnica deve ser reservado para obstruções distais, embora na nossa experiência pessoal esta modalidade seja apenas reservada para obstruções rectais, em que recorremos a próteses de libertação proximal. Recomenda-se uma distância de cerca de 3-4 cm entre a junção canal anal-recto e a extremidade da prótese para evitar tenesmo e falsas vontades após a colocação da mesma.

Colocação TTS: o procedimento é sobreponível ao anterior. A grande diferença é que a prótese é passada através do canal do aparelho e libertada sob visão directa e controlo fluoroscópico.As próteses disponíveis no mercado são de libertação distal. O tamanho da prótese é escolhido de acordo com o comprimento da lesão, devendo a prótese ter, pelo menos, 3cm mais que a extensão do tumor. A colocação TTS (Figs. 24.2 e 24.5) é mais fácil e permite o acesso a qualquer segmento do cólon. Por vezes, em oclusões agudas com mais de 24-48 horas

Figuras 24.2A a E Técnica de colocação TTS ("trough the scope") de uma prótese metálica auto-expansível numa neoplasia do cólon obstructiva a nível do ângulo hepático

Fig. 24.2A Visualização e canulação da estenose com um catéter de triplo lumen.

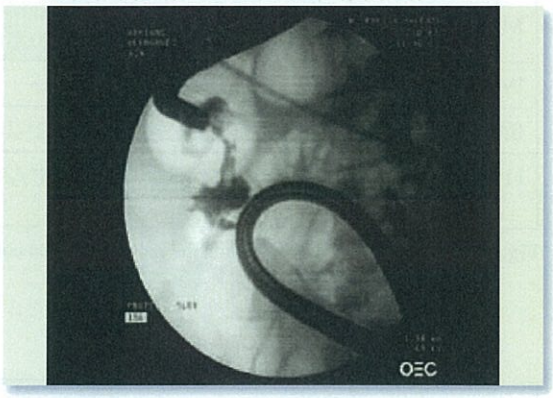

Fig. 24.2B Injecção de contraste para definir a anatomia da estenose e posterior passagem do fio guia.

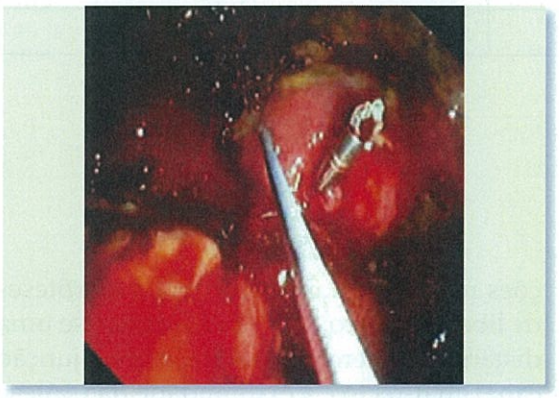

Fig. 24.2C Visualização da estenose, já com clip de marcação e fio guia rígido.

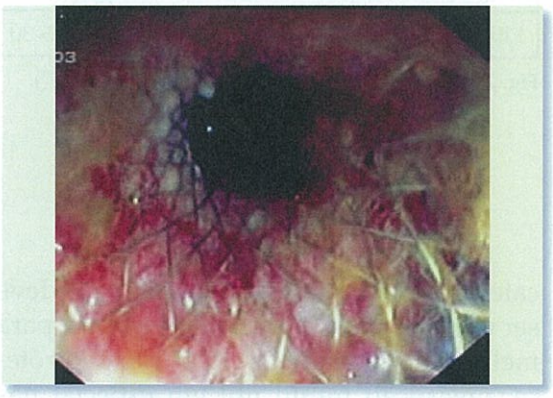

Fig. 24.2D Visualização endoscópica da prótese bem implantada.

Fig. 24.2E Imagem fluoroscópica da prótese bem implantada.

de evolução, o endoscopista não visualiza o tumor e apenas vê mucosa edemaciada e colapsada que está cerca de 2-3 cm antes da lesão. Nestes casos é útil recorrer a um gastroscópio convencional (habitualmente este tipos de situações ocorrem em lesões do cólon esquerdo) que pelas suas menores dimensões e maior flexibilidade permite um melhor posicionamento no lúmen colónico e uma consequente mais fácil abordagem da lesão com o catéter e o guia. Após colocação do guia, introduz-se um colonoscópio até à lesão com o fio a servir de referência (não existe nenhuma prótese colónica TTS cujo catéter de inserção passe no canal de trabalho de um gastroscópio convencional).

Quando se coloca uma prótese considera-se a existência de sucesso técnico se após a libertação da mesma houver patência do seu lúmen o que se verifica com injecção de contraste através da prótese. O sucesso clínico é definido pela descompressão colónica imediata e melhoria clínica e imagiológica, durante as primeiras 96 horas após a intervenção endoscópica. Depois da inserção e libertação da prótese os doentes devem ser cuidadosamente monitorizados para exclusão de complicações e avaliação do sucesso clínico. Deve manter-se dieta zero e entubação nasogástrica até ser evidente o restabelecimento do trânsito intestinal e da melhoria clínica. A programação de uma intervenção cirurgica não deve ser precipitada, sendo fundamental uma preparação intestinal lenta e gradual, que não deve ser iniciada antes das 48 horas.

Resultados e utilidade clínica do recurso a PMAE

A utilização de PMAE na neoplasia do cólon engloba dois cenários diferentes: como "ponte para a cirurgia" em doentes com potencial para ressecção cirurgica curativa e como terapêutica paliativa em doentes sem condições cirurgicas, seja por doença disseminada ou por patologia associada grave.

Antes do aparecimento da terapêutica endoscópica a cirurgia era a única opção para o tratamento da obstrução colónica. A cirurgia de urgência tem uma morbilidade pós-operatória que pode ir até 45-50% e uma mortalidade que pode atingir os 15-20%[4]. Em geral, doentes que se apresentam com oclusão intestinal tem, com maior probabilidade, doença mais avançada, comorbilidades e frequentemente mais idosos, aumentando o risco da cirurgia.[3,14]

Colocação como "ponte para a cirurgia"

Em doentes propostos para cirurgia curativa a descompressão obtida pela colocação de uma prótese metálica permite o tempo necessário para a preparação pré-operatória, a correcção da desidratação e do desiquilíbrio hidroelectrolítico e a instituição de um suporte nutricional adequado.

Numa metanálise recente [13], englobando 54 trabalhos e 1198 doentes (791 como terapêutica paliativa e 407 como "ponte para cirurgia") o sucesso técnico no grupo como "ponte para cirurgia" foi de 91,9% e o sucesso clínico foi de 71,7% (nestes trabalhos o sucesso clínico foi definido não só como melhoria da oclusão, mas também pela ausência de necessidade de colostomia). Nesta série o sucesso clínico é bastante inferior ao técnico por várias razões que impediram a realização de cirurgia numa só fase, obrigando a uma colostomia: neoplasias síncrones não detectadas, doença localmente muito avançada e preparação inadequada, em especial se houver precipitação na preparação antes da cirurgia.

Outro estudo sistemático[14], englobando 58 publicações, refere sucesso técnico em 85% dos doentes, dos quais 95% foram operados numa só etapa.

Num trabalho comparativo entre PMAE antes da cirurgia e cirurgia de urgência [17], a anastomose primária foi possível em 84,6% no grupo PMAE, enquanto que nos doentes operados de urgência a cirurgia numa só etapa só foi possível em 41,1% dos casos. O tempo de internamento e o número de complicações foi mais baixo no grupo de doentes PMAE antes da operação. Uma metanálise recente [18] que analisa 10 trabalhos, compara a eficácia entre a colocação de PMAE e a cirurgia em tumores colo-rectais. Os autores concluem que as PMAE levam a uma redução do tempo de internamento, da mortalidade, da morbilidade, do número de colostomias e que a existência de uma prótese "*in situ*" não interfere com o acto cirurgico, não evitando uma ressecção potencialmente curativa [19,20]. Existem vários relatos[21,22,23] sobre modelos de decisão do ponto de vista económico e das vantagens para o doente. Estes autores ao compararem o custo-benefício das duas estratégias possíveis (PMAE antes da cirurgia versus cirurgia de urgência), referem que o recurso a prótese tem uma menor mortalidade e morbilidade, diminuição do número de colostomias com a melhoria da qualidade de vida e redução do custo económico por doente. Estes trabalhos defendem que a colocação de próteses como "ponte para cirurgia", sempre que possível, deve ser oferecida como terapêutica de escolha aos doentes com obstrução maligna colo-rectal.

Colocação como terapêutica paliativa

Em doentes com neoplasia colo-rectal e sem indicação cirurgica a oclusão intestinal é uma complicação frequente[3]. A ressecção cirurgica paliativa, defendida por alguns autores[24,25], não provou o aumento da sobrevida[26], e um estudo sugere que a mortalidade operatória na terapêutica paliativa da neoplasia colo-rectal pode chegar aos 6%[27]. A colostomia criada na cirurgia descompressiva, é definitiva em 50% dos casos[27], diminuindo a qualidade de vida dos doentes[5]. Numa revisão sistemática[13] de 1198 casos (791 no grupo paliativo) a taxa de sucesso técnico foi de 93.35% e a de sucesso clínico foi de 91,9%. Noutro estudo de metanálise [14] o sucesso técnico obtido foi de 90% e o clínico de 88%. Estudos[22, 28] de custo-benefício para a terapêutica paliativa com PMAE versus cirurgia referem vantagens na mortalidade e morbilidade, dias de hospitalização, colostomias definitivas e custo por doente na abordagem da obstrução maligna colo-rectal com PMAE como terapêutica paliativa.

Uma das principais preocupações nesta modalidade terapêutica é a morbilidade e a patência das próteses a longo termo. Muitos dos estudos englobam poucos doentes, tem seguimentos curtos ou incompletos e frequentemente utilizam diferentes tipos de próteses [29,30,31]. As duas metanálises disponíveis[13 e 14] apresentam um elevado número de casos mas são escassos na informação da morbilidade e patência das próteses a longo prazo e ainda sobre eventuais implicações da quimioterapia. A série publicada[29], que engloba maior número de casos (n=52) com um seguimento longo (apenas 3 doentes estavam vivos na altura do relato), apresenta 19.2% dos doentes com obstruções provocadas por neoplasias que não a colo-rectal e aborda apenas estenoses do cólon esquerdo tratadas com vários tipos de próteses. O sucesso técnico e clínico foi obtido em 96,1% dos casos, a sobrevida média foi de 88 dias e 14% dos doentes necessitaram de colostomia. Outro estudo[32], englobando 28 doentes seguidos até ao seu falecimento, faz uma análise prospectiva

da paliação definitiva com PMAE (todas do mesmo fabricante) no tumor colo-rectal obstructivo. Apresenta um sucesso clínico e técnico de 100% e um tempo médio de hospitalização de 9.2 dias após a colocação das próteses. Quatro doentes (14,2%) necessitaram de colostomia definitiva por carcinomatose peritoneal. Mas o mais interessante deste estudo é que 35,7% dos casos tinham lesões obstructivas a montante do ângulo esplénico, e 53,5% dos doentes foram sido submetidos a quimioterapia sem complicações. Isto sugere que lesões obstructivas localizadas a montante do cólon esquerdo podem ser paliadas com a mesma taxa de sucesso das lesões a jusante do ângulo esplénico, mesmo em doentes submetidos a quimioterapia.

Complicações

As complicações relacionadas com a colocação de PMAE em lesões obstructivas do cólon continuam a ser um problema e não são incomuns.

A *perfuração* é a complicação mais grave, podendo ser causa de morte e levando a uma intervenção cirurgica de urgência na maior parte dos casos. Numa revisão de 1198 casos [13], refere 3,7% casos de perforação, sendo a maioria durante as primeiras 24-72 horas. Neste estudo 17,7% das perforações foram tardias. Outra metanálise ([14]) refere perforações em 4% dos doentes. Estes estudos de revisão [1,11,13,14] referem que a dilatação com balão da estenose é uma das principais causas de perfuração e que esta manobra deve ser evitada. Outra causa de perforação é a manipulação excessiva com fio guia para obtenção do acesso ao segmento estenosado, sugerindo que a utilização de guias hidrofílicos diminui esta complicação[32]. Uma causa rara de perforação é a expansão da prótese contra um tecido necrosado e frágil.

Uma complicação frequente é a *migração*, principalmente com próteses cobertas. Khot et al.[14] refere migração em 10% dos casos, a maior parte delas ocorrendo nos primeiros 30 dias. Na revisão sistemática de Sebastian et al.[13] a migração ocorreu em 11.8% dos doentes. Neste estudo a taxa de migração de próteses cobertas (30,58%) foi significativamente superior quando comparada com o uso de próteses não cobertas. Uma série [32], com PMAE descobertas não apresenta migrações, mesmo com 10 doentes (35,6%) com lesões proximais (transverso, ângulo hepático e ascendente distal), onde o diâmetro do cólon é maior, sugerindo que o recurso a PMAE em estenoses fora do cólon esquerdo não aumenta o risco de migração.

Outra complicação é a *reobstrução*, por crescimento tumoral através de uma malha não coberta, ou por crescimento nos topos da prótese. Na metanálise de Sebastian et al.[13] 7,3% dos doentes tiveram reobstrução clinicamente significativa, sendo a principal razão o crescimento tumoral através de uma malha não coberta. Neste estudo o tempo médio para a reobstrução foi de 24 semanas. Estes doentes podem ser tratados, com árgon plasma, com a injecção de substâncias como o álcool absoluto, embora a terapêutica mais eficaz (em especial se a sobrevida expectável do doente não for muito reduzida) seja a colocação de uma PMAE por dentro da que está invadida[1,11,13,14,32]. Nesta revisão sistemática a taxa de reobstrução das próteses cobertas foi significativamente menor que a das não cobertas (4,7% versus 7,8%). Na metanálise de Khot et al.[14] os autores referem 10% de reobstruções. Um estudo[32] com seguimento até ao falecimento de todos os doentes, refere uma taxa de obstrução em 14.3% com um tempo médio de paliação de 40 semanas. Todos os doentes foram paliados com uma segunda prótese (Fig. 24.3), sem

Figuras 24.3A a C Reobstrução de prótese da transição recto-sigmoide por crescimento tumoral através das malhas da prótese, 5 meses após a sua colocação

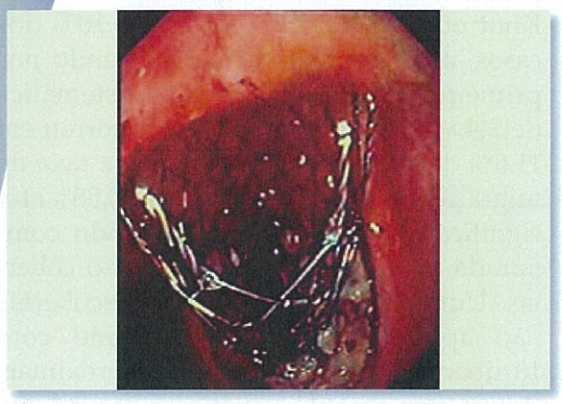

Fig. 24.3A Prótese em posição aparentemente funcionante.

Fig. 24.3B Crescimento tumoral dentro da prótese levando à oclusão quase total do lúmen intestinal.

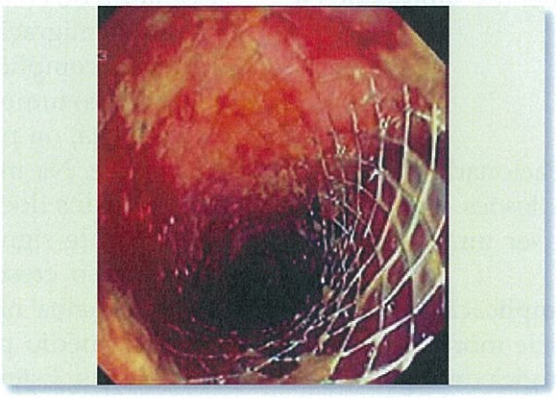

Fig. 24.3C Aspecto de nova prótese, colocada dentro da existente, com resolução da obstrução.

necessidade de outras intervenções, sugerindo a sua eficácia e maior comodidade para o doente. A a reobstrução ocorre a longo prazo (habitualmente entre 4-10 meses), sendo maior em próteses não cobertas. Contudo, o risco de migração das próteses cobertas não é negligenciável devendo ser ponderado o recurso a este tipo de próteses em doentes que tem uma esperança de vida geralmente curta. Finalmente alguns doentes desenvolvem reobstrução intestinal, por carcinomatose peritoneal, com vários locais de obstrução, obrigando a uma colostomia definitiva.

Uma complicação rara é a *hemorragia* tardia embora não seja evidente que o sangramento do tumor é devido à prótese. São raros os estudos que referem e abordam esta complicação. Na hemorragia o tratamento de eleição é o recurso ao árgon plasma através das malhas da prótese (Fig. 24.4).

A mortalidade das PMAE é abordada nas duas principais metanálises (13,14) que referem valores de 0,58% e 1% respectiva-

Figuras 24.4A e B Terapêutica endoscópica com árgon plasma de uma neoplasia sangrante 3 meses após a paliação de uma estenose obstructiva com prótese metálica descoberta

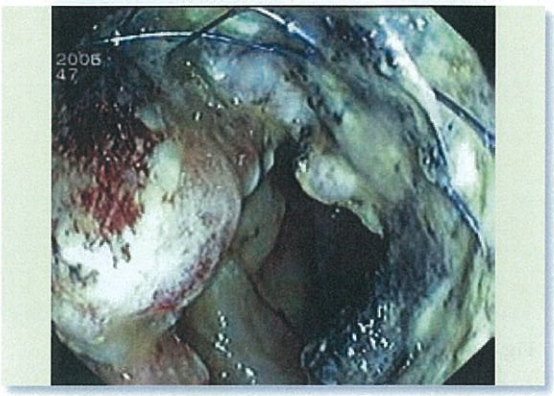

Fig. 24.4A Prótese do cólon com crescimento tumoral através da malha e sangrante.

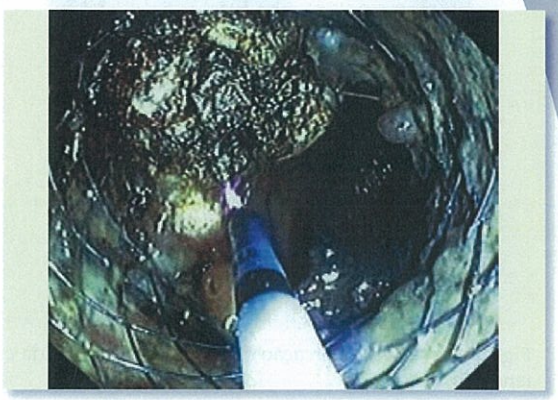

Fig. 24.4B Controlo da hemorragia após aplicação de árgon plasma através das malhas da prótese.

Figuras 24.5A a G Colostomia no flanco esquerdo por câncer colorretal em agosto de 2005. Tumor metacrônico. Suboclusão/oclusão intestinal. Descompressão imediata após colocação da prótese

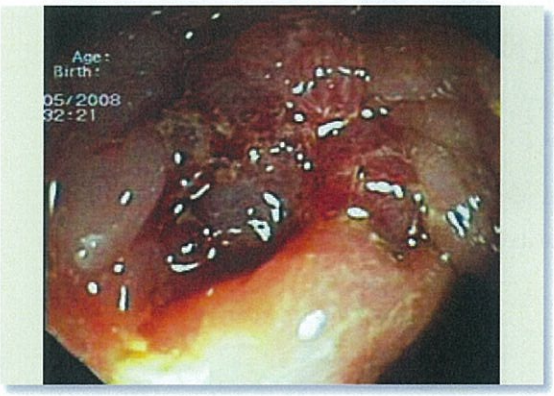

Fig. 24.5A Estenose tumoral.

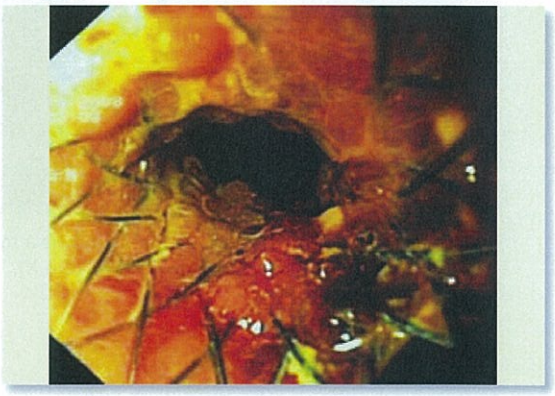

Fig. 24.5B Visão dentro da prótese ao nível da obstrução.

Fig. 24.5C Prótese abaixo da obstrução.

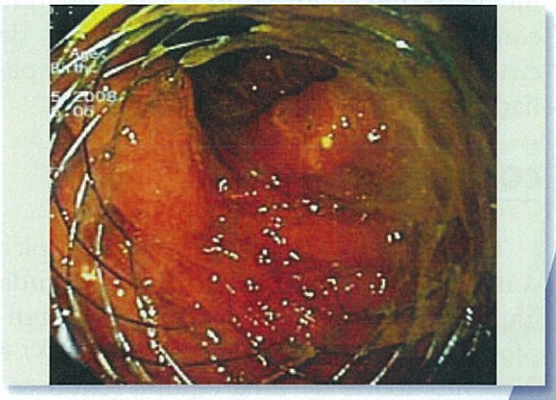

Fig. 24.5D Cólon a montante da prótese.

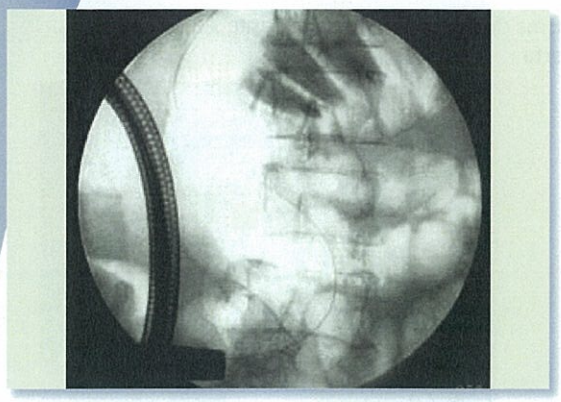

Fig. 24.5E Clip de marcação e fio-guia a montante da estenose (raio X).

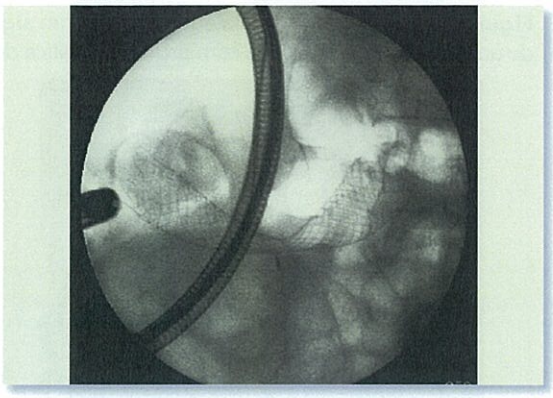

Fig. 24.5F Prótese colocada, aberta (raio X).

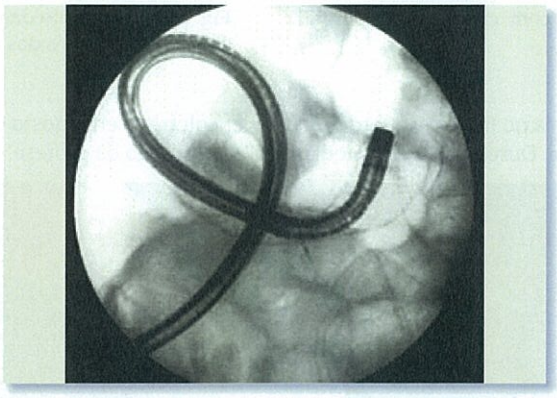

Fig. 24.5G Controle a montante da prótese com endoscópio pediátrico (raio X).

mente, o que se torna irrelevante quando comparado com os números elevados da cirurgia na "ponte para cirurgia", e na paliação definitiva.

CONCLUSÕES

O sucesso da terapêutica endoscópica com PMAE na obstrução colónica aguda implica uma estrutura que reuna condições técnicas (equipamento de raios X) e disponibilidade de uma equipa (endoscopista experiente, anestesista, enfermeiros e técnicos de raios X) treinada e com disponibilidade alargada.

A nossa experiência e a análise da literatura demonstram que a utilização de PMAE na obstrução colónica como "ponte para a cirurgia", ou na paliação definitiva é a técnica de primeira escolha. É eficaz, segura, provavelmente com claro custo-benefício para o doente e principalmente aumenta a qualidade de vida evitando colostomias temporárias ou definitivas.

Referências

1. Baron T, Harewood G. Enteral self-expandable stents. Gastrointest Endosc 2003; 58:421-432
2. Wingo PA, Cardinez CJ, Landis SH.Long- term trends in cancer mortality in the United States. *Cancer* 2003;97(12 suppl):3133-3275.
3. Deans GT, Krukowski ZH, Irwin ST. Malignant obstruction of the left colon. *Br J Surg* 1994; 81: 1270-1276.
4. Leitman IM, Sullivan JD, Brams D, et al. Multivariate analysis of the morbidity and mortality from initial surgical management of obstructing carcinoma of the colon. *Surg Gynaecol Obstet* 1992; 174: 513-518.
5. Neugent KP, Daniels P, Stewart B, et al. Quality of life in stoma patients. *Dis Colon Rectum* 1999; 42: 1569-1574.
6. Oz MC, Forde KA. Endoscopic alternatives in the management of colonic strictures. *Surgery* 1990; 108:513-19.
7. Spinelli P, Mancini A, Dal Fante M. Endoscopic treatment of gastrointestinal tumors: indications and results of laser photocoagulation and photodynamic therapy. Sem Surg Oncol 1995; 11:307-18.
8. Hoekstra HJ, Verschueren RCJ, Oldhoff J, et al. Palliative and curative electrocoagulation for rectal cancer. *Cancer* 1985; 55:210-213.
9. Gevers AM, Macken E, Hiele M, et al. Endoscopic laser therapy for palliation of patients with distal colorectal carcinoma: analysis of factors influencing long-term outcome. *Gastrointest Endosc* 2000; 51:580-85.
10. Nassif T, Prat F, Meduri B, et al. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metallic stents: results of a multicenter study. *Endoscopy* 2003; 35:483-89.
11. Baron T, Harewood G. Enteral self-expandable stents. Gastrointest Endosc 2003; 58:421-32.
12. Dohmoto M. New method: endoscopic implantation of rectal stent in palliative treatment of malignant stenosis. *Endoscopia Digestiva* 1991; 3:1507-1512.
13. Sebastian S, Johnston S, Geoghegan T, et al. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. *Am J Gastroenterol* 2004; 99:2051-2057.
14. Khot U, Lang A, Murali K, et al. Systematic review of the efficacy and safety of colorectal stents. *Br J Surg* 2002; 89:1096-1102.
15. Camunez F, Echenagusia A, Simo G, et al. Malignant colorectal obstruction treated by means of self-expanding metallic stents: effectiveness before surgery and in palliation. *Radiology* 2000; 216:492-97.
16. Kim JH, Park SY, Lee KJ, et al. New covered through-the-scope (TTS) stent for malignant colorectal obstruction: Long-term results. *Gastroenterol* 2002; 55:A491.
17. Martinez-Santos C, Lobato RF, Fradejas JM, et al. Self-expandable stent before elective surgery vs emergency surgery for the treatment of malignant colorectal obstructions: Comparison of anastomosis and morbidity rates. *Dis Colon Rectum* 2002; 45:401-406.
18. Tilney HS, Lovegrove RE, Purkayastha S, sains PS, Weston-Petrides GK, Darzi AW, Tekkis PP, Heriot AG. Comparison of colonic stenting and open surgery for malignant large bowel obstruction. *Surg Endosc* 2007;21:225-233.
19. Adler DG, Young Fadok TM, Smyrk T. Preoperative chemoradiaton therapy after placement of a self-expanding metal stent in a patient with an obstructing rectal cancer: Clinical and pathologic findings. *Gastrointest Endosc* 2002; 55:435-437
20. Bethge N, Sommer A, Gross U. Human Tissue responses to metal stents implanted in vivo for the palliation of malignant stenosis. *Gastrointest Endosc* 1996; 43:536-602.
21. Targownik LE, Spiegal BM, Sack J, Hines OJ, Dulai GS, Gralnek IM, Farrell JJ. Colonic stent vs. Emergengy surgery of acute left sided malignant colonic obstruction: a decision analysis. *Gastrointest Endosc* 2004; 60:865-874
22. Siddiqui A, Khandelwal N, Anthony T, Huerta S. Colonic stent versus surgery for the management of acute malignant colonic obstruction: a decision analysis. *Aliment Pharmacol Ther* 2007; 26:1379-1386.
23. Govindarajam A, Naimark D, Coburn NG, Smith AJ, Law CH. Use of colonic stents in emergent malignant left colonic obstruction: a Markow chain Monte Carlo decision analysis. *Dis Colon Rectum* 2007; 50:1811-1824.
24. Liu SK, Church JM, Lavery IC, Fazio VW. Operation in patients with incurable colon cancer-is it worthwhile? *Dis Colon Rectum* 1997; 40:11-14.
25. Makela J, Haukipuro K, Laitinen S, Kairaluoma MI. Palliative operations for colorectal cancer. *Dis Colon Rectum* 1990; 33:846-850.
26. Lau PWK, Lorentz TG. Results of surgery for malignant bowel obstruction in advanced, unresectable, recurrent colorectal cancer. *Dis Colon Rectum* 1993; 36:61-64.
27. Harris GJC, Senagore AJ, Lavery IC, et al. Factors affecting survival after palliative resection of colorectal carcinoma. *Colorectal Dis* 2002; 4:31-35.
28. Osman HS, Rashid HI, Sathananthan N, Parker MC.The cost effectiveness of self expanding metal stents in the management of malignant left-sided large bowel obstruction. *Colorectal Dis* 2000; 2:233-37.
29. Law W, Choi H, Lee Y, et al. Palliation for advanced malignant colorectal obstruction by self-

expanding metallic stents: prospective evaluation of outcomes. Dis Colon Rectum 2004; 47:39-43.
30. Spinelli P, Mancini A. Use of self-expanding metallic stents for palliation of rectosigmoid cancer. *Gastrointest Endosc* 2001; 53:203-206.
31. Lobato FR, Pinto I, Paul L, et al. Self-expanding prostheses as a palliative method in treating advanced colorectal cancer. *Int Surg* 1999; 84:159-62.
32. Canena J, Romão C, Liberato M, Coutinho A, Neves B. Colorectal stents used for definitive palliation in obstructing colorectal cancers. Long term follow up. *Can J Gastroenterol* 2005; 19 (suppl): AR 607.

ARTIGO 4

Canena J, Liberato M, Marques I, Rodrigues C, Lagos A, Patrocínio S, Tomé M, Pires E, Romão C, Coutinho A, Veiga P, Neves B, Deus J, Além H, Gonçalves J.

Sustained relief of obstructive symptoms for the remaining life of patients following placement of an expandable metal stent for malignant colorectal obstruction.

Rev Esp Enferm Dig 2012 [aceite para publicação]

Title:

Sustained relief of obstructive symptoms for the remaining life of patients following placement of an expandable metal stent for malignant colorectal obstruction

Running title:

Palliative treatment of colorectal obstruction by SEMS

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ABSTRACT

Background: Self-expanding metal stents are currently being used as a definitive palliative treatment for malignant colorectal obstruction in patients with incurable disease. Few studies have followed large numbers of patients from stent placement until death, and those few have reported conflicting results in the long-term clinical outcome data.

Aims: This study evaluated the clinical effectiveness of stent placement for malignant colorectal obstruction throughout the patients' lives and related factors affecting stent patency, clinical success and complications.

Methods: This was a multicentre, retrospective study of 89 consecutive patients who had undergone attempted expandable stent placement for symptomatic malignant colorectal obstruction during a 10-year period. Data were collected to analyse the sustained relief of obstructive symptoms throughout the patients' lives, as well as the technical success, immediate clinical success, stent patency, complications, reinterventions, survival, prognostic factors associated with stent patency and long-term clinical efficacy and risk factors for complications.

Results: Technical and immediate clinical success were achieved in 95.5% and 91.0% of patients, respectively. A total of 68/89 patients (76.4%) maintained relief of obstruction from stent implantation until death without reintervention. Twenty patients (22.5%) had complications including perforation (n=4, 4.5%), stent obstruction (n=8, 9.0%), migration (n=5, 5.6%) and haemorrhage (n=3, 3.4%). Stent-related mortality was seen in 1 patient (1.1%). The estimated median survival and estimated mean stent patency were 87.0 and 322.7 days, respectively. In total, 12 of the initial 89 patients (13.5%) needed a colostomy for long-term relief of the obstructive symptoms. Univariate and multivariate analysis detected no significant prognostic factors associated with stent patency, long-term clinical efficacy and risk factors for complications; however, the multivariate logistic model revealed a non-significant trend by which the use of chemotherapy was a risk factor for migration (OR=11.89; P=0.06).

Conclusions: For palliation of incurable malignant colorectal obstruction, expandable stents can provide sustained relief of obstruction in approximately ¾ of patients. The procedure is associated with acceptable morbidity, need for reintervention and minimal mortality.

INTRODUCTION

Colorectal cancer is one of the most common malignancies worldwide (1). In patients with colorectal cancer, obstruction occurs in 15% to 20% (2). Most of these patients have advanced disease and are often elderly, with significant comorbidities (2,3,4). In this group of patients, curative resection is not frequently feasible (4,5). Therefore, palliation is the primary aim in these patients (3,6,7). Emergency surgical decompression is associated with high mortality and morbidity figures (8,9). In addition, surgery often involves creation of a colostomy, reversal of which would not be possible in up to 50% of patients. This intervention would thus have a profound negative impact on quality of life (7,8,9).

First reported by Dohmoto et al. (10), self-expandable metal stents (SEMS) have been increasingly used as a minimally invasive, nonsurgical treatment for either palliation or pre-operative bridging to 1-stage surgery procedure in malignant colorectal obstruction (1-10). A pooled analysis of 1198 patients demonstrated an immediate clinical success rate of 92.7% in the palliative group (11); however, complications were recorded including perforations (3.8%), migration (11.8%), re-obstruction (7.3%) and stent-related mortality (0.58%). A systematic review comparing endoscopic palliation with surgery suggested that stenting was associated with more positive outcomes when compared with surgery, including overall shorter hospital stays, and a lower rate of serious adverse events (9).

Although the initial decompression rate using SEMS in acute colorectal obstruction is high, there are concerns about the long-term clinical efficacy and late complications of the stents in the palliative setting. Few studies followed the majority of patients until death after stent placement, and there is a small amount of long-term clinical outcomes data with conflicting results. Recent studies reported that a single palliative SEMS implantation is associated with long-term (until death) success rates up to 80%, although the complication rate is nearly 25% (6,7,12,13). These results, however, conflict with other studies reporting short- and long-term clinical failure in more than 50% of patients, along with a high number of severe complications (4,5). Furthermore, several risk factors have been associated with stent patency, complications and clinical outcomes, as well as with conflicting results (1,6,12,13,14). The question remains: are SEMS used for definitive palliation of malignant colorectal obstruction as successful as those used as a bridge to surgery?

The aim of this study was to evaluate the sustained relief of obstructing symptoms from stent placement until death in all patients, including the incidence of complications and the need for reinterventions, risk factors for complications and prognostic factors associated

with stent patency and long-term clinical efficacy after SEMS placement in the palliative treatment of patients with malignant colorectal obstruction.

METHODS

Patients and setting

Interventional endoscopy database records from 4 institutions were retrospectively reviewed to identify all patients who had undergone consecutive attempted SEMS placement for symptomatic malignant colorectal obstruction between October 2001 and August 2011. The following criteria were used for inclusion in this study: 1-palliative intent to treat in patients with obstructive symptoms, 2-histologically confirmed malignancy, 3-inoperable disease based on advanced tumour stage, metastatic disease or medical comorbidity and 4-complete follow-up until patient death at the time of data collection. The exclusion criteria were as follows: 1-evidence of bowel perforation or other obstructions in the gastro-intestinal tract, 2-previous palliative stent placement for the same condition and 3-patients with tumoral strictures and no obstructive symptoms.

Colorectal obstruction was diagnosed by clinical findings and confirmed using a colonoscopy or computed tomography. The data were collected from a variety of sources, including patients' charts (manual and electronic), clinical notes, radiology and endoscopic reports, our prospective database, follow-up clinic visits and telephone interviews with treating physicians or family during follow-up or at the time of manuscript preparation. Several investigators participate in this task to obtain the following data: patient demographics, technical success, clinical success, stent model, stent diameter, type of malignancy (intrinsic or extrinsic), location of obstruction, complications, reinterventions, palliative chemotherapy, need for surgery and survival. Patients with incomplete data were excluded from the study. This study was conducted at 4 institutions (3 tertiary referral academic centres and 1 general district hospital). All patients provided informed written consent prior to their procedures. Each ethics committee involved approved this retrospective study.

Technique and stents

The technique used for stent placement has been described elsewhere (2, 15). Briefly, all procedures were performed with patients in the left lateral position under sedation with propofol administered by an anaesthesiologist. In some cases, patients were shifted to the supine position during the procedure and stent deployment for a better anatomic view under fluoroscopy. No oral bowel preparation was given, and patients underwent bowel cleansing by

using repeated enemas. The stricture was assessed with a triple-lumen biliary catheter and a biliary guidewire under endoscopic and fluoroscopic guidance. The length of the stricture was assessed either endoscopically or fluoroscopically by injection of water-soluble contrast. Balloon dilatation of the stricture was not performed in all cases. The distal end of the stenosis was marked with a haemostatic clip. The stent delivery system was advanced through the stricture, and the stent was deployed under fluoroscopic and endoscopic control. Stent placement was performed by one of several endoscopists (7 in total), during regular time, all with experience in pancreatobiliary endoscopy. Each endoscopist had, at least, a mean number of attempts per month of 1.5. Three different types of stent were used: 1) from October 2001 to November 2005, the Wallstent enteral stent (Boston Scientific, Natick, Massachusetts, USA), 20 or 22 mm in diameter and 6 or 9 cm in length was used by a through-the-scope method; 2) between October 2002 and November 2005, the Ultraflex Precision (Boston Scientific, Natick, Massachusetts, USA), 25 mm in diameter (mid-body) and 6, 9 or 12 cm in length was used for several cases of malignant obstruction located in the rectum or distal sigmoid colon; 3) from November 2005 to the end of this study, the WallFlex colonic stent (Boston Scientific, Natick, Massachusetts, USA), 22 or 25 mm in diameter (mid-body) and 6, 9 or 12 cm in length was used in all cases. The stent diameter and length were selected at the discretion of the endoscopist.

Twenty-four hours after stent deployment, all patients underwent a plain abdominal X-ray to verify stent expansion and correct position and to assess relief of obstruction. After stent insertion, all patients were placed on a low-residue diet with laxatives to prevent stool impaction of the stent.

End points and definitions

The primary endpoint was long-term clinical efficacy, defined as sustained relief of obstructive symptoms without reintervention. Secondary endpoints included technical success, immediate clinical success, stent patency, complications, reinterventions, survival, prognostic factors associated with stent patency and long-term clinical efficacy and risk factors for complications. Technical success was defined as accurate stent deployment across the stricture, with patency visualised both fluoroscopically and endoscopically. Immediate clinical success was defined as colonic decompression and relief of obstructive symptoms within 24 hours after stent placement (1,6). Stent patency was defined as the period between stent placement and recurrence of obstructive symptoms caused by stent dysfunction due to malignant stent obstruction (tumour overgrowth or ingrowth) or migration. Complications

were defined as any adverse event related to stent placement. Complications were also divided into early (within 7 days) and late. Stent migration was diagnosed if the stent moved from its initial position and was unable to cover the entire stenosis, leading to recurrence of obstructive symptoms. Reintervention was defined as any procedure performed after the initial stent placement, including endoscopic resolution of stool impaction, subsequent colonic stent insertion due to malignant stent restenosis or migration, balloon dilatation, stent removal, argon plasma coagulation or surgery.

Follow-up

Follow-up data were obtained by reviewing patients' electronic and manual charts and clinical notes from regular clinic visits and by performing telephone interviews with the treating physician or family at the time of manuscript preparation. Patients were followed until death in all cases. In the case of recurrent obstructive symptoms during follow-up, patients contacted their treating physician in the institution for clinical evaluation. During clinical evaluation, repeated colonoscopy was conducted for suspected stent dysfunction. Reinterventions were performed when necessary, considering the clinical situation and patient preference. Elective colostomy was performed after failure of endoscopic therapy.

Statistical analysis

All study outcomes were evaluated on an intention-to-treat basis. The cumulative time until complications, stent patency and patient survival were estimated by the Kaplan-Meier product limit method. For the calculation of the stent patency period, death before stent dysfunction was considered a censored observation. The 95% CI for long-term clinical efficacy was calculated with the Clopper-Pearson (exact) method. Potential risk factors for complications and prognostic factors associated with long-term clinical efficacy were assessed by univariate analysis followed by a multiple logistic regression. Univariate analysis was conducted using the $\chi 2$ test for categorical variables and Student's *t* test for continuous variables. To determine independent prognostic factors potentially associated with stent patency, multivariate Cox proportional hazard models were used. Age, sex, stent diameter (22 mm or less or 25 mm), type of malignancy (intrinsic or extrinsic), location of obstruction (left colon, right colon, anastomosis) and palliative chemotherapy were the variables included in the univariate and multivariate analysis. All reported *P* values were for a 2-tailed test, and a $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the software package SPSS (Statistical Package for the Social Sciences) 18 (IBM Corporation, New York, USA).

RESULTS

In total, 89 patients (54 males and 35 females) with a mean age of 74.0 years (range: 39-97 years) were enrolled in the study. The patients' baseline data are shown in Table 1.

Technical and immediate clinical success

Placement of a colorectal SEMS was attempted in 89 patients. Successful insertion was achieved in 85 of 89 patients (95.5%). There were no differences in technical success rates for stents placed in the right side of colon compared with the left side of the colon (93.8% vs. 95.9%; *P*=0.71 by univariate analysis). In 4 patients, technical failure during stent placement was caused by the inability to pass the stricture with a guidewire. All 4 patients underwent successful emergent surgery with a colostomy. Immediate clinical success was achieved in 81 of 89 attempts (91.0%) and in 81 of 85 successfully inserted stents (95.3%). Of the 85 patients with technical success, only in 81 patients improved their obstructive symptomatology because the remaining 4 patients developed stent-related perforations, as discussed later. One patient with advanced disease died several hours after the onset of the complication. The other 3 patients underwent successful emergency surgery and required no further intervention until death.

Sustained relief of obstruction

Relief of obstruction without intervention was maintained from stent insertion until death in 68 of 89 patients (76.4%, 95% CI 66.2%-84.8%) (Fig. 1 and Table 2) and in 68 of the 81 patients (83.9%) in whom insertion had immediate clinical success. The long-term clinical efficacy rates by location were as follows: 14 of 16 patients (87.5%) with stents placed in the right side of the colon and 54 of 73 patients (74.0%) with stents placed in the left side of the colon (*P*=0.25). During follow-up 6/89 patients (6.7%) were readmitted for suspected reobstruction that was proven to be attributed to disease progression and not to SEMS dysfunction as these patients were submitted to colonoscopy. Univariate (Table 3) and multivariate analysis (logistic model) showed that age, sex, stent diameter, type of malignancy, location of the stricture and palliative chemotherapy were not significantly associated with long-term clinical efficacy.

Complications, reinterventions and risk factors for complications

In total, 20 of 89 patients (22.5%) experienced complications after the procedure (Table 4). Early complications, namely perforations, were seen in 4 of 89 patients (5.1%).

Perforations occurred after stent placement after a mean interval of 1 day (range, 1-2). One patient died as a consequence of the perforation (stent-related mortality: 1.1%), and the remaining 3 patients underwent successful emergent surgery. Following surgery, these patients were free from obstruction until death. Late complications were observed in 16 of 89 patients (17.9%), including stent obstruction (n=8, 9.0%), migration (n=5, 5.6%) and haemorrhage (n=3, 3.4%). Malignant restenosis was experienced at 58, 68, 75, 92, 101, 111, 121 and 366 days after stent placement (median time to reobstruction: 96.5 days). One patient with reobstruction required successful surgery with a colostomy, and in the remaining 7 patients, stent obstruction was successfully managed by subsequent stent insertion with resolution of obstructive symptoms. All of these 7 patients maintained relief of obstructive symptoms until death. Bleeding from the tumour through the mesh of the stent was seen in 3 patients. The haemorrhage was successfully managed by endoscopic intervention using argon plasma coagulation without the need for transfusion. Migration was encountered in 5 patients at 14, 21, 23, 114 and 196 days after stent placement (median time to migration: 23 days). One patient with migration was successfully managed by subsequent insertion of a stent with a larger diameter, and the remaining 4 patients were submitted to surgery with colostomy. All 5 patients were free from obstructive symptoms until death. Kaplan-Meier analysis estimated that the mean time to complications after stent insertion was 288.2 days (range, 1-366) (95% CI 237.4-237.4) (Fig. 2). In total, 12 of the initial 89 patients (13.5%) needed a colostomy for long-term relief of the obstructive symptoms. Univariate analysis and the multivariate logistic model revealed no significant risk factors associated with complications; however, a logistic model for individual complications (migration, obstruction and perforation) showed a non-significant trend towards the use of palliative chemotherapy as a risk factor for migration (OR=11.89; 95% CI=0.90-157.47; *P*=0.06) (Table 5).

Survival, stent patency and prognostic factors for stent patency

The median and mean survival periods were 87.0 (range, 4-565) (95% CI 43.9-130.1) and 116.0 days (95% CI 92.5-139.5) (Fig. 3), respectively. The survival rates were 21.3% (95% CI 12.8%-29.9%) at 6 months and 4.5% (95% CI 0.2%-8.8%) at 1 year. Loss of stent patency occurred in 13 of 89 patients (14.6%) as a result of stent dysfunction (stent obstruction in 8 patients and migration in 5 patients). The mean stent patency was 322.7 days (range, 14-366) (95% CI 273.4-372.0) (Fig. 4). Kaplan-Meier method did not estimate median stent patency because more than 50% of observations were censored early in the analysis. Multivariate Cox regression analysis showed that age (HR 1.07, 95% CI 0.97-1.18; *P*=0.15), sex-female (HR 3.95, 95% CI 0.80-19.56, *P*=0.92), stent diameter-22mm (HR 1.14, 95% CI 0.30-4.25; *P*=0.85), type of

malignancy-colorectal (HR 0.22, 95% CI 00.4-1.27, *P*=0.09), location of the stricture-right/left (HR 0.15, 95% CI 0.01-1.54; *P*=0.11), and palliative chemotherapy (HR 5.51, 95% CI 0.86-35.29; *P*=0.07) were not significantly associated with stent patency.

DISCUSSION

According to our findings in a retrospective, single-arm, multicentre study, the use of a SEMS for definitive palliation of malignant colorectal obstruction was associated with the sustained, lifelong relief of obstructive symptoms without the need for reintervention in 76.4% of patients. The complication rate was 22.5%, and perforation was seen in 4.5% of the patients. The stent-related mortality rate was 1.1%. In total, 12 of the initial 89 patients (13.5%) needed a colostomy for long-term relief of the obstructive symptoms. The multivariate logistic model revealed a non-significant trend by which the use of palliative chemotherapy was a risk factor for migration (*P*=0.06).

SEMS were developed to provide rapid and effective relief of colonic obstruction and are an effective alternative to surgery. Several studies have suggested that there are advantages of stents over emergency surgery, either as a bridge to elective 1-stage surgery or as a palliative treatment (1,9,16). Three randomised trials have compared colostomy to endoscopic stenting for palliation of malignant colorectal obstruction (5,17,18). One study enrolling 30 patients showed that placement of a metal stent yielded similar outcomes when compared with surgery, but the stent was associated with a better quality of life for the patient and with fewer costs (17). In another study enrolling 22 patients, endoscopic stenting was significantly more effective in terms of operative time, restoration of bowel function, restoration of oral food intake and reduction in median hospitalisation (18). However, a recent trial was terminated prematurely because of the high number of perforations (n=6) in the nonsurgical arm, which resulted in 3 deaths among 10 patients (5). The authors concluded that the high perforation rate could be either specifically WallFlex-related or enteral-stent-related in patients on chemotherapy. In contrast, one study conducted in the same year as the previously cited randomised trial and using the WallFlex stent was associated with a perforation rate below 5% (18), which is in line with previous studies using other stents (11,14,20).

The results of prospective trials and of recent retrospective studies further demonstrated the effectiveness of SEMS in the palliative management of malignant colorectal obstruction (6,7,12,13,14,21). In this study, sustained relief of obstructive symptoms without reintervention was the primary outcome. A total of 76.4% of the patients were free from

obstruction until death. These results were measured on an intention-to-treat basis; per-protocol analysis yielded an improved long-term clinical efficacy of 83.9%. Furthermore, among the 14.6% of patients in whom reobstruction was caused by stent dysfunction, the placement of another stent prolonged the benefit of the majority (8/13, 61.5%) of endoscopically treated patients. In this study, no significant prognostic factors for long-term clinical efficacy have emerged. One study reported that shorter stents (<10 cm) and distal colorectal obstruction are associated with better stent outcomes (12). One additional important observation in our study is the similar long-term clinical efficacy between stents placed in the left side of the colon and SEMS placed in the right side of the colon (87.5% vs. 74.0% respectively). In this study, the number of included patients with obstruction in the proximal colon was relatively high (n=16), and the effectiveness of proximal colon stenting was previously reported in a multicentre retrospective study of 21 patients (22). Finally, in the present study, there was a substantial difference between the estimated mean survival (116.0 days) and mean stent patency (322.7 days), suggesting that colorectal stenting is able to keep the majority of patients free from obstruction until death.

Few studies have addressed the long-term sustained relief of colorectal obstruction from stent placement until death, as the majority of reports have either limited follow-up or a significant number of patients lost to follow-up. A prospective multicentre study addressed the long-term clinical efficacy of colorectal stents in 44 patients with malignant colonic obstruction. During the study, 14 patients died and 12/14 (86%) of the non-survivors were clinical successes (7). A large retrospective study conducted over a 9-year period analysed the outcomes of 168 patients who underwent SEMS placement for palliation. At 6 months, the estimated clinical success rate was 77.2%, and relief of obstruction was maintained from stent implantation until death in 108/122 of the patients (88.5%) (6). Taken together, the results of these studies and of the current study provide evidence that the long-term clinical efficacy of SEMS can be maintained until death in the great majority of patients. Furthermore, the benefits of stenting can be of high value in obstructed patients with a relatively short expected survival, as surgery in these patients may even be considered unethical, having a profoundly negative impact on quality of life (2,13).

In this study, technical success was achieved in 95.5% of the patients, a rate consistent with the largest published pooled analysis, which reported a technical success rate of 93.24% (range 64% to 100%) (11). In the current study, there were no differences in the technical success rates for stents placed in the right versus the left side of the colon (93.8% vs. 95.9%), suggesting that the through-the-scope technique makes all tumour locations accessible from a

technical perspective. In the present study, immediate clinical success was observed in 91.0% of the patients who were able to avoid surgery. These results were in keeping with the results of the previously cited pooled analysis, in which clinical success was achieved in 88.56% of the patients (range, 55-100%) (11).

When SEMS placement is considered for definitive palliation of malignant colorectal obstruction, safety is an important issue. The most frequent complications are perforations, stent obstruction, stent migration and bleeding. In this study, the complication rate was 22.5%, very similar to the results of other studies with an overall complication rate of 25% (6,11,14); however, relevant complications (namely perforations) are not common. In this study, perforation was seen in 4.5% of patients. This result is in line with the literature, in which perforation occurred in 0% to 9% of cases, with an average of 5% (6,7,11,13,14,21). Proposed risk factors for perforation include balloon predilatation, concomitant chemotherapy and bevacizumab-based chemotherapy (5,6,13,17,18,23). In this study, balloon dilatation was not done and chemotherapy was not associated with perforation in multivariate analysis, as previously reported by others (1). However, the addition of bevacizumab to cancer therapy significantly increases the risk of colorectal perforation, and this risk is further increased in patients submitted to SEMS placement for palliative colorectal obstruction (5,13,23). In this study, the stent migration rate was 5.1%, which is low when compared with older studies reporting values between 9% and 16% (11,14). In fact, the problem of stent migration seems to be declining as a result of increasing use of stents specifically designed for colons with larger diameters. In the current study, 56.2% of the patients were submitted to stents with diameters of 25 mm, and this approach may explain our low migration rate. In this study, the multivariate logistic model showed a non-significant trend by which the use of palliative chemotherapy constituted a risk factor for migration. This result suggests that concomitant chemotherapy may enhance tumour reduction, leading to migration in the long-term. One of the most common complications of colorectal stenting is stent reobstruction. In this study, the stent occlusion rate was 9.0%, which is in line with recent literature reporting an occlusion rate between 9% and 17% (1,4,6,12). Recently, the insertion of an additional stent has become standard in the treatment of stent occlusion. In our study, among the 9.0% of patients in whom reobstruction was seen, subsequent stent placement further increase the benefit of stenting in the majority (7/8, 87.5%) of patients treated with SEMS.

Several limitations of our study should be taken into account. First, this was a study with a retrospective design limiting the number of included patients because some of the identified consecutive patients had incomplete data and were excluded from the analysis. Our

data may therefore have been subject to selection bias. Another potential weakness is the single-arm design, with no comparison to other available treatments, especially to palliative surgery. We suggest that further prospective randomised studies are needed. Surgery must be compared to endoscopic stenting in a large population in order to have adequate power to detect minor differences in outcome. In these proposed studies, long-term complications and quality of life should be carefully evaluated. The endoscopists involved in the procedures were very experienced, and we cannot exclude a poorer outcome in community or district general hospitals. However, in a large cohort of patients Garcia-Cano *et al.* reported similar results between referral centers and smaller hospital suggesting that colonic stent placement could be feasibly performed in general endoscopic practice (20). The strengths of our study are the design, which allowed us to follow a cohort of patients from stent insertion until death in all cases, and the relatively large sample size.

In conclusion, our data suggest that the placement of a SEMS for definitive palliation of incurable malignant colorectal obstruction is a useful tool that can provide sustained relief of obstruction without reintervention in approximately 75% of patients. The procedure provides rapid and effective relief of obstruction and is associated with acceptable morbidity, acceptable need for reintervention and minimal mortality.

REFERENCES

1 - Lee HJ, Hong SP, Cheon JH, Kim TI, Min BS, Kim NK, et al. Long-term outcome of palliative therapy for malignant colorectal obstruction in patients with unresectable metastatic colorectal cancers: endoscopic stenting versus surgery. Gastrointest Endosc 2011;73:535-42

2 - Repici A, Ferreira DP. Expandable metal stents for malignant colorectal strictures. Gastrointest Endoscopy Clin N Am 2011;21:511-33

3 – Self-expanding metal stents as non-surgical palliative therapy for malignant colonic obstruction: time to change the standard of care? [editorial]. Gastrointest Endosc 2007;66:928-30

4 - Fernández-Esparrach G, Bordas JM, Giráldez MD, Ginès A, Pelissé M, Sendino O, et al. Severe complications limit long-term clinical success of self-expanding metal stents in patients with obstructive colorectal cancer. Am J Gastroenterol 2010;105:1087-93

5 - van Hooft JE, Fockens P, Marinelli AW, Timmer R, van Berkel AM, Bossuyt PM, et al. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy 2008;40:184-91

6 - Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. Gastrointest Endosc 2010;71:560-72.

7 - Repici A, Fregonese D, Costamagna G, Dumas R. Kähler G, Meisner S, et al. Ultraflex precision colonic stent placement for palliation of malignant colonic obstruction: a prospective multicenter study. Gastrointest Endosc 2007;66:920-27

8 – Self-expanding metal stents in malignant colonic obstruction: have we covered all angles? [editorial]. Gastrointest endosc 2007:67:937-39

9 - Watt AM, Faragher IG, Griffin TT, Rieger NA, Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg 2007;246:24-30

10 - Dohmoto M, Rupp KD, Hohlbach G. Endoscopically-implanted prosthesis in rectal carcinoma, Dtsch Med Wochenschr 1990;115:915;[in German]

11 - Sebastian S, Johnston S, Geoghegan T, Torreggiani W, Buckley M. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. Am J Gastroenterol 2004; 99:2051-57

12 - Jung MK, Park SY, Jeon SW, Cho CM, Tak WY, Kweon YO, et al. Factors associated with the long-term outcome of a self-expandable colon stent used for palliation of malignant colorectal obstruction. Surg Endosc 2010 Mar;24:525-30.

13 - Manes G, de Bellis M, Fuccio L, Repici A, Masci E, Ardizzone S, et al. Endoscopic palliation in patients with incurable malignant colorectal obstruction by means of self-expanding metal stent: analysis of results and predictors of outcomes in a large multicenter series. Arch Surg 2011;146:1157-62.

14 - Ptok H, Meyer F, Marusch F, Steinert R, Gastinger I, Lippert H, et al. Palliative stent implantation in the treatment of malignant colorectal obstruction. Surg Endosc 2006; 20:909-14

15 – Baron TH. Colonic stenting, technology, and outcomes for malignant and benign disease. Gastrointest Endoscopy Clin N Am 2005;15:757-71

16 – Law WL, Choi HK, Chu KW. Comparison of stenting with emergency surgery as palliative treatment for obstructing primary left-sided colorectal cancer. Br J Surg 2003;90:1429-33

17 - Xinopoulos D, Dimitroulopoulos D, Theodosopoulos T, Tsamakidis K, Bitsakou G, Plataniotis G, et al. Stenting or stoma creation for patients with inoperable malignant colonic obstructions? Results of a study and cost-effectiveness analysis. Surg Endosc 2004;18:421-26

18 - Fiori E, Lamazza A, De Cesare A, Bononi M, Volpino P, Schillaci A, et al. Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res 2004;24:265-68

19 – Repici A, De Caro G, Luigiano C, Fabbri C, Pagano N, Preatoni P, et al. WallFlex colonic stent placement for management of malignant colonic obstruction: a prospective study at two centres. Gastrointest Endosc 2008;67:77-84

20 - García-Cano J, González-Huix F, Juzgado D, Igea F, Pérez-Miranda M, López-Rosés L, et al. Use of self-expanding metal stents to treat malignant colorectal obstruction in general endoscopic practice (with videos). Gastrointest Endosc 2006;64:914-20

21 – Small AJ, Baron TH. Comparison of Wallstent and Ultraflex stents for palliation of malignant left-sided colon obstruction: a retrospective, case-matched analysis. Gastrointest Endosc 2008;67:478-88

22 – Repici A, Adler DG, Gibbs CM, Malesci A, Preatoni P, Baron TH. Stenting of the proximal colon in patients with malignant large bowel obstruction: techniques and outcomes. Gastrointest Endosc 2007;66:940-44

23 – Hapani S, Chu D, Wu S. Risk of perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009;10:559-68

Table 1. Baseline patient data.

Characteristic	
Gender	
Male, n (%)	54 (60.7)
Female, n (%)	35 (39.3)
Age (years), mean±SD (range)	74.0+10.6 (39-97)
Site of obstruction	
Rectum, n (%)	18 (20.2)
Sigmoid colon, n (%)	49 (55.1)
Descending colon, n (%)	4 (4.5)
Splenic flexure, n (%)	2 (2.2)
Transverse colon, n (%)	12 (13.5)
Hepatic flexure, n (%)	4 (4.5)
Stricture location	
Right side of the colon, n (%)	16 (18.0)
Left side of the colon, n (%)	73 (82.0)
Etiology	
Colorectal, n (%)	85 (95.5)
Extrinsic compression, n (%)	4 (5.1)
Type of stent	
Wallstent, n (%)	39 (43.8)
Ultraflex, n (%)	10 (11.2)
WallFlex, n (%)	40 (44.9)
Stent diameter, mm	
≤22, n (%)	39 (43.8)
≥25, n (%)	50 (56.2)
Chemotherapy	
Yes, n (%)	24 (27.0)
No, n (%)	65 (73.0)

SD, standard deviation

Table 2. Outcomes after attempted stent placement for symptomatic malignant colorectal obstruction in 89 patients

Outcomes	
Technical success, n/total (%)	84/89 (95.5)
Immediate clinical success, n/total (%)	81/89 (91.0)
Long-term sustained relief of obstruction without intervention, n/total (%)	68/89 (76.4)
Long-term sustained relief of obstruction after subsequent stent placement because of stent dysfunction, n/total (%)	76/89 (85.4)
Patients needing a colostomy for long-term relief of the obstructive symptoms, n/total (%)	12/89 (13.5)
Complications, n/total (%)	20/89 (22.5)
Mortality procedure related, n/total (%)	1/89 (1.1)

Table 3. Univariate analysis of prognostic factors associated with long-term clinical efficacy.

	Clinical Success, n (%)		
	Yes	No	*P*
Sex			0.71
Male	42 (77.8)	12 (22.2)	
Female	26 (74.3)	9 (25.7)	
Age (Mean±SD)	73.8±10.90	74.9±9.8	0.67
Stricture location			0.25
Right colon	14 (87.5)	2 (12.5)	
Left colon	54 (74.0)	19 (26.0)	
Stent diameter			0.16
22 mm	27 (69.2)	12 (30.8)	
25 mm	41 (82.0)	9 (17.0)	
Etiology			0.20
Colorectal	66 (77.6)	19 (22.4)	
Extrinsic	2 (50.0)	2 (50.0)	
Chemotherapy			0.45
Yes	17 (70.8)	7 (29.2)	
No	51 (78.5)	14 (21.5)	

SD, standard deviation

Table 4. Complications and management.

Complications	N (%)	Management (n)
Perforation	4 (4.5)	Surgery (4)
Stent dysfunction	13 (14.6)	
Obstruction	8 (9.0)	Surgery (1), subsequent stent insertion (7)
Migration	5 (5.6)	Surgery (4), subsequent stent insertion (1)
Haemorrhage	3 (3.4)	Argon plasma coagulation (3)
Total	20 (22.5)	-

Table 5. Results of a multivariate logistic model to evaluate risk factors for complications.

	Migration			Obstruction			Perforation		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age	1.05	0.92-1.19	0.47	1.12	0.99-1.26	0.08	0.97	0.87-1.08	0.55
Sex-female	3.14	0.30-32.54	0.34	3.02	0.51-17.91	0.22	0.43	0.04-4.56	0.48
Stent diameter									
(22mm)	1.19	0.14-10.45	0.89	2.06	0.35-12.11	0.42	0.49	0.05-5.13	0.55
Location									
Right colon	0.00	NC	0.99	0.41	0.04-4.56	0.47	0.00	NC	0.99
Etiology									
Colorectal	0.25	0.01-4.53	0.35	0.35	0.02-5.13	0.45	0.00	NC	0.99
CT	11.89	0.90-156.47	0.06	2.48	0.50-13.08	0.35	0.00	NC	0.99

CT, Chemotherapy; NC, not computed

Figures

Fig. 1 Long-term sustained relief of obstruction without reintervention throughout the patients' lives after palliative stent placement (solid line) and 95% CI (dashed line).

Fig. 2 Kaplan-Meier estimated time until the onset of complications.

Fig. 3 Kaplan-Meier curves of estimated survival.

Fig. 4 Estimated stent patency based on Kaplan-Meier analysis.

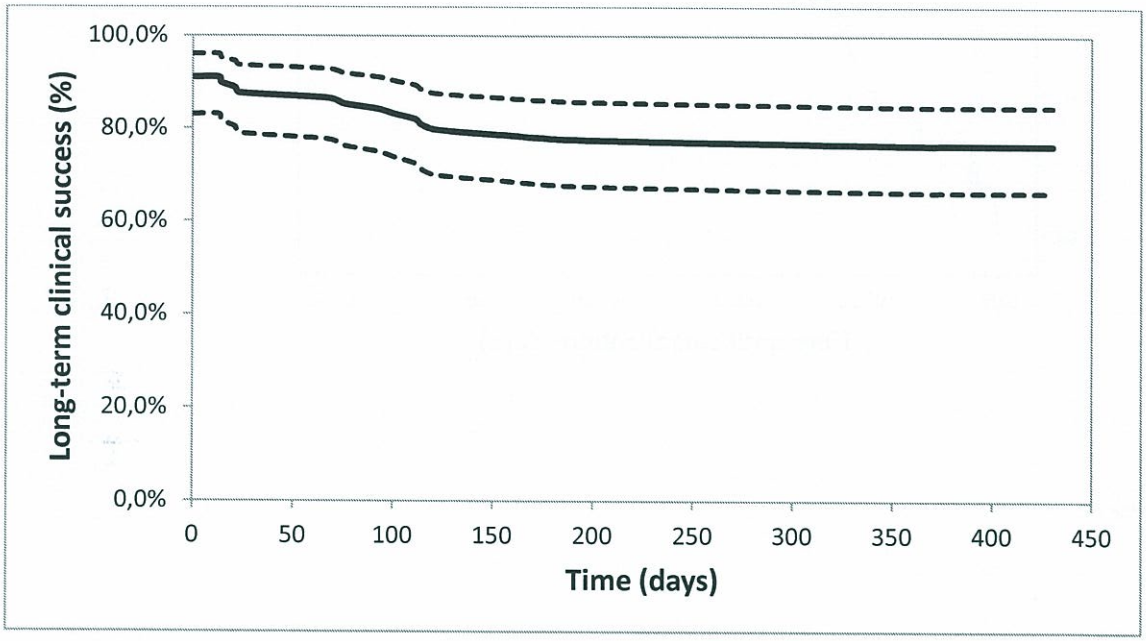

Fig. 1

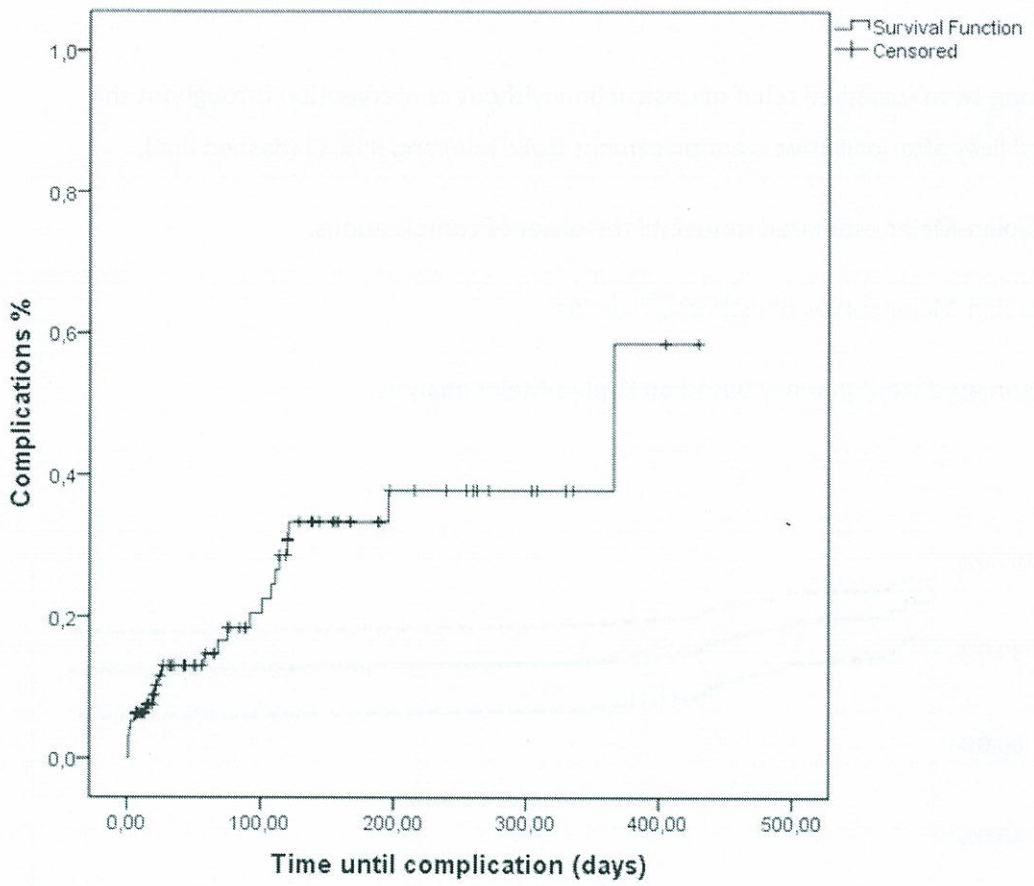
Survival Function
Censored
1,0
0,8
0,6
0,4
0,2
0,0
Complications %
0,00
100,00
200,00
300,00
400,00
500,00
Time until complication (days)

Fig. 2

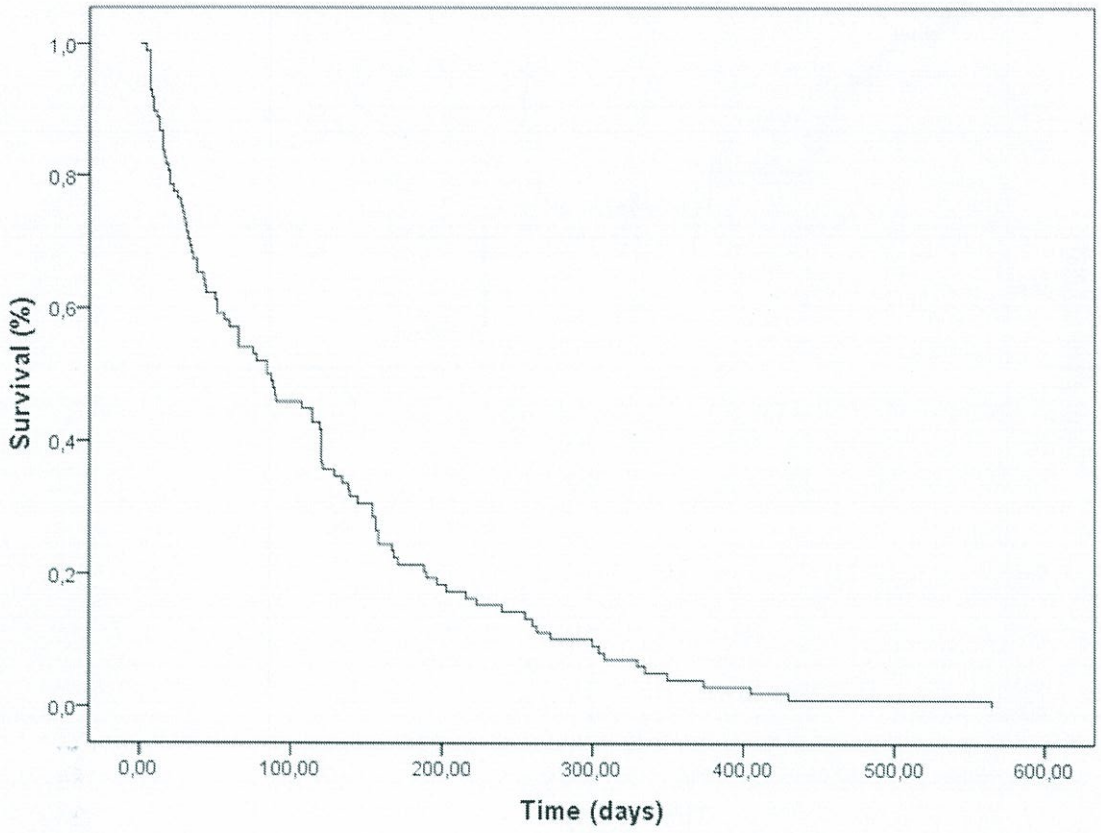
1,0
0,8
0,6
0,4
0,2
0,0
Survival (%)
0,00
100,00
200,00
300,00
400,00
500,00
600,00
Time (days)

Fig. 3

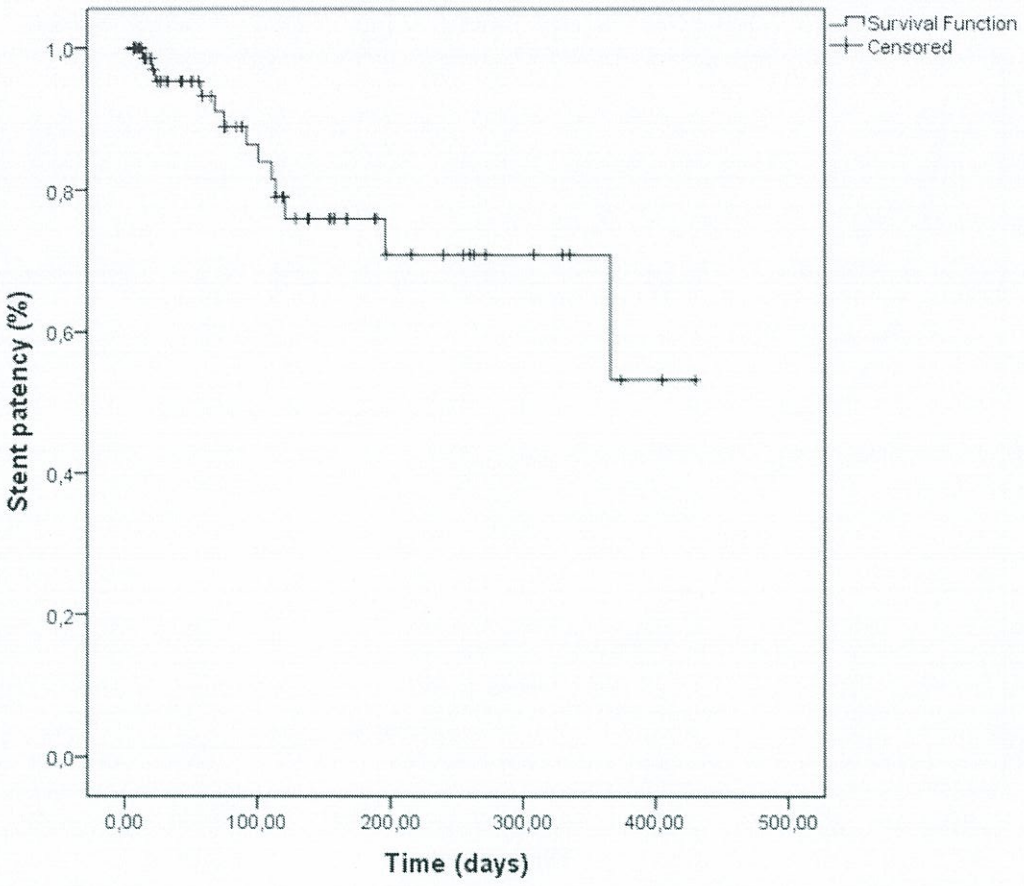
Survival Function
Censored
Stent patency (%)
1,0
0,8
0,6
0,4
0,2
0,0
0,00
100,00
200,00
300,00
400,00
500,00
Time (days)

Fig. 4

ARTIGO 5

Canena J, Liberato M, Rio-Tinto R, Pinto-Marques P, Romão C, Coutinho A, Neves B, Silva MF.

A comparison of the temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures: A prospective multicentre study

[enviado para publicação]

Title:

A comparison of the temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures: A prospective multicentre study

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Abstract

Background

Refractory benign esophageal strictures (RBESs) have been treated with the temporary placement of different self-expanding stents with conflicting results. We compared the clinical effectiveness of 3 types of stents: self-expanding plastic stents (SEPSs), biodegradable stents, and fully covered self-expanding metal stents (FCSEMSs), for the treatment of RBES.

Methods

This study prospectively evaluated 3 groups of 30 consecutive patients with RBESs who underwent temporary placement of either SEPSs (12 weeks, n=10), biodegradable stents (n=10) or FCSEMSs (12 weeks, n=10). Data were collected to analyze the technical success and clinical outcome of the stents as evaluated by recurrent dysphagia, complications and reinterventions.

Results

Stent implantation was technically successful in all patients. Migration occurred in 11 patients: 6 (60%) in the SEPS group, 2 (20%) in the biodegradable group and 3 (30%) in the FCSEMS group (*P*=0.16). A total of 8/30 patients (26.6%) were dysphagia-free after the end of follow-up: 1 (10%) in the SEPS group, 3 (30%) in the biodegradable group and 4 (40%) in the FCSEMS group (*P*=0.27). More reinterventions were required in the SEPS group (n=24) than in the biodegradable group (n=13) or the FCSEMS group (n=13) (*P*=0.24). Multivariate analysis showed that stricture length was significantly associated with higher recurrence rates after temporary stent placement (HR=1.37; 95% CI=1.08-1.75; *P*=0.011).

Conclusions

Temporary placement of a biodegradable stent or of a FCSEMS in patients with RBES may lead to long-term relief of dysphagia in 30 and 40% of patients, respectively. The use of SEPSs seems least preferable, as they are associated with frequent stent migration, more reinterventions and few cases of long-term improvement. Additionally, longer strictures were associated with a higher risk of recurrence.

Introduction

Benign esophageal strictures are often caused by esophageal reflux, the ingestion of caustic substances, esophageal surgery, and radiation therapy [1, 2, 3, 4, 5, 6, 7]. These patients most commonly present with dysphagia [3, 5]. Treatment of benign esophageal strictures with serial endoscopic dilatation using bougies or balloons has been established as a standard therapy [2, 3, 6], and it is associated with an immediate 80-90% success rate of relieving dysphagia [3, 6]. However, 30-60% of benign strictures will recur during long-term follow-up. Furthermore, in complex strictures that are usually longer (>2 cm), tortuous, angulated or have a severely narrowed diameter, the recurrence rate is considerably higher [3, 5, 7]. In these patients, repeated sessions of dilatation without long-term clinical success are associated with increased the risk of developing complications, patient discomfort and recurrent dysphagia; thus, an alternative treatment strategy should be considered [2, 3, 7]. Surgical procedures, including gastric pull-up and enteral replacement, are potentially curative, but they are associated with high rates of morbidity and mortality, and many patients are not be good surgical candidates or willing to undergo surgery [1, 3, 6]. Theoretically, temporary placement of expandable esophageal stents permits a longer-lasting dilatation effect, maintains luminal patency and simultaneously stretches the stricture [3-6]. Previous studies have proposed the use of temporary self-expandable metal stents (SEMS) with discouraging results due to the high rate of complications, including embedding of the uncovered metal portion of the stent in the esophageal wall, new stricture formation, necrosis and ulcerations from the stents themselves [2-9]. To avoid complications of partially covered/uncovered stents, temporary placement of 3 different types of expandable stents have been used for the treatment of refractory benign esophageal strictures (RBES): self-expanding plastic stents (SEPSs), biodegradable stents and fully covered SEMSs. Several studies have evaluated the clinical effectiveness of SEPSs [2, 4, 6, 10-17]. Although initial studies with SEPSs showed promising results pertaining to dysphagia relief in the great majority of patients [10, 11], recent studies have shown less favorable outcomes, with a clinical success rate well below 50% [2, 4, 6, 12, 13, 14]. Furthermore, SEPS are also associated with various complications, especially high stent migration rates [2, 11, 13, 14]. Biodegradable stents have recently been developed and can serve as an alternative for SEPS. Saito et al. reported results from 2 series of patients who received poly-l-lactic esophageal stents [18, 19]. Recent studies have used a novel stent composed of the biodegradable polymer polydiaxone [4, 20, 21]. Taken together, these preliminary case series using biodegradable stents have shown encouraging results. Finally, an alternative to SEPSs and biodegradable stents in the treatment of RBES is offered by fully covered SEMSs [1, 3, 22,

23]. However, a recent meta-analysis [24] did not include studies with biodegradable stents, and only one study compared SEPSs and biodegradable stents [4]. Thus, no study has included or compared the 3 types of stents available for the treatment of RBES, and no case series have addressed the outcomes of patients treated with a fully covered Wallflex stent.

This study compared 3 groups of consecutive patients with RBES who underwent temporary placement of SEPSs, biodegradable stents and fully covered SEMSs. Data were collected to analyze the technical success and clinical outcomes of the stents as evaluated by recurrent dysphagia, complications and reinterventions.

Materials and Methods

Patients and setting

Between July 2005 and March 2011, 3 consecutive cohorts of patients with RBES were enrolled in the study and followed prospectively. One of 3 different types of stents were placed, at different times, in 30 consecutive patients: a SEPS, a biodegradable stent or a fully covered SEMS. The stent used was chosen accordingly with the practice at that time in the participating centre. Patients with esophageal fistulas or leaks, suspicion of malignancy or an upper esophageal sphincter within 3 cm of the stricture were excluded from the study. This study was conducted at a total of 4 referral academic centres (Pulido Valente Hospital, Faculty of Medical Sciences, Lisbon, Portugal; Cuf Infanto Santo Hospital, Lisbon, Portugal; Santo António dos Capuchos Hospital, Lisbon, Portugal; and Garcia de Orta Hospital, Almada, Portugal). All patients provided informed written consent prior to undergoing stent placement. Each institutional review board involved approved this study.

End points and definitions

The primary end point was clinical success defined as the resolution of dysphagia symptoms after the end of long-term follow-up (grade 0-1). Secondary end points included technical success, safe removal of the stents, complications and the need for reinterventions. Dysphagia was graded using a previously described scale as follows: grade 0=able to eat normal diet/no dysphagia; grade 1=able to swallow some solid foods; grade 2=able to swallow only semi solid foods; grade 3=able to swallow liquids only; grade 4=total dysphagia [25]. RBES were defined, using a previously defined definition, as the inability to achieve a lumen diameter of 14 mm over five sessions at 2-week intervals or as a result of an inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter of 14 mm had been achieved [26]. This definition applies only when there is no inflammation at the stricture site. Technical success or

successful stent placement was defined as deployment of the stent across the lesion with patency visualized both fluoroscopically and endoscopically. Complications were defined as any adverse event related to stent placement. Complications were also categorized as major (severe events such as perforations, hemorrhage necessitating transfusion, severe pain, or aspiration) and minor (non-life-threatening, such as mild chest pain, globus, reflux symptoms, stent migration, or tissue hyperplasia). Stent migration was defined as either radiographic evidence of the stent within the stomach or endoscopic visualization of the stent having moved from the initial placement location. Reintervention was defined as any procedure performed after initial stent placement, which included stent removal or stent repositioning due to migration, dilatation, additional stent placement and surgery, but did not include scheduled stent removal.

Technique and stents

Before stent placement, all patients underwent an esophagogram. All procedures were performed with patients in the left lateral position under sedation with propofol administered by an anesthesiologist. A guidewire was passed through the stricture, and dilatation was performed as needed using either a balloon dilator or a Savary-Guilliard dilator at the discretion of the operator. After dilatation, if needed, internal radiopaque markers were placed at the distal and proximal edges of the stricture. Stents were deployed under fluoroscopic guidance. Endoscopy was repeated immediately after stent placement for the purpose of visualizing the proximal part of the stent to assess adequate placement and deployment of the stent. Resumption of oral intake was permitted on the same day, and patients were cautioned about aspiration risk when necessary. All patients were placed on proton pump inhibitors after stent placement.

The SEPS used in this study was the Polyflex stent (Boston Scientific, Natick, Massachusetts). This stent is made of polyester netting and is completely covered with a silicone membrane. The proximal end of the stent is flared (4 and 5 mm larger than the body diameter) to prevent stent migration. The stent is manually mounted on a delivery system ranging from 12-14 mm (36-42 French) depending on the stent diameter. The Polyflex stent is available in 3 lengths (10, 12 and 15 cm) and 3 body diameters (16, 18 and 21 mm). Radiopaque markers are placed at both ends and in the middle to aid fluoroscopic visualization. The biodegradable stent used was the Ella stent (Ella-CS, Hradec Kralove, Czech Republic), which is manufactured from commercially available polydioxanone absorbable surgical suture. The stent is not removable, is radiolucent and has radiopaque markers at both ends and in the middle to aid fluoroscopic

visualization. The stent must be manually loaded onto a 9.4 mm (28 French) delivery system immediately before implantation. The Ella stent is available in 4 body diameters (18, 20, 23 and 25 mm) with lengths ranging from 60 to 135 mm. The stent has flared ends (5 and 6 mm larger than the body diameter) to reduce migration rates. The stent begins to degrade after 4 to 5 weeks, and the degradation process is completed within 2 to 3 months after placement (Fig. 1). The fully covered SEMS used was the Wallflex stent (Boston Scientific, Natick, Massachusetts), which is composed of platinol and is entirely covered with a silicone covering. The stent has flared ends (the flare is 5 mm larger than the body diameter) to better assist in anchoring the stent, and the proximal end has a blue removal suture to facilitate stent removal (Fig. 2). The stent has a 6.17 mm (18.5 French) delivery system and is available in 3 lengths (10, 12 and 15 cm) and 2 body diameters (18 and 23 mm). We used the largest body diameter available in all cases: 21 mm for SEPS, 25 mm for biodegradable stents and 23 mm for fully covered SEMS. The removal of plastic and metal stents was planned at 3 months after placement in all patients. All stents were removed with rat-tooth forceps.

Follow-up

The follow-up continued from stent insertion until at least 8 months after stent removal/degradation/migration in all patients. Endoscopies (to detect asymptomatic migration and/or hyperplastic tissue overgrowth), assessments of dysphagia and investigations of any potentially stent-related symptoms were conducted at 1, 2 and 3 months. After stent removal/stent degradation, patients were contacted on a monthly basis and asked to grade their dysphagia using the scale previously described in this manuscript. After 6 months, patients were submitted to endoscopy and then followed on a 2-month basis. In the case of recurrent dysphagia during follow-up, patients contacted their medical assistant in the institution for analysis and reintervention when needed.

Statistical analysis

The intention-to-treat method was used in all analyses. The $\chi 2$ test, Kruskal-Wallis test and the Mann-Whitney *U* test were used to calculate the statistical significance of different demographic and clinical variables when appropriate. Dysphagia scores, taken at baseline, at 4 weeks and after stent removal/dysphagia recurrence, were compared using the Wilcoxon signed-rank test. The dysphagia-free period (esophageal patency) during follow-up after stent removal/degradation/migration was evaluated by the Kaplan-Meier method, and groups were compared using the log-rank test. Multivariate Cox proportional hazard models with forward selection were used to evaluate the multivariate factors potentially affecting the dysphagia-

free period after temporary stenting. Age, sex, type of stent, length and location (upper+lower esophagus, middle esophagus or anastomotic) of stricture were the variables included in the analysis. A Poisson regression was conducted to determine possible factors affecting the number of reinterventions. All reported P-values were for two-sided test, and a *P*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences) 18 (IBM Corporation, New York, USA).

Results

Patients

Between July 2005 and March 2011, 37 patients with RBES underwent endoscopic insertion of 3 different types of self-expanding stents. Seven of these patients were excluded from the analysis for the following reasons: incomplete data concerning clinical effectiveness and follow-up (3 patients) or loss to follow-up (4 patients) with data only available in a retrospective fashion.

In total, 30 patients (16 males and 14 females) with a mean age of 53.5 years (range: 27-79 years) were enrolled in the study. Ten patients were included in each group. Patient demographics, stricture characteristics, indications for stent placement and baseline dysphagia scores are summarized in Table 1. There were no significant differences in the demographics and baseline characteristics among the 3 groups defined earlier in the Methods section.

Stent placement, removal and degradation

Stent implantation was technically successful (Table 2) in all patients without procedure-related complications. Migration occurred, as discussed later, in 11 patients: 6 in the SEPS group, 2 in the biodegradable stent group and 3 in the fully covered SEMS group. At the 3-month scheduled endoscopy, biodegradable stents that were still in place appeared to be almost dissolved. At the 6-month endoscopy, there were no traces of the previously placed biodegradable stents. All SEPSs and fully covered SEMSs that had migrated into the stomach were subsequently removed or repositioned. Migrated biodegradable stents were left to fragment in the stomach and were not associated with any symptoms or complications. SEPS and fully covered SEMS that remained in position for the intended 3-month temporary placement were retrieved successfully with no procedural complications.

Clinical effectiveness and evaluation of dysphagia

Stent placement outcomes are shown in Table 2. Overall, regarding clinical success, a total of 8/30 patients (26.6%) who received temporary self-expandable stents were dysphagia-free after a median follow-up time of 23.4 months (range: 8-66 months). In the SEPS group, 1 patient (10%) was dysphagia-free after a median group follow-up time of 42.7 months (range: 16-66 months). Following temporary placement of a biodegradable stent, 3 patients (30%) were dysphagia-free after a median follow-up time of 18.5 months (range: 11-21 months). Of the 10 patients treated with fully covered SEMS, 4 (40%) were dysphagia-free after a median follow-up time of 10 months (range: 8-12 months). There were no significant differences in the clinical successes of the 3 types of stents (P=0.27) [SEPS vs. biodegradable stent (*P*=0.58); SEPS vs. fully covered SEMS (*P*=0.30); biodegradable stent vs. fully covered SEMS (*P*=0.64)]. Kaplan-Meier analysis (Fig. 3) showed that the cumulative period of dysphagia-free (esophageal patency) during follow-up was not significantly longer in patients treated with SEPS (mean 11.1 months, 95% CI 0.0-23.75), biodegradable stents (mean 19.5 months, 95% CI 4.64-34.36) or fully covered SEMS (mean 23.1 months, 95% CI 8.44-37.76) (*P*=0.67). The estimated relative risk of dysphagia recurrence [hazard ratio (HR)] was 1.34-fold higher in the SEPS group than in the biodegradable stent group (95% CI 0.50-3.58). Temporary placement of SEPSs resulted in a HR in these patients that was 1.6-fold higher than in patients who submitted to temporary fully covered SEMS placement (95% CI 0.58-4.41). The HR was 1.15-fold higher in the biodegradable group than in the fully covered SEMS group (95% CI 0.39-3.41). Multivariate Cox hazard analysis showed that the length of stricture (HR=1.37; 95% CI 1.08-1.75; *P*=0.011) was the only factor associated with the period of dysphagia-free after temporary stent placement. Longer strictures had at higher risk of recurrence. Dysphagia score evolution for the 3 groups is shown in Fig. 4. Dysphagia scores improved significantly from the pre-treatment scores to the scores at 4 weeks after stent placement (*P*<0.001) in the 3 groups. However, when comparing the dysphagia scores at baseline and after stent removal/dysphagia recurrence differences were significant in the biodegradable stent group (2.8±0.42 vs. 2.0±0.82; *P*=0.02) and fully covered stent group (2.7±0.48 vs. 1.6±1.26; *P*=0.008), but these differences were not observed in the SEPS group (2.8±0.42 vs. 2.4±1.26; *P*=0.10).

Complications

Complications (Table 3) occurred in 7 patients (9 complications) who received a Polyflex stent, in 5 patients (7 complications) who received an Ella stent and in 6 patients (6 complications) who received a Wallflex stent (P=0.38). In the SEMS group, 1 patient experienced both

moderate chest pain and reflux symptoms, and another patient had moderate chest pain before stent migration. In the biodegradable stent group, 1 patient experienced severe chest pain before stent migration, and 1 patient with tissue ingrowth experienced major bleeding. Minor complications (n=9) occurred more frequently after SEPS placement than after biodegradable stent placement (n=5) or fully covered SEMS placement (n=6), although this difference was not statistically significant (*P*=0.21). Globus sensation occurred in 1 patient after treatment with a Wallflex stent. Although the proximal flare of the stent was positioned 4 cm below the upper esophageal sphincter, the patient experienced an increasing globus sensation leading to early removal of the stent (3 weeks). Importantly, tissue hyperplasia (ingrowth) was observed in 3 patients submitted to temporary biodegradable stent placement (*P*=0.086). Hyperplasia was associated with major bleeding in 1 patient and with recurrent dysphagia in 2 patients. Migration occurred more frequently after SEPS placement than after biodegradable stent placement or fully covered SEMS placement, although this difference was not statistically significant (*P*=0.16); [SEPS vs. biodegradable stent (*P*=0.06); SEPS vs. fully covered SEMS (*P*=0.17); biodegradable stent vs. fully covered SEMS (P=0.61)]. Stent migration was observed in 6 patients at 2, 3, 4, 5, 6 and 6 weeks after SEPS placement. Migration occurred in 2 patients at 3 and 4 weeks after biodegradable stent placement and in 3 patients at 2, 3 and 4 weeks after temporary placement of a fully covered SEMS. Major complications occurred in 2 patients after biodegradable stent placement. One patient developed severe thoracic pain requiring treatment with morphine, and the other patient developed heavy bleeding with a significant drop in hemoglobin level. The latter patient was admitted to receive a blood transfusion, and the hemorrhage stopped without further intervention.

Follow-up and reinterventions

Overall, 22 patients (73.3%) were submitted to reinterventions (Table 2), which included dilatation, repeat stenting and surgery. More reinterventions were required in the SEPS group (n=24) than in the biodegradable stent group (n=13) or the group with temporary placement of a fully covered SEMS (n=13). These differences were not significant based on the Kruskal-Wallis test (*P*=0.24). However, Poisson regression showed that fully covered SEMSs and biodegradable stents resulted in a significantly lower number of reinterventions (B =-0.87; *P*<0.05). Migration was observed in 6 patients after SEPS placement. One patient underwent surgery, and the other 5 patients underwent further stenting with either SEPSs (3 patients, 7 stents) or fully covered SEMSs (2 patient, 2 stents). Two patients are still being treated with temporary stent placement (fully covered SEMSs, which migrated again and were repositioned), and 3 patients underwent surgery. Three patients had their SEPSs removed after

3 months and developed recurrent dysphagia. One is still being treated with repeat dilatations, and 2 required surgery. After surgery, one patient had a post-surgical stricture successfully managed by repeated dilatations. In the biodegradable group, stent migration was observed in 2 patients. One patient required surgery, and a post-surgical stricture developed after 3 months. The patient was unsuccessfully managed with a biodegradable stent and is currently under monthly dilatation therapy. The other patient was submitted to repeat dilatations and finally to further stenting with a fully covered SEMS, which migrated into the stomach and was repositioned twice. There were five patients in whom a biodegradable stent completely dissolved in place; they each presented with recurrent dysphagia. Two required surgery and were dysphagia-free (score 0-1), and the remaining 3 are still being treated with repeat dilatations. Stent migration occurred in 3 patients after temporary placement of a fully covered SEMS. Two patients were submitted to further stenting with a fully covered SEMSs (2 stents per patient with new migrations and repositioning of the stent), and the third patient is being treated with repeat dilatations. Of the 3 patients with successful fully covered SEMS removal (one patient had his stent removed at 3 weeks due to globus) and dysphagia recurrence, one patient was further treated with another fully covered stent for 6 months and was dysphagia-free (score 0-1) at 12 weeks after removal of the second stent. One patient was treated with repeat dilatations, and the remaining patient required surgery and is dysphagia-free (score 0-1). For the 22 patients in whom clinical success was not achieved, the mean time to dysphagia recurrence after stent removal/migration/degradation was 4 weeks (range: 2-9 weeks), and there were no significant differences in the time to recurrence in patients treated with SEPSs (mean: 4.3 weeks, range: 2-9 weeks), biodegradable stents (mean: 3.8 weeks, range: 2-9 weeks) or fully covered SEMSs (mean: 3.8 weeks, range: 2-8 weeks) (P=0.75) [SEMS vs. biodegradable stent (P=0.95); SEPS vs. fully covered SEMS (P=0.61); biodegradable stent vs. fully covered SEMS (P=0.54)].

Discussion

According to our findings in a prospective, nonrandomized study of 3 consecutive cohorts of patients with RBES, temporary placement of a biodegradable stent or a fully covered SEMS may lead to a long-term dysphagia-free period in 30 and 40% of patients, respectively. The use of SEPS seems to be least preferable, as it is associated with frequent stent migration, more reinterventions and few cases (10%) of long-term improvement. A long stricture was the only significant factor associated with a higher recurrence rate after temporary stent placement.

Unfortunately, unsuccessful management of benign esophageal strictures by serial endoscopic dilatation using bougies or balloons occurs, and the management of these refractory strictures has been considered challenging [4, 5, 7, 27]. Surgery can provide definitive treatment but has been associated with considerable mortality and morbidity, including the development of new anastomotic strictures [2-9]. Partially covered metal stents, which are highly effective in the palliation of malignant esophageal strictures, are associated with high complication rates and are not recommended for RBES [28]. Thus, in a group of patients who have few treatment options available, temporary stent placement can be considered, especially if the procedure is associated with a low complication rate. However, stent placement should be reserved for true refractory strictures, as defined earlier in the Methods section [26]. In our study, all patients were first submitted to serial dilatations during a number of sessions ranging from at least 5 to 10 attempts (some patients were referred from community hospitals where the number of dilatations was greater than 20). Furthermore, all patients were further submitted to several sessions (3 to 6) of intralesional 4-quadrant steroid injections. As proposed by Siersema et al. [4, 5, 7, 27], temporary stent placement was a late step in the treatment strategy of benign esophageal strictures.

There are several case series that have evaluated the outcomes of SEPS with conflicting results (Table 4). Some initial studies have shown good results with large numbers of patients (76.5-94%) being dysphagia-free at the end of follow-up and few complications [10, 11, 15]. However, more recent studies have shown less favorable outcomes, tempering the initial enthusiasm, with success rates between 0 and 30% [2, 6, 12, 13, 14].

Regarding clinical success, the results of our study are clearly in line with those of recent studies [2, 6, 12, 13, 14]. At the end of the follow-up period, only 1 patient was dysphagia free. Migration was observed in 60% of our patients. Again, this is in accordance with some studies that have reported migration rates between 52.9 and 85% [2, 11, 13, 14]. One explanation for our high migration rate could be the duration of the study (3 months); longer stenting times are associated with higher risks of migration [2, 11]. In our study, half (n=3) of the patients had a stent migration after 4 weeks. Alternatively, another explanation could be associated with the result that 8 patients had strictures located in the distal esophagus or in anastomotic areas, as these locations have been associated with higher migration rates for SEPS [2]. Clinically significant tissue hyperplasia was not observed in our study as one might expect from a fully covered device, and this result is in line with the literature [2, 4, 6, 10-16] and also with a recent pooled analysis where tissue in- and overgrowth was uncommon [17].

Theoretically, a biodegradable stent is ideal for the treatment of RBES as it becomes embedded in the esophageal wall, reducing migration rates, dissolving spontaneously after placement and decreasing the need for reinterventions to remove the stent. Furthermore, a stent made from a material with good tissue compatibility should overcome/reduce the in- and overgrowth of reactive tissue. Three recent studies have reported preliminary results with the new Ella stent [4, 20, 21]. An initial prospective study with 21 patients demonstrated a long-term improvement in 9/21 of the patients (42.9%) [20]. Migration occurred in 2 patients (9.5%), and clinically significant tissue hyperplasia was observed in 1 patient (4.75%). Severe post-stenting pain developed in 3 patients, and minor bleeding was observed in 1 patient. In a prospective study comparing Polyflex stents with ELLA stents, the temporary placement of a biodegradable stent was curative in 6/18 patients (33%) [4]. Major complications occurred in 4 patients (2 had severe retrosternal pain and 2 had hemorrhaging). Clinically significant tissue in- and overgrowth was observed in 2/18 patients (11%). A recent prospective case series of 10 patients who underwent Ella stent placement for benign esophagogastric anastomotic strictures showed a clinical success rate of 70% [21]. No migration was observed, and no complications were observed. Signs of tissue hyperplasia were noticed in 4 patients; however, this was associated with reobstruction and symptoms of dysphagia in only 2 patients.

In our study, 30% of patients were dysphagia-free at the end of the follow-up period, which is in accordance with 2 previously described studies that have reported a clinical success between 33 and 42.9% [4, 20]. Our migration rate was 20%; however, although this was similar to the rate reported by van Boeckel et al. [4], this result was unexpected. We anticipated that the embedding of the uncovered stent into the esophagus would prevent migration. In our study, migration occurred in 2 initial patients, and both had long strictures. Eventually, it was found that length selection of the stent was not the best preventative measure of early migration. After the 2 episodes of migration, we began to perform larger balloon dilatation of the stent immediately after deployment to further embed the stent into the esophageal mucosa and reduce the risk of migration. Clinically significant hyperplasia (ingrowth) was observed in 3/10 patients (1 bleeding, 2 reobstructions); this rate was slightly higher than the rates from the 3 studies previously described [4, 20, 21]. The uncovering of the stent may facilitate hyperplasia along with the eventual chemical reaction of the esophageal mucosa with the polydioxanone. However, the low rate of in- and overgrowth found in the literature and in this study suggests that the biodegradable stent has good tissue compatibility.

Removable, fully covered SEMS are an alternative to SEPS and biodegradable stents. Their fully covered design is thought to induce less reactive hyperplasia, making these stents easier to

remove and facilitating stenting over longer periods [3, 23, 28]. Few published studies, mostly retrospective, have looked at the outcomes of the use of fully covered SEMSs, and they have reported variable data. One interventional radiology study evaluated the effectiveness of temporary stenting in 55 patients [1]. Three different types of stents were left in place from 1 week to 6 months, and long-term symptom relief was reported in 31% (17/55) of patients. Migration and tissue hyperproliferation were observed in 25 and 31% of patients, respectively. Using the Alimaxx stent, Eloubeidi et al. reported their results from a study of 19 patients [3]. Clinical success was achieved in 21% of patients, no tissue hyperplasia was reported and migration rates were 37%. A recent study retrospectively reviewed 24 patients with refractory post-esophagogastric anastomosis strictures [23]. The stents were removed within 4-8 weeks after placement, and 17/24 patients (70.8%) were free from dysphagia at the end of the follow-up period (12 months) as evaluated by intention-to-treat analysis. Tissue hyperplasia was not observed, and migration was observed in only 1 patient (4.2%). Well-tolerated chest pain and reflux symptoms were the most frequent complications reported.

Our study is the first prospective case series to report the outcomes of treatment with a fully covered Wallflex stent. This stent is easy to implant and can be safely removed. However, complications do occur, and migration was the most common complication observed. Migration is frequent for fully covered stents because of the reduced anchoring capacity of these devices [1, 3, 4, 28]. Migration occurred in 3 patients (30%), which is in accordance with the results of 2 previously cited reports (25 and 37%) [1, 3]. Compared with the SEPS used in our study, which are also fully covered stents, the migration rate of the Wallflex stent was reduced by a factor of 2 (30% vs. 60%). We believe that this result was related to the larger diameters, stronger radial force and the design of the Wallflex stent, which has 2 flared ends. Alternatively, the Polyflex stent has only 1 flared end. Another concern with temporary stent placement is tissue hyperplasia. The fact that these stents do not become embedded in the esophageal wall makes clinically significant tissue in- and overgrowth less likely to occur. In our study of 10 patients, no clinically significant tissue hyperplasia was observed, which is in accordance with other reports [3, 23]. Only interventional radiology studies have reported significant tissue hyperplasia [1, 22], which should be interpreted with caution because there was no endoscopic visualization of such tissue hyperproliferation. Furthermore, in our study, one patient was submitted to further stenting over 6 months, and, after that period, the stent was safely removed without signs of hyperplasia. Overall, 4 patients (40%) had long-term resolution of their symptoms after stent removal, which is comparable to the results of 4

earlier studies reporting different clinical successes: 31% [1], 21% [3], 48% [22] and 70.8% [23] (average: 42.5%).

Although not statistically significant, the results of biodegradable stents or fully covered SEMSs were superior to those of SEPSs in terms of several variables. For example, the estimated time of dysphagia-free after temporary stenting with a biodegradable stent or a fully covered SEMS was almost 2-fold higher than after placement of a SEPS. While stents were in place, there was a significant difference in the dysphagia scores compared to baseline scores for all stents; all stents were equally effective. However, when comparing baseline dysphagia to post-treatment scores, a significant difference was found in the fully covered group and the biodegradable group but not in the SEPS group; this is a consequence of the differing clinical success rates of the 3 stents. Overall, in the SEPS group, only 1 patient experienced long-term improvement. An explanation for this could be the high rate of SEPS migration when compared with the other 2 stents used. Patients with fully covered or biodegradable stents had their stents in place for longer periods, which may indicate that longer stenting times correlate with higher success rates [4, 10, 11]. The optimal time of stenting is unknown and has been a subject of debate as clear guidelines have yet to emerge. In our multivariate analysis, the length of the stricture was the only factor associated with higher recurrence rates after temporary stent placement. Thus, it is possible that longer strictures would require longer treatment as suggested elsewhere [1, 7, 22, 29]. The optimal duration of temporary stenting can also be influenced by the underlying cause of injury or by the time since the injury to the esophagus occurred [22, 29].

Stenting is safe. In our study, with the exception of migrations, the number of complications was low and, and the complications that occurred were well tolerated. Only 2/30 patients (6%) had significant complications (1 case of bleeding and 1 case of severe pain), which is consistent with most published studies using different expandable stents [2, 3, 4, 10, 11, 12, 14, 15, 17, 20, 21, 24, 23, 30]. The safety of the procedure in association with reasonable clinical success in a group of patients that is very difficult to manage makes temporary stent placement an appealing option.

Poisson regression showed that fully covered SEMSs and biodegradable stents resulted in a significantly lower number of reinterventions. More reinterventions were required in the SEPS group, which was due to the higher migration rate along with the lower clinical success rate of SEPSs. One of the reinterventions in all groups was restenting. The clinical effectiveness of restenting is limited. While stents are in place, patients benefit from another dysphagia-free

period, but after stent removal, the number of patients who experience long-term clinical success is low. This result is consistent with several studies [1, 2, 12, 14, 22, 23]. In our study, restenting was performed in 9 patients, and only one was dysphagia-free after the restenting procedure was performed. In those patients whose primary stent migrated, the second stent generally migrated as well, regardless of whether it was the same or a different fully covered stent, which is in line with other studies in the literature [1, 2, 14, 22]. After migration, restenting with fully covered devices is of poor value; therefore, we suggest restenting with a biodegradable stent which seems to be a better option, as it is associated with a lower migration rate due to the potential embedding of the biodegradable stent in the esophagus.

We suggest that further prospective randomized studies are needed to compare biodegradable stents with fully covered SEMS to determine clinical effectiveness, optimal duration of stenting, value of restenting for longer periods, cost and patient satisfaction.

The present study has several limitations. First, our nonrandomized design could have introduced sampling bias. However, there were no major differences in location, etiology or stricture length between the 3 groups studied. Another potential weakness is the different time to follow-up for the 3 groups. The SEPS group had a longer follow-up period, which could have influenced the final outcome because, theoretically, the longer the follow-up period the higher the probability of dysphagia recurrence. However, in our study, all patients had at least 8 months of follow-up after stent removal/degradation/migration, and most other studies showed that the benefits of temporary stenting decreased rapidly with time for non-responders [1, 12, 20, 21, 23]. In our study, no patient had recurrent dysphagia after 9 weeks following stent removal/migration/degradation (Fig. 3). Thus, different follow-up times were not likely to be associated with the poor results found in the SEPS group. Our study had a relatively low number of patients per group, which limited the study's statistical strength. However, most of the studies using self-expanding stents have small population sizes due to the low incidence of RBES, and studies with a patient population large enough to have adequate power to detect minor outcome differences are generally impractical. Finally, this study was performed in tertiary referral centers, and we cannot exclude the possibility of obtaining a poorer outcome in community hospitals.

The strengths of our study are the prospective design with a relatively long-term follow-up. To our knowledge, this is the first study to compare the 3 types of self-expanding stents available for the treatment of RBES and the first case series to report the outcomes of patients treated with a fully covered Wallflex stent.

In conclusion, our data suggest that the temporary placements of biodegradable stents and fully covered SEMSs have similar utility in the treatment of RBES, as they were associated with clinical success in 1/3 of our patients. Of the 3 available stents, SEPSs were associated with the worst clinical success rate as well as with a higher number of migrations and reinterventions. Taken together, temporary stenting for RBES may be useful, especially in those patients in whom other therapeutic options are unavailable. However, better stents and different strategies are needed to overcome the difficulties of managing these patients, particularly when a long stricture is present.

References

1 – Kim JH, Song HY, Choi EK, Kim KR, Shin JH, Lim JO. **Temporary metallic stent placement in the treatment of refractory benign esophageal strictures: results and factors associated with outcome in 55 patients**. *Eur Radiol* 2009; **19**:384-390

2 – Holm AN, Levy JG, Goustout CJ, Topazian MD, Baron TH. **Self-expanding plastic stents in treatment of benign esophageal conditions.** *Gastrointest Endosc* 2008; **67**:20-25

3 – Eloubeidi MA, Talreja JP, Lopes TL, Al-Awabdy BS, Shami VM, Kahaleh M. **Success and complications associated with placement of fully covered removable self-expandable metal stents for benign esophageal diseases (with videos).** *Gastrointest Endosc* 2011; **73**:673-681

4 – van Boeckel PG, Vleggaar FP, Siersema PD. **A comparison of temporary self-expanding plastic and biodegradable stents for refractory benign esophageal strictures.** *Clin Gastroenterol Hepatol* 2011; **9**:653-659

5 – Siersema PD. **Stenting for benign esophageal strictures**. *Endoscopy* 2009; **41**:363-373

6 – Dua KS, Vleggaar FP, Santharam R, Siersema PD. **Removable self-expanding plastic esophageal stent as a continuous, non-permanent dilator in treating refractory benign esophageal strictures: a prospective two-center study.** *Am J Gastroenterol* 2008; **103**:2988-2994.

7 – Siersema PD, Wijkerslooth LR. **Dilatation of refractory benign esophageal strictures**. *Gastrointest Endosc* 2009; **70**:1000-1012

8 – Ackroyd R, Watson DI, Devitt PG, Jamieson GG. **Expandable metallic stents should not be used in the treatment of benign esophageal strictures.** *J Gastroenterol Hepatol* 2001; **16**:484-487

9 - Sanda GS, Marcon NE. **Expandable metal stents for benign esopagheal obstruction.** *Gastrointest Endosc Clin N Am* 1999; **9**:437-446

10 – Repici A, Conio M, De Angelis C, Battaglia E, Musso A, Pellicano R, Goss M, Venezia G, Rizzetto M, Saracco G. **Temporary placement of an expandable polyester silicone-covered stent for treatment of refractory benign esophageal strictures**. *Gastrointest Endosc* 2004; **60**: 513-519

11 – Evrard S, Le Moine O, Lazaraki G, Dormann A, El Nakadi I, Deviere J. **Self-expanding plastic stents for benign esophageal lesions.** *Gastrointest Endosc* 2004; 60:894-900

12- Oh YS, Kochman ML, Ahmad NA, Ginsberg GG. **Clinical outcomes after self-expanding plastic stent placement for benign strictures.** *Dig Dis Sci* 2010; **55**:1344-48

13 – Triester SL, Fleischer DE, Sharma VK. **Failure of self-expanding plastic stents in treatment of refractory benign esophageal strictures.** *Endoscopy* 2006; **38**: 533-537

14 – Barthel JS, Kelley ST, Klapman JB. **Management of persistent gastroesophageal anastomotic strictures with removable self-expandable polyester silicon-covered (Polyflex) stents: an alternative to serial dilatation.** *Gastrointest Endosc* 2008; **67**:546-552

15 – Martin RC, Woodall C, Duvall R, Scoggins CR. **The use of self-expanding silicone stents in esophagectomy strictures: less cost and more efficiency.** *Ann Thorac Surg.* 2008; 86:436-440

16 – Garcia-Cano J. **Dilatation of benign strictures in the esophagus and colon with the polyflex stent: a case series study.** *Dig Dis Sci* 2008; **53**: 341-346

17 – Repici A, Hassan C, Sharma P, Conio M, Siersema P. **Systematic review: the role of self-expanding plastic stents for benign esophageal strictures.** *Alim Pharm Ther* 2010; **31**:1268-1275

18 - Saito Y, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, Nitta N, Murata K, Fujiyama Y. **Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection.** *Dig Dis Sci* 2008; **53**:330-333.

19 - Saito Y, Tanaka T, Andoh A, Minematsu H, Hata K, Tsujikawa T, Nitta N, Murata K, Fujiyama Y. **Usefulness of biodegradable stents constructed of poly-*l*-lactic acid monofilaments in patients with benign esophageal stenosis.** *World J Gastroenterol* 2007; **13**:3977-3980

20 - Repici A, Vleggaar FP, Hassan C, van Boeckel PG, Romeo F, Pagano N, Malesci A, Siersema PD. **Efficacy and safety of biodegradable stents for refractory benign esophageal strictures: the BEST (Biodegradable Esophageal Stent) study.** *Gastrointest Endosc* 2010; **72**:927-934.

21 – van Hooft JE, Henegouwen MI, Rauws EA, Bergman JJ, Busch OR, Fockens P. **Endoscopic treatment of benign anastomotic esophagogastric strictures with a biodegradable stent.** *Gastrointest Endosc* 2011; **73**:1043-1047

22 – Song HY, Jung HY, Park SI, Kim SB, Lee DH, Kang SG, Il Min Y. **Covered retrievable expandable nitinol stents in patients with benign esophageal strictures: Initial experience.** *Radiology* 2000; **217**:551-557

23 – Liu J, Hu Y, Cui C, Li Y, Lin X, Fu J. **Removable, fully covered, self-expandable metal stents for the treatment of refractory benign esophagogastric anastomotic strictures.** *Dysphagia* 2011; DOI: 10.1007/s00455-011-9361-1, August 09

24 – Thomas T, Abrams KR, Subramanian V, Mannath J, Ragunath K. **Esophageal stents for benign refractory strictures: a meta-analysis.** *Endoscopy* 2011: **43**:386-393

25 - Knyrim K, Wagner H, Bethge N, Keymling, Vakil N. **A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer.** *N Engl J Med* 1993; **329**:1302-1307.

26 – Kockman ML, McClave SA, Boyce HW. **The refractory and the recurrent esophageal stricture: a definition [Letter to Editor].** *Gastrointest Endosc* 2005; **62**:474-475

27 – Wijkerslooth LR, Vleggaar FP, Siersema PD. Endoscopic management of difficult or recurrent esophageal strictures. ***Am J Gastroenterol*** 2011; **106**:2080-2091

28 – Sharma P, Kozarek R. **Role of esophageal stents in benign and malignant diseases.** *Am J Gastroenterol* 2010; **105**:258-273

29 – Siersema PD, Hirdes MM. **What is the optimal duration of stent placement for refractory, benign esophageal strictures?** *Nat Clin Pract Gastroenterol Hepatol* 2009; **6**:146-147

30 – Wong RF, Adler DG, Hilden K, Fang JC. **Retrievable esophageal stents for benign indications.** *Dig Dis Sci* 2008; **53**:322-329

Figures

Figure 1

(A) Endoscopic view of a biodegradable stent immediately after placement

(B) Endoscopic appearance of the process of biodegradation at 2 months

(C) Endoscopic appearance of tissue hyperplasia 3 months after stent degradation

Figure 2

(A) Endoscopic view of an anastomotic stricture before stent placement

(B) Endoscopic view of a fully cover SEMS 3 months after stent deployment

(C) Endoscopic appearance of the initial stricture 3 months after stent removal

Figure 3

Cumulative period free of dysphagia (esophageal patency) curves by Kaplan-Meier analysis in patients treated using self-expandable plastic stent (SEPS), biodegradable (BD) stent and fully cover self-expandable metal stent (SEMS). Although not statistically significant there is an advantage using fully cover SEMS and BD stent vs. SEPS. The benefits of stenting decreased rapidly with time and esophageal patency appeared to plateau between 8-9 weeks for all stents.

Figure 4

Clustered multiple variables graph with mean dysphagia scores over time after temporary placement of self-expandable plastic stent (SEPS), biodegradable (BD) stent and fully cover self-expandable metal stent (SEMS). Bars represent 95% CI for mean. Dysphagia score improved significantly from baseline level to 4 weeks after stent placement ($p<0.001$) in the 3 groups. Dysphagia score improved significantly from baseline level to post treatment for BD stent and fully cover SEMS but not for SEPS. (final post-treatment after stent removal and dysphagia recurrence for all patients).

Table 1 Patient demographics, characteristics of strictures, indications for stent placement and baseline dysphagia scores

	SEPS (n=10)	BD Stent (N=10)	FCSEMS (n=10)	*P*
Sex, n (%)				0.53
Male	5 (50%)	4 (40%)	7 (70%)	
Female	5 (50%)	6 (60%)	3 (30%)	
Age (years), mean (range)	52.7 (28-67)	57.2 (42-79)	50.7 (27-78)	0.63
Characteristics of stricture				
Lenght (cm), mean (range)	2.9 (1-5)	2.9 (1-8)	2.8 (1-6)	0,91
Location, n (%)				0.14
Upper Esophagus	-	-	2 (20%)	
Mid esophagus	2 (20%)	-	2 (20%)	
Lower esophagus	4 (40%)	4 (40%)	3 (30%)	
Anastomotic	4 (40%)	6 (40%)	3 (30%)	
Indication for stent placement, n (%)				0.2
Peptic stricture	1 (10%)	3 (30%)	3 (30%)	
Caustic	1 (10%)	1 (10%)	1 (10%)	
Radiation induced	2 (10%)	-	-	
Post-surgical	4 (10%)	6 (10%)	3 (30%)	
Idiophatic	2 (20%)	-	3 (30%)	
Dysphagia score before stent placement, mean (±SD)	2.8 (0.42)	2.8 (0.42)	2.7 (0.48)	0.84

SEPS Self-expandable plastic stent, BD Biodegradable, FCSEMS Fully cover self-expandable metal stent

Table 2 Technical success, clinical outcome, dysphagia evolution and reinterventions after temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures

	SEPS (n=10)	BD Stent (N=10)	FCSEMS (n=10)	*P*
Technical success, n (%)	10 (100%)	10 (100%)	10 (100%)	-
Clinical success	1 (10%)	3 (30%)	4 (40%)	0,27
Dysphagia score, mean (±SD)				
At 4 weeks	0.7 (0.48)	0.4 (0.52)	0.5 (0.53)	0,4
Post-stenting	2.4 (1.26)	2.0 (0.82)	1.6 (1.26)	0.23
Time to dysphagia recurrence (weeks), mean (range)	4.3 (2-9)	3.8 (2-9)	3.8 (2-8)	0.75
Reinterventions, n	24	13	13	0.24
Final outcome, n (%)				-
Successful treatment	1 (10%)	3 (30%)	4 (40%)	
Repeat stenting	2 (20%)	1 (10%)	3 (30%)	
Dilatations	1 (10%)	3 (30%)	2 (20%)	
Surgery	6 (60%)	3 (30%)	1 (10%)	
Follow-up (months), median (range)	43 (16-66)	18.5 (11-21)	10 (8-12)	-

SEPS Self-expandable plastic stent, BD Biodegradable, FCSEMS Fully cover self-expandable metal stent, Time to dysphagia recurrence in patients without clinical success, Post-stenting score in all patients after dysphagia recurrence/long-term free of dysphagia

Table 3 Minor and major complications after temporary placement of 3 different self-expanding stents for the treatment of refractory benign esophageal strictures

Complications	SEPS (n=10)	BD Stent (N=10)	FCSEMS (n=10)	*P*
Total, n in number of patients, n (%)	9 in 7 (70)	7 in 5 (50)	6 in 6 (60)	0.38
Minor, n (%)	9 (90)	5 (50)	6 (60)	0.21
Globus sensation	0	0	1	-
Stent migration	6	2	3	0.16
Reflux symptoms	1	0	1	-
Moderate chest pain	2	0	1	-
Tissue hyperplasia (in or overgrowth)	0	3	0	0.086
Major, n (%)	0	2 (20)	0	-
Hemorrhage	0	1	0	-
Severe chest pain	0	1	0	-

SEPS Self-expandable plastic stent, BD Biodegradable, FCSEMS Fully cover self-expandable metal stent,

Table 4 Case series evaluating the outcomes of self-expandable plastic stents for benign esophageal diseases

Author (reference)	Patients (n)	Esophageal strictures (n)	Clinical Success n (%)	Complications
Evrard et al [11]	21	17	13/17 (76.5%)	Migration 9/17 (52.9%)
Repici et al [10]	15	15	12/15 (80%)	Migration 1/15 (6.7%)
Martin et al [15]	42	18	17/18 (94.4%)	Migration 1/18 (5.5%)
Holm et al [2]	30	22	5/83 interventions (6%)	Migration 53/83 stents placed (63.9%)
Dua et al [6]	40	40	12/40 (25%)	Migration 8/40 (22%) Perforation 2/40 (5%) Bleeding 3/40 (7.5%) Mortality 1/40 (2.5%)
Oh et al [12]	13	13	3/13 (23%)	Migration 4/13 (30.8%)
Triester et al [13]	5	5	0/5 (0%)	Migration 3/5 (60%) Perforation 1/5 (20%) Severe chest pain 1/5 (20%)
Barthel et al [14]	8	8	1/8 (12.5%)	Migration 11/13 (85%)

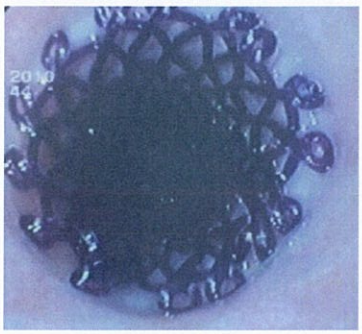


Fig 1 (A)

Fig 1 (B)

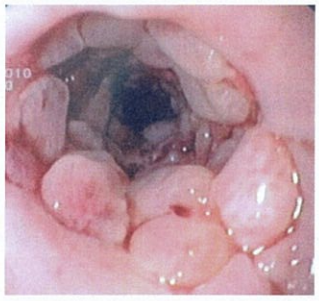
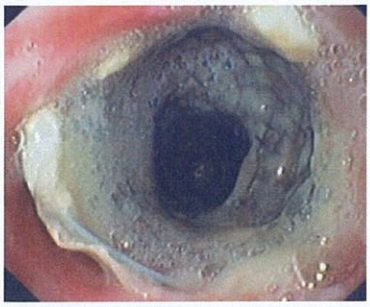


Fig 1 (C)

Fig 2 (A)



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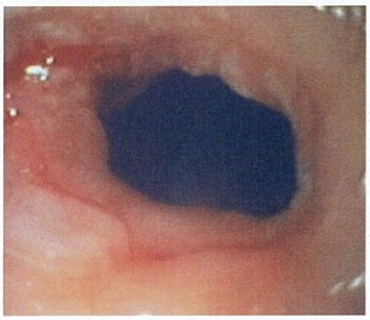

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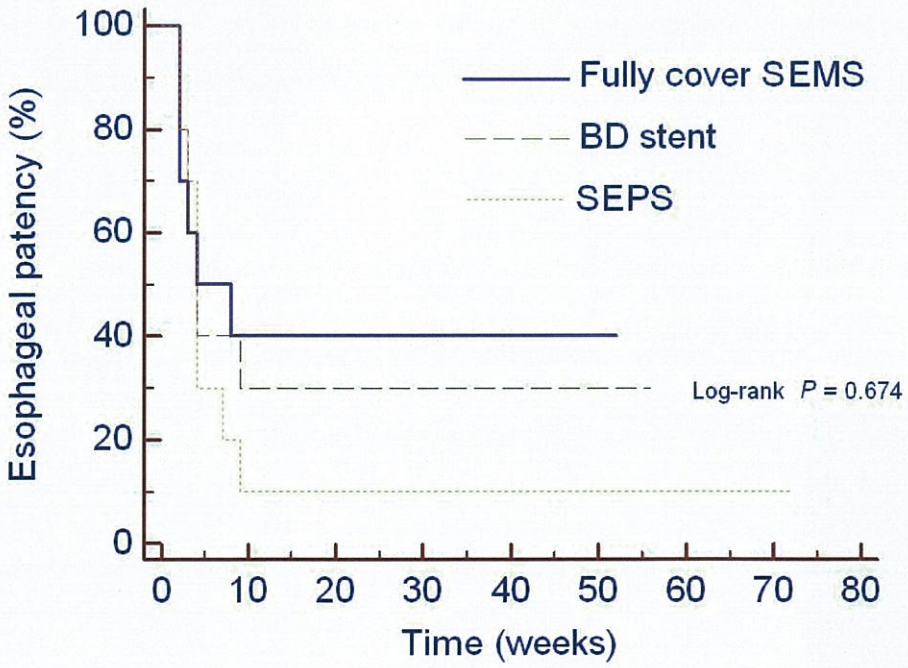

Fig 3

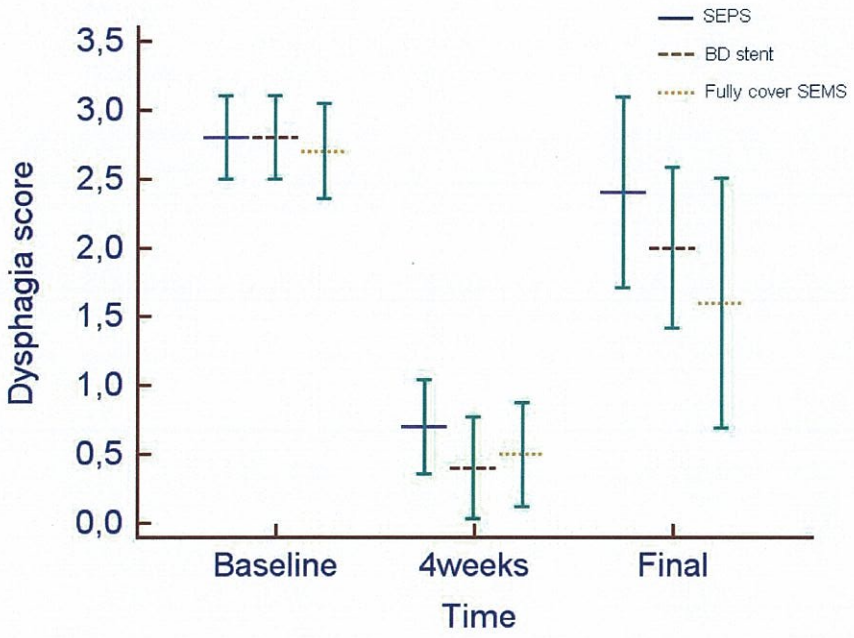
SEPS
BD stent
Fully cover SEMS
Dysphagia score
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
Baseline
4weeks
Final
Time

Fig 4

ARTIGO 6

Canena J, Liberato M, Horta D, Romão C, Coutinho P.

Short-term stenting using fully covered self-expandable metal stents for the treatment of refractory biliary leaks, post-sphincterotomy bleeding and perforations.

Surg Endosc 2012 [aceite para publicação]

Title:

Short-term stenting using fully covered self-expandable metal stents for the treatment of refractory biliary leaks, post-sphincterotomy bleeding and perforations

Short title

Fully covered SEMS and benign biliary conditions

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Abstract

Background:

Fully covered self-expandable metal stents (FCSEMS) have been used as a rescue therapy for several benign biliary tract conditions (BBC). Long-term stent placement commonly occurs and prolonged FCSEMS placement is associated with the majority of the complications reported. This study evaluated the duration of stenting and the efficacy and safety of temporary FCSEMS placement for 3 BBC: refractory biliary leaks, post-sphincterotomy bleeding and perforations.

Methods:

This was a retrospective case series with the long-term follow-up of 25 patients who underwent FCSEMS placement for BBC. This study included 17 patients with post-cholecystectomy refractory biliary leaks who had previously undergone unsuccessful sphincterotomy and plastic stent placement, 4 patients with difficult to control post-sphincterotomy bleeding and 4 patients with a perforation following endoscopic sphincterotomy. Stents were removed according to clinical evidence of problem resolution. The review included stenting duration, safe FCSEMS removal, clinical efficacy, complications and long-term outcomes. During the follow-up period, ERCP and cholangioscopy procedures were performed to exclude the possibility of bile duct lesions development.

Results:

Complete resolution of the initial condition was achieved in all patients. Patients with biliary leaks had a median stent duration time of 16 days (range, 7-28). Patients with bleeding had stents removed after a median time of 6 days (range, 3-15). Patients with perforations had their stents removed after a median time of 29.5 days (range, 21-30). There were no complications related to stenting.

Conclusions:

Temporary placement of a FCSEMS for 30 days or less is an effective rescue therapy for refractory biliary leaks, difficult to control post-ES bleeding and perforations. Duration of stenting should be different for each type of condition. Stents can be safely removed, and short-term stenting is associated with the absence of early and late complications.

Keywords Fully covered self-expandable metal stents · Refractory biliary leaks · Benign biliary tract conditions · Endoscopic retrograde cholangiopancreatography · Post-sphincterotomy bleeding · Duodenal perforations

Introduction

Since its introduction in 1968 [1], endoscopic retrograde cholangiopancreatography (ERCP) has evolved into a sophisticated therapeutic endoscopic examination, and the placement of biliary plastic stents has become one of the cornerstones of the procedure. Initially, due to the small diameter of the working channel of the endoscope, it was only possible to place small caliber plastic stents. However, the 1982 [2] development of duodenoscopes with 4.2-mm working channels allowed the use of large-bore (10-11.5 French) plastic stents. Ten-French stents are now the standard caliber because the use of 11.5-Fr plastic stents is more technically challenging and does not increase stent patency [3]. Plastic stents are routinely used to treat benign biliary conditions (BBCs) such as biliary leaks [4, 5, 6], strictures [7], post-sphincterotomy bleeding (post-ES bleeding) [8] and perforations [9, 10].

Clinically significant biliary leaks can occur after hepatobiliary surgery and are the main cause of post-operative bile leaks following laparoscopic cholecystectomy procedures [4, 5]. Despite the widespread use and efficacy of ERCP in the diagnosis and treatment of biliary leaks [4, 5, 6, 11, 12], a variety of percutaneous and surgical treatments have been proposed [13, 14]. Biliary sphincterotomy alone [5], use of large-bore transpapillary biliary stents [5] or a combination of both therapies have become the first-line interventions for the treatment of bile leaks [4, 5]. Although there is no consensus as to the optimal endoscopic intervention, recent data suggest that a combination of biliary sphincterotomy and placement of a transpapillary biliary stent has a better outcome for the treatment of high-grade biliary leaks [4, 14]. Endoscopic management of bile leaks is safe and efficacious with a high success rate [4, 5, 6, 11, 12]. Nevertheless, there are reports of difficult-to-treat, refractory bile leaks that require multiple endoscopic interventions and sometimes surgery [4, 5].

Endoscopic sphincterotomy (ES) is a fundamental procedure of therapeutic ERCP. Complications following ES can include bleeding [8, 9, 15] and perforations [9, 10]. The incidence of post-ES bleeding varies from 0.76-2% to 10-48% [8, 15], depending on the definition applied. Post-ES bleeding is classified as immediate or delayed according to the time of presentation [8, 15, 16], and it is associated with increased morbidity and mortality [8, 9, 17]. Endoscopic treatments include injection treatment, thermal therapy, endoclips and balloon tamponade, which can be applied individually or in combined treatments. These procedures are associated with the placement of large-bore plastic stents to further tamponade the bleeding site and to maintain biliary drainage [8, 15]. In a small percentage of

cases, refractory bleeding occurs that requires angiographic embolization or surgery [8, 15]. Another post-ES complication is perforation, which occurs in 0.35% and 0.48-0.72% of cases [9, 10]. Although conservative management with intravenous antibiotics, fluids, a nil-by-mouth regimen and the placement of large bore plastic stents is efficacious, surgery is sometimes required [9, 10].

Because the use of plastic stents is not able to resolve problematic cases, gastroenterologists have looked to self-expandable metal stents (SEMSs), which have large diameters and demonstrate a prolonged duration of patency, as a rescue therapy for difficult-to-treat patients. Because uncovered SEMSs soon become embedded into the body tissues, their removal is difficult, if not impossible, which limits their use in BBC [3, 18, 19]. Covered SEMS were designed to prevent the tumor ingrowth and reactive tissue hyperplasia through the stent mesh. This cover prevented the metal from embedding into the biliary tract, allowing for removability [3, 19, 20, 21, 22]. The first covered stents were coated in the middle and had both ends uncovered. Although efficacy has been shown [19, 20, 21, 22], studies using partially covered SEMS in several BBCs reported early complications, including duodenal or proximal migration and pancreatitis [21]. Later complications also occurred and included duodenal or proximal migration and cholecystitis [20, 21]. Furthermore, because the initial portion of the partially covered SEMS can be embedded in the bile duct, its removal can be difficult, particularly in cases of proximal migration. This embedding can result in late stricture formation at the site of embedding [19, 20, 21, 22, 23].

Fully covered SEMSs (FCSEMSs) were designed to maintain long-term patency and can be used to treat BBCs. The full coverage of the stent decreased the incidence of complications and made stent removal safer and easier [3, 24, 25, 26]. Although not approved by the Food and Drug Administration, temporary FCSEMS placement is an excellent option in a subgroup of patients with BBCs that does not respond to plastic stent placement or to the usual endoscopic therapies [3, 24, 25, 26]. However, recent papers using FCSEMSs in BBCs [3, 24, 25, 26] reported complications, including duodenal migration [24, 26], bile duct ulcerations [25], de novo choledocholithiasis [25], strictures [3, 25] and even periampullary adenoma [25]. Furthermore, optimal stenting duration has not been well studied, and long-term stent placement commonly occurs [3, 19, 25]. Prolonged FCSEMS placement is associated with the majority of the complications reported and has not been shown to increase efficacy [3, 25, 26], except in the treatment of strictures [3, 24, 27].

This study evaluated the optimal duration of stenting and the efficacy and safety of temporary FCSEMS placement for the treatment of 3 BBC: refractory biliary leaks, difficult-to-control post-ES bleeding and perforations. Our primary hypothesis was that short-term stenting (30 days or less) would effectively treat the examined BBC without the development of early or late complications.

Materials and methods

Patients and setting

An interventional endoscopy database was retrospectively reviewed to identify all of the patients referred for ERCP who were treated with an FCSEMS as a rescue treatment for refractory biliary leaks, difficult-to-control post-ES bleeding and perforations between March 2007 and May 2011. As an additional inclusion criterion, all stents were required to have been removed within 30 days of placement. The endoscopic and medical reports and the radiological findings of these patients were reviewed to collect the following data: patient demographics, indication for ERCP, duration of stenting, treatment outcomes, complications, and specific information for each group of patients. This study was conducted at a total of four institutions: three tertiary referral academic centers (Pulido Valente Hospital, Faculty of Medical Sciences, Lisbon, Portugal; Cuf Infanto Santo Hospital, Lisbon, Portugal; Professor Doutor Fernando Fonseca Hospital, Amadora, Portugal) and one community hospital (José Joaquim Fernandes Hospital, Beja, Portugal). All patients provided informed written consent prior to their procedures. Each institutional review board involved approved this retrospective study.

Definitions

Refractory biliary leaks were defined as leaks that failed to close after endoscopic intervention with a combination of biliary sphincterotomy and placement of a large-bore (10-Fr) transpapillary biliary stent regardless of biliary leak location (cystic stump, common bile duct/common hepatic duct, Luschka). All the plastic stents used had, at least, a length of 7-cm. High-grade biliary leaks were defined as leaks observed fluoroscopically prior to intrahepatic opacification [4]. Ceased bile output was defined as biliary drainage of less than 5 ml/day in percutaneous drains.

Difficult-to-control post-ES bleeding was defined as a hemorrhage where usual endoscopic measures [8, 15, 16] were attempted but failed to achieve hemostasis. Immediate post-ES bleeding episodes were defined as episodes that occurred at the time of

sphincterotomy [8, 15] while delayed post-ES bleeding episodes were defined as bleeding that began hours to several days after the end of the ERCP procedure [8, 16]. Bleeding severity was graded as mild, moderate or severe using the following previously described validated grading system [16]. Mild bleeding was defined by clinical evidence of gastrointestinal bleeding, hemoglobin decrease of less than 3 g/dl and no need for transfusion while moderate bleeding was defined by the need for transfusion (4 units or less). Severe bleeding was defined by the need for transfusion (5 units or more) or rescue intervention (angiographic or surgical). Immediate post-ES bleeding that required endoscopic treatment was considered, at minimum, as mild bleeding. At the time of the procedures, perforations were recognized by the characteristic contrast extravasation and retroperitoneal air on CT scans, regardless of their association with subcutaneous emphysema.

Complications were defined as any adverse events related to FCSEMS placement. Early complications were defined as complications that occurred while stents were in place. Early complications, if any, were reported separately for FCSEMS insertion and removal. Late complications were defined as those complications that occurred after FCSEMS removal. Migration (distal or proximal), pancreatitis, cholecystitis, bile duct and duodenal ulcerations, de novo choledocholithiasis and late strictures were carefully monitored using previously defined definitions [16, 20, 23, 25, 27].

Intervention and follow-up

All procedures were performed or supervised by 2 experienced pancreatobiliary endoscopists (J.C. and M.L.). ERCP procedures were performed in the prone position under sedation with propofol administered by an anesthesiologist. All of the endoscopic examinations were performed using a therapeutic duodenoscope (TJF-160R, TJF-160VR, TJF-Q180V, Olympus, Tokyo, Japan). Although all FCSEMSs used had a 10-mm luminal diameter, the length varied from 40 to 80 mm (Tables 1, 2 and 3). From March 2007 to December 2009, two different stents were used: the Hanarostent (M.I. Tech, Seoul, South Korea) and the Niti-S (Taewoong Medical, Seoul, South Korea). After January 2010, the Wallflex (Boston Scientific, Natick, Massachusetts, USA) biliary stent was used in all cases. All patients underwent or had previously undergone a biliary sphincterotomy prior to FCSEMS placement. When the gallbladder was still present, FCSEMSs were placed below the cystic-duct insertion. In patients with bile leaks, the stent length (Table 1) was selected to enable leak coverage. After clinical evidence of the complete resolution of the initial condition, patients were scheduled for a second ERCP where the FCSEMS was removed through the scope using rat-toothed forceps or

a cold snare at the discretion of the endoscopist. If, after pulling the stent, resistance was encountered, the stent was fixed to the tip of the duodenoscope with the forceps or the snare, and the instrument and the stent were removed together. After stent removal, a cholangiogram was performed to evaluate the initial problem and possible ductal injury. The majority of patients underwent a follow-up ERCP procedure weeks to months after FCSEMS removal to determine if late strictures had developed.

At the moment of control ERCP a subset of patients with normal cholangiogram and a previous history of one or more episodes of transient cholestasis were submitted to choledochoscopy to exclude minor bile duct defects (tissue hyperplasia). Cholangioscopy procedures were performed using the "mother-baby" technique. In this approach, a fiber-optic cholangioscope (CHF-BP30, Olympus, Tokyo, Japan) connected to a high-resolution system (Olympus, Tokyo, Japan) was utilized.

Long-term follow up was obtained by reviewing clinical notes provided by regular clinic visits, lab results, imaging, cholangiography procedures performed weeks to months after stent removal (when available), cholangioscopy data, and structured telephone interviews with patients or family at the time of manuscript preparation.

Results

A total of 6267 records for ERCP procedures that occurred between March 2007 and May 2011 were identified in the endoscopy database. Twenty-nine patients who met the inclusion criteria were identified. Four of these patients were excluded for the following reasons: incomplete data concerning endoscopic procedures and follow-up (3 patients) and unavailability of informed written consent (1 patient).

A total of 25 patients (9 male and 16 female) with a median age of 55 years (range, 29-91; mean, 56.2) were enrolled in the study. All stents were safely removed with a snare or rat-toothed forceps. Complete resolution of the initial BBC was confirmed in all patients. Patients were followed-up for a median of 123.5 weeks (range, 14-214; mean, 113.3) following FCSEMS removal. One patient in the post-ES bleeding group was lost to follow-up because he underwent surgery for an ampullary tumor and died 5 days post-surgery. Nevertheless, he was included in the study because his FCSEMS was removed and his initial clinical condition had resolved. All other patients completed the follow-up. For further detailed analysis, patients were divided into the following 3 groups that were defined earlier in the Methods section:

refractory biliary leaks (Table 1), post-sphincterotomy bleeding (Table 2) and perforations (Table 3).

Refractory biliary leaks

FCSEMSs were placed in 17 patients with post-cholecystectomy refractory biliary leaks. The median patient age was 55 years (range, 32-89; mean, 56.8). Final diagnoses included 12 cystic-stump high-grade leaks and 5 common bile duct/common hepatic duct leaks. During the first ERCP procedure, all patients had high-grade leaks (4), and they were treated with a combination of biliary sphincterotomy and placement of a large-bore (10-Fr) transpapillary biliary stent, at least 7-cm long. Patients who were non-responsive to the initial endoscopic therapy were identified according to clinical grounds and individual assessment. Similar or increased levels of percutaneous drainage and worsening images were the most commonly utilized criteria to determine endoscopic treatment failure. The second ERCP procedure with FCSEMS placement was performed after a median time interval of 10 days (range, 7-18; mean, 10.1) after the first procedure. One patient had a second ERCP on day 6 post-ERCP to place a second large-bore (10-Fr) plastic stent without success, leading to FCSEMS placement on day 10 post-ERCP.

Subsequent to FCSEMS placement, percutaneous drain output ceased after a median time of 3 days (range, 2-8; mean, 3.7). When comparing the drainage output of the common bile duct/common hepatic duct leaks with the cystic-stump leaks, drainage ceased more quickly in the patients with cystic stump leaks, with a median time to cessation of 3 days compared to 6 days. FCSEMSs were removed after a median time of 16 days (range, 7-28; mean, 16.6). Follow-up was completed for all patients after a median time of 125 weeks (range, 14-214; mean, 127.8).

The 5 patients with common bile duct/common hepatic duct leaks exhibited major bile duct injuries with associated strictures detected at the time of the first ERCP. After FCSEMS removal, patients were treated with multiple plastic stents for 9-12 months. Four patients had clinical resolution of their strictures while maintaining minor bile duct defects, and one patient was still in endoscopic treatment at the time of manuscript preparation.

Post-sphincterotomy bleeding

FCSEMSs were placed in 4 patients with difficult to treat post-ES bleeding. Patients had a median age of 60 years (range, 37-91; mean, 62). Bleeding was immediate in one patient with a periampullary diverticulum (Fig. 1) and was delayed in 3 patients, occurring on days 2, 3

and 7 post-ERCP. All patients were submitted to endoscopic measures to achieve hemostasis without success. Two hemorrhages were considered minor, with both patients exhibiting melena and hemoglobin drop; moderate and severe bleeding were observed in the remaining two patients. The first 3 patients underwent the second ERCP procedure on the day following clinical presentation of bleeding. In the patient with severe bleeding, the second ERCP procedure was delayed 4 days (due to a long holiday weekend). We hypothesize that the delay in treatment was the main cause of the severity of bleeding; the patient required the transfusion of 10 units of blood. Following FCSEMS placement, there were no signs or symptoms of recurrent GI bleeding. Stents were removed after a median time of 6 days (range, 3-15; mean, 7.5). Follow-up was completed for 3 patients after a median time of 16 weeks (range, 14-20; mean, 16.7).

Perforations

Four patients with a median age of 43 years (range, 29-76; mean, 47.8) underwent FCSEMS placement as a rescue therapy for perforation closure following endoscopic biliary sphincterotomy. All the perforations were recognized at the time of the procedure based on characteristic contrast extravasation. All patients had a CT scan showing retroperitoneal air and leaks, and two patients exhibited associated subcutaneous emphysema (Fig. 2). According to the endoscopist who performed the procedures, a zipper cut during ES was the most common cause of perforation. None of the patients underwent precut papillotomy, which has been suggested as a risk factor for perforation (10). The four patients were admitted to the intensive care unit (ICU) and treated with intravenous antibiotics, fluids, and a nil-by-mouth regimen. The median length of ICU stay was 2.5 days (range, 1-4). The two patients with subcutaneous emphysema required mechanical ventilation for bilateral pneumothorax for one day. Patients were discharged from the hospital after a median of 10 days (range, 7-12) post-FCSEMS placement, and stent removal was performed as an outpatient procedure. FCSEMSs were left in place for a median time of 29.5 days (range, 21-30; mean, 27.5 days). Follow-up was completed for all patients after a median time of 132 weeks (range, 72-160; mean, 124 weeks).

Complications and follow-up

There were no initial complications related to FCSEMS placement or removal. Four patients, 2 in the post-ES bleeding group and 2 in the perforation group, exhibited two- to three-fold increases in serum amylase values in the absence of pain following FCSEMS placement; these increases were assumed to be a consequence of the ERCP procedures. At the

time of extraction, the endoscopist thought that 7 stents had slid several mm into the duodenum. Because the largest portion of the stent was still inside the bile duct and there was clinical resolution of the initial conditions, these movements were not considered stent migration. None of the 5 patients (2 in the bleeding group and 3 in the perforation group) who had an intact gallbladder presented with cholecystitis. There were no cases of duodenal ulcerations or de novo choledocholithiasis found within FCSEMS and bile duct at the time of stent removal.

During the long-term follow-up of the 24 patients, bile leak recurrence, episodes of rebleeding or delayed complications (e.g., abscesses or strictures) related to perforations were not observed in any of the patients. Follow-up ERCP procedures were performed in 18 patients (11 in the bile leak group, 3 in the bleeding group and 4 in the perforation group) after a median time of 51 weeks (range, 12-110; mean, 52.7). In 15 patients, the results of the ERCP were normal. The other 3 patients had minor stricture/bile duct defects that were without clinical significance and were related to injuries obtained during cholecystectomy. When the bile duct dimensions at the moment of FCSEMS placement and the follow-up cholangiography performed months later were compared, there was no evidence of bile duct enlargement due to FCSEMS placement. In the 25 patients mid bile duct diameter was initially measured with values ranging from 6mm to 12mm. After FCSEMS placement the bile duct assumed the shape and diameter of the stent (for bile duct < 10mm), returning to normal after FCSEMS removal.

Cholangioscopy procedures were performed in 6 patients (4 in the bile leak group and 2 in perforation group). In the perforation group patients and in one of the bile leak group patients who had a cystic-stump leak (Video 1), the choledochoscopy results were normal without evidence of minor bile duct defects or tissue hyperplasia. The other three patients, who presented with bile duct/common hepatic duct leaks, exhibited minor strictures (fibrous ring) of the bile duct at the site of strictures being treated with long-term plastic stenting. Above the minor defect/stricture, in the place where the initial portion of the FCSEMS was placed, no defects or evidence of reactive tissue hyperplasia were observed (Video 2).

Discussion

According to our findings, temporary placement of a FCSEMS for 30 days or less is an effective rescue therapy for several BBCs and is free from early complications. The median time of FCSEMS removal varied depending upon the BBC; FCSEMSs were removed after 6 days in patients with difficult-to-control post-ES bleeding, after 16 days in patients with complex biliary leaks and after 29.5 days in patients with perforations. Patients underwent long-term

follow-up, including cholangiography and cholangioscopy procedures, without evidence of late complications. These results suggest that the short duration of stenting was a key factor for the absence of FCSEMS-related complications.

Bile leaks after cholecistectomy are traditionally managed with endoscopic techniques consisting of transpapillary placement of large-bore (10-Fr) plastic stents with or without biliary sphincterotomy [4, 5, 19, 22]. For simple leaks such as small cystic duct leaks (low-grade leaks) and Luschka's duct leaks, the success rate of endoscopic treatment is high. Bile leak closure is achieved because the transpapillary high-pressure gradient is decreased or eliminated with the endoscopic procedures. However, in a small subset of patients with more complex leaks (high-grade cystic stump leaks, common bile duct/common hepatic duct leaks, bile leaks after liver transplantation or large leaks following partial cholecystectomy) successful closure can be more problematic, leading to an increased number of procedures or even surgery [4, 5, 19, 22]. Refractory bile leaks can be treated by FCSEMS. The large stent diameter diverts more flow away from the leak site, causing a significant decrease of the pressure gradient at the ampullary level. Furthermore, the FCSEMS directly covers the leak site. Baron *et al.* [19] first reported the use of partially (n=2) and fully covered (n=1) SEMSs in 3 patients with complex biliary leaks of the gallbladder bed following open subtotal cholecystectomy procedures. In 2 patients, the leaks had not responded to the endoscopic intervention of a combination of ES and a large-bore plastic stent; in the third patient, a FCSEMS was the initial option. Stents were removed 9, 5 and 3 weeks later, and no major complications were reported. The authors suggested that until more data were available, stents should remain in place for an arbitrary time of ≤3 months. Interestingly, bile drainage output decreased markedly in one week or less following SEMS placement.

A study with 16 patients used partially covered SEMS to treat 8 cystic-stump leaks, 5 Luschka's duct leaks, 2 partial cholecystectomy leaks, and 1 liver transplant anastomotic leak [20]. These patients had previously undergone unsuccessful plastic stent placement or had severe comorbidities that prevented multiple interventions. Of the patients studied, 15 responded to partially covered SEMS placement. Stents were left in place for a median time of 3 months (range, 1-17), and the authors reported complications in 2 patients (1 proximal and 1 distal migration). Information regarding external drainage or recommendations concerning stenting duration were not available.

Wang *et al.* [25] reported the first case series using FCSEMS to treat a heterogeneous group of patients with complex leaks that were defined as biliary leaks that failed ERCP

intervention, bile leaks after cadaveric orthotopic liver transplantation and complicated cholecystectomies with large bile leaks. The bile leaks in all 13 patients resolved, and FCSEMSs were removed in 11 patients after a median time 103 days (range, 67-493). However, several complications were reported. Ten of the 11 patients had de novo choledocholithiasis within the FCSEMS. Two patients presented with strictures that developed after stent removal; the strictures were located at the previous location of the proximal edge of the FCSEMS. One of the strictures required treatment with balloon dilation and stent placement for 7 months. In 5 of 7 patients who underwent choledochoscopy at the time of stent removal, ulceration was seen where the fins anchored the stent into the bile duct. Again, no information regarding external bile drain output was available. The authors advocated that the stents may be reasonably left in place for more than 6 weeks.

In a prospective study of FCSEMS placement for a variety of BBCs [3], one patient with a large intrahepatic fistula after excision of a hydatic cystic was treated with a FCSEMS. The FCSEMS remained in place for 36 days, despite the fact that external drainage stopped 24 hours after insertion. In a recent case report [28], a patient with a Luschka's duct leak treated with an FCSEMS after unsuccessful endoscopic management with ES and plastic stent placement had the stent removed after 28 days. Again, the authors reported an almost immediate decrease in the bile output from the percutaneous drain.

In this study, we examined two types of refractory biliary leaks that exhibited a 100% success rate following FCSEMS treatment; these results compare with other reports using partially or fully covered SEMS [19, 20, 25]. The leaks in our study (high-grade cystic stump leaks or common bile duct/common hepatic duct leaks) failed initial endoscopic treatment with placement of large-bore (10-Fr) plastic stents and biliary sphincterotomy which has been reported by other studies [5, 19, 20, 25]. A variety of endoscopic techniques other than placement of FCSEMS could have been chosen in the cases presented here. One option is the placement of multiple large-bore (10-Fr) plastic stents at lower cost to further decrease transpapillary high-pressure gradient. However plastic stents can occlude possibly before leak closure and furthermore one of our patients was treated with 2 large-bore plastic stents without success increasing costs and leading to another ERCP to FCSEMS placement. In our series, the bile output from the percutaneous drains ceased after a median time of 3 days (range, 2-8) following FCSEMS placement. This result is comparable to earlier studies [3, 19, 28], suggesting that stents could be removed earlier than previously reported (for both partially and fully covered SEMS). In our study, stents were removed after a median time of 16 days, which deviated from earlier studies [20, 25]. The median time interval between ceased

biliary drainage and FCSEMS removal was 12 days (range, 5-26). Bile drainage ceased after 2-4 days (median 3) for cystic-stump leaks while bile drainage for even more complex leaks associated with major common bile duct/common hepatic duct injuries ceased between 5 and 8 days (median 6) following FCSEMS placement. Upon FCSEMS removal, leaks were sealed in all cases, suggesting that stents can be removed safely 10-15 days after cessation of bile drainage. Taken together, these findings suggest that for refractory bile leaks, stents can be safely removed after no longer than 3 weeks.

In a recent report [26], five patients were treated with temporary FCSEMSs for difficult-to-control post-ES bleeding. The stent worked through mechanical tamponade of the bleeding site. Three patients were treated for immediate bleeding, and two patients were treated for delayed hemorrhage. Four patients were previously submitted to other endoscopic measures (including embolization in one patient) but failed to achieve hemostasis. The stents were removed in 3 patients at 2, 4 and 8 weeks; stents had completely migrated spontaneously without complications in two patients at 4 weeks. No other complications were reported. The authors estimated that a 2-4-week duration of FCSEMS placement would be appropriate in this setting.

We studied a cohort of patients submitted to FCSEMS placement after the failure of several endoscopic treatments for post-ES bleeding. Two mild cases, 1 moderate case and 1 severe case of bleeding were treated. This treatment resulted in immediate hemostasis in all patients, and no further interventions were needed, which is consistent with the report of Shah *et al.* [26]. In our study, patients with post-ES bleeding had their stents removed after a median time of 6 days. In one patient in whom the stent remained in place for 3 days, anticoagulant therapy was resumed five days after stent removal, and no signs of rebleeding were observed. In a study by Shah *et al.* [26], anticoagulants were resumed with stents in place, and again no signs or symptoms of recurrent GI bleeding were detected. Because the hemostatic effect appears to be immediate and stenting works through a tamponade effect, this result suggests that stents can be safely removed no longer than 1 week after placement and that patients with anticoagulant therapy can resume therapy while stents are in place.

Garcia-Cano *et al.* [3] used an FCSEMS to close two perforations after ES. Patients were managed conservatively, and stents were removed after a mean time of 96 days. The covering seals the perforation, perhaps with a strong occlusion pressure, allowing for a safe and faster recovery. We used FCSEMS to treat 4 perforations. All patients were admitted to the ICU, and 2 patients required mechanical ventilation. Perforations were detected during ERCP

procedures on account of large extravasation of contrast in all 4 patients and subcutaneous emphysema in 2 patients leading to respiratory failure, suggesting that perforations were severe. With the FCSEMS approach, all patients recovered rapidly and resumed oral feeding less than one week after perforation detection. Furthermore, the patients were rapidly discharged from hospital, and FCSEMS removal, which occurred after a median time of 29.5 days, was performed as an outpatient procedure. More importantly, no complications, such as papillary strictures or abscesses, were detected during follow-up. These data suggest that FCSEMSs are effective in treating post-ES perforations and are associated with rapid, complication-free recovery. We do not advocate SEMS placement for microperforations with minor retroperitoneal air where most patients will do well with medical management and placement of a plastic stent. We suggest the use of FCSEMS in more severe perforations with major leaks and/or subcutaneous emphysema detected at the time of ERCP. The stents where removed within 30 days of placement but eventually, due to the rapid recovery of all patients in our series stents can be removed even earlier (i.e. before discharge from hospital).

The majority of patients had a follow-up ERCP following FCSEMS removal. These examinations were scheduled by medical assistants to evaluate possible late bile duct injury several months after stent removal. There were raising concerns about the development of late strictures several months after FCSEMS removal and this was the main cause for the referral of patients to a control ERCP. Seven patients did not undergo the follow-up ERCP; one patient died, one patient was still in endoscopic treatment at the time of manuscript preparation, and the remaining five patients declined further endoscopic procedures despite being available for follow-up.

The FCSEMS used had no fins for anchoring. Nevertheless, the proximal edge of the stent can potentially cause bile duct damage, leading to reactive tissue hyperplasia and possibly to the development of a late stricture. Although this stent effect on the biliary epithelium may be related to long-term stent placement, we intended to exclude this possibility after short-term stenting with cholangioscopy screenings. At the time of follow-up ERCP patients with normal cholangiogram but who had a previous history of at least one episode of transient cholestasis were submitted to cholangioscopy to determine if tissue hyperplasia/minor bile defects had developed. Choledochoscopy results were normal in three patients. The other 3 patients had previously been treated for a stricture caused at the time of cholecystectomy. In all cases, there were no bile duct lesions above the remaining minor stricture, which had an endoscopic appearance of a fibrous ring.

Patients with bile duct/common hepatic duct leaks had associated strictures, and their FCSEMSs were removed following the clinical resolution of leaks. Strictures were subsequently treated by multiple placements of plastic stents (not FCSEMS). Although reports exist suggesting that temporary FCSEMS placement in benign strictures offers a potential alternative to the multiple plastic stent strategy [21, 24, 27], these findings have been challenged in the literature [29]. We treated 7 patients with benign biliary strictures using FCSEMS (unpublished data), and we observed complications in six patients. Three patients developed de novo choledocholithiasis and stent occlusion, one patient exhibited proximal stent migration and two patients exhibited distal stent migration. The FCSEMS were removed, and the patients were subsequently treated with multiple plastic stents. Until more data are available, we use plastic stents to treat benign biliary strictures.

When FCSEMS placement is considered for BBCs, cost is an important issue. Although no studies are available on this matter, FCSEMS placement as a rescue therapy is likely to be cost-effective because the prevention of several procedures (including surgery) offsets the cost of the stents. Complications have been reported in papers using FCSEMS to treat BBCs [3, 24, 25, 26, 27]. One common complication is stent migration which has been reported previously [24, 26]. Stent migration is associated with short stents (i.e. 4cm) that tend to migrate easily. In our series we did not observe any migration and we only used 2 short stents in 2 patients with an intact gallbladder and low cystic-duct insertion. In our study complications did not develop in any patients following FCSEMS placement. Furthermore, after long-term follow-up, no patients exhibited signs of FCSEMS-related complications. We believe that most of the FCSEMS-associated complications are related to the duration of stenting. The association between short-term stenting and the absence of complications strongly support this hypothesis. A subset of our patients did one additional ERCP after FCSEMS removal on account of safety reasons. As suggested by our study short-term placement of FCSEMS is safe and we do not advocate control ERCPs in the future for patients submitted to short-term (i.e. 30 days or less) FCSEMS placement.

Several limitations of our study should be taken into account. This was a retrospective study where stent removal was not scheduled according to specific endpoints. In the leak group, no patients with bile leaks after cadaveric orthotopic liver transplantation or with large leaks following partial cholecystectomy were included; these types of leaks can be problematic, leading to increased stenting durations [22, 25, 30]. Nevertheless, in a report of 3 patients outlining the SEMS treatment of bile leaks after open subtotal cholecystectomy, Baron *et al.* [22] noted a dramatic decrease of bile output in a short period of time suggesting

that these leaks can also be treated with short-term stenting. Patients with post-ES bleeding had a shorter follow-up compared to the other groups; the effect of the stents appeared to be immediate, and very late rebleeding was unusual. These patients had a median time of stenting of 6 days, and there was no evidence that such very short-term stenting was associated with late bile duct injury. We suggest that further studies are needed with a prospective design, where time of stent removal should be a primary endpoint. In these proposed studies, biliary drainage should be carefully monitored and used as a marker for scheduled stent removal in patients experiencing bile leakage.

The strengths of our study are the early removal of stents, the long-term follow-up, the use of control cholangiography and choledochoscopy procedures in a subset of patients and the relatively large sample size. To our knowledge, this is the first study concerning the duration of FCSEMS placement and the largest series of patients treated with FCSEMS for BBCs other than benign strictures.

In conclusion, our data suggest that FCSEMS placement for 30 days or less is efficacious at resolving complex biliary leaks, difficult-to-control post-ES bleeding and perforations. Duration of stenting should be different for each type of condition. Stents can be safely removed, and short-term stenting is associated with the absence of early and late complications.

References

1. McCune WS, Shorb PE, Moscovitz H (1968) Endoscopic cannulation of the ampulla of Vater: a preliminary report. Ann Surg 167:752–756

2. Huibregtse K, Tytgat GN (1982) Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis. Gut 23:371-5.

3. Garcia-Cano J, Taberna-Arana L, Jimeno-Ayllón C, Martínez-Fernández R, Serrano-Sanchez L, Reyes-Guevara A, Viñuelas-Chicano M, Gómez-Ruiz C, Morillas-Ariño M, Pérez-Garcia J, Pérez-Vigara G, Pérez-Sola A (2010) Use of fully-covered self-expandable metallic stents for the management of benign biliary conditions. Rev Esp Enferm Dig 102:526-532

4. Sandha GS, Bourke MJ, Haber GB, Kortan PP (2004) Endoscopic therapy for bile leak based on a new classification: results in 207 patients. Gastrointest Endosc 60:567–574

5. Kaffes AJ, Hourigan L, De Luca N, Byth K, Williams S, Bourke M (2005) Impact of endoscopic intervention in 100 patients with suspected postcholecystectomy bile leak. Gastrointest Endosc 61:269–275

6. Katsinelos P, Kontouras J, Paroutoglou G, Chatzimavroudis G, Germanidis G, Zavos C, Pilpilidis I, Paikos D, Papaziogas B (2008) A comparative study of 10-Fr vs. 7-Fr straight plastic stents in the treatment of postcholecystectomy bile leak. Surg Endosc 22:101-106

7. Costamagna G, Pandolfi M, Mutignani M, Perri V, Spada C, Pandolfi M, Galasso D (2001) Long-term results of endoscopic management of postoperative bile duct strictures with increasing number of stents. Gastrointest Endosc 54:162-168

8. Ferreira LE, Baron TH (2007) Post-sphincterotomy bleeding: who, what, when, and how. Am J Gastroenterol 102:2850–2858

9. Andriulli A, Loperfido S, Napolitano G, Niro G, Valvano M, Spirito F, Pilotto A, Forlano R (2007) Incidence rates of Post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 102:1781-1788

10. Enns R, Eloubeidi M, Mergener K, Jowell P, Branch M, Pappas T, Baillie J (2002) ERCP-related perforations: risk factors and management. Endoscopy 34:293-298

11. Coté GA, Ansstas M, Shah S, Keswani RN, Alkade S, Jonnalagadda SS, Edmundowicz SA, Azar RR (2010) Findings at endoscopic retrograde cholangiopancreatography after endoscopic treatment of postcholecistectomy bile leaks. Surg Endosc 24:1752–1756

12. Simmons DT, Petersen BT, Goustout CJ, Levy MJ, Topazian MD, Baron TH (2008) Risk of pancreatitis following endoscopically placed large-bore biliary plastic stents with and without biliary sphincterotomy for management of postoperative bile leaks. Surg Endosc 22:1459-1463

13. Cozzi G, Severini A, Civelli E, Millela M, Pulvirenti A, Salvetti M, Romito R, Suman L, Chiaraviglio F, Mazzaferro V (2006) Percutaneous transhepatic biliary drainage in the management of postsurgical biliary leaks in patients with nondilated intrahepatic bile ducts. Cardiovasc Intervent Radiol 29:380–388

14. Tsalis KG, Christoforidis EC, Dimitriadis CA, Kalfadis SC, Botsios DS, Dadoukis JD (2003) Management of bile duct injury during and after laparoscopic cholecistectomy. Surg Endosc 17:31–37

15. Leung J, Chan F, Sung J, Chung S (1995) Endoscopic sphincterotomy-induced hemorrhage: A study of risk factors and the role of epinephrine injection. Gastrointest Endosc 42:550–554.

16. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N (1991) Endoscopic sphincterotomy complications and their management: An attempt at consensus. Gastrointest Endosc 37:383–393.

17. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA (2001) Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol 96: 417-423

18. Dumonceau J, Deviere J, Delhaye M, Baize M, Cremer M (1996) Plastic and metal stents for postoperative benign bile duct strictures: the best and the worst. Gastrointest Endosc 47:8–17

19. Baron T. Covered self-expandable metal stents for benign biliary tract diseases (2011) Curr Opin Gastroenterol 2:262-267

20. Kahaleh M, Sundaram V, Condron S, De La Rue S, Hall J, Tokar J, Friel C, Foley E, Adams R, Yeaton P (2007) Temporary placement of covered self-expandable metallic stents in patients with biliary leak: midterm evaluation of a pilot study. Gastrointest Endosc 66: 52-59

21. Kahaleh M, Behm B, Clarke B, Brock A, Shami V, De La Rue S, Sundaram V, Tokar J, Adams R, Yeaton P (2008) Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (with video). Gastrointest Endosc 67: 446-454

22. Baron T, Poterucha J (2006) Insertion and removal of covered expandable metal stents for closure of complex biliary leaks. Clin Gastroenterol Hepatol 4:381-386

23. Ho H, Mahajan A, Gosain S, Jain A, Brock A, Rehan ME, Ellen K, Shami VM, Kahaleh M (2010) Management of complications associated with partially covered biliary metal stents. Dig Dis Sci 55: 516-522

24. Mahajan A, Ho H, Sauer B, Phillips MS, Shami VM, Ellen K, Rehan M, Schmitt TM, Kahaleh M (2009) Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation (with video). Gastrointest Endosc 70: 303-309

25. Wang A, Ellen K, Berg C, Schmitt TM, Kahaleh M (2009) Fully covered self-expandable metallic stents in the management of complex biliary leaks: preliminary data - a case series. Endoscopy 41: 781-786.

26. Shah J, Marson F, Binmoeller K (2010) Temporary self-expandable metal stent placement for treatment of post-sphincterotomy bleeding. Gastrointest Endosc 72:1274-1278

27. Park D, Lee S, Lee T, Ryu C, Kim H, Seo DW, Park SH, Lee SK, Kim MH, Kim SJ (2011) Anchoring flaps versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study (with videos). Gastrointest Endosc 73:64-70

28. Hwang JC, Kim JH, You BM, Kim JH, Kim HW, Kim MW (2011) Temporary placement of a newly designed, fully covered, self-expandable metal stent for refractory bile leaks. Gut liver 5:96-99

29. van Boeckel P, Vleggar F, Siersema P (2009) Plastic or metal stents for benign extrahepatic biliary strictures: a systematic review. BMC Gastroenterology 9:96

30. Shah JN, Ahmad NA, Shetty K, Kockman ML, Long WB, Brensinger CM, Pfau PR, Olthoff K, Markmann J, Shaked A, Reddy KR, Ginsberg GG (2004) Endoscopic management of biliary complications after adult living donor liver transplantation. Am J Gastroenterol 99: 1291-1295

Table 1 Demographics, indications, detailed treatment data and follow-up for patients with refractory biliary leaks

Age/sex	Origin of leak	Time interval (days) between ES+plastic stent (initial ERCP) and FCSEMS delivery	External drain bile output ceased (days after FCSEMS)	Duration of stenting (days)/ FCSEMS length (cm)	Follow up (weeks)/control ERCP (weeks)/ choledochoscopy (Yes/NA)
39/F	CBD/CHD	12	6	18/8	14/NA/NA
45/M	Cystic stump	10	2	28/6	30/24/Yes
38/M	CBD/CHD	10	8	21/8	52/48/Yes
32/M	CBD/CHD	8	6	18/8	104/90/Yes
73/F	Cystic stump	18	3	20/6	36/30/NA
47/F	CBD/CHD	14	5	21/8	124/110/Yes
73/F	Cystic stump	7	2	7/6	208/50/NA
84/M	Cystic stump	14	2	14/6	206/52/NA
62/F	Cystic stump	7	2	14/6	205/70/NA
74/F	Cystic stump	7	3	14/8	214/54/NA
89/F	Cystic stump	7	2	14/6	154/100/NA
62/F	Cystic stump	7	3	14/8	123/60/NA
39/F	Cystic stump	8	4	15/8	165/NA/NA
48/M	Cystic stump	10	3	15/6	180/NA/NA
42/F	Cystic stump	10	3	16/6	125/NA/NA
55/F	Cystic stump	12	4	16/8	130/NA/NA
64/M	CBD/CHD	10*	5	18/8	104/NA/NA

F female, M Male, CBD/CHD common bile duct/common hepatic duct, ES endoscopic sphincterotomy; ERCP endoscopy retrograde cholangiopancreatography, FCSEMS Fully covered self-expandable metal stent, NA not available, *patient was submitted, on day 6, to a second ERCP to place a second large-bore plastic stent.

Table 2 Clinical characteristics and treatment data of patients with post-sphincterotomy bleeding

Age / Sex	Indication	Comorbid conditions/ risk factors for bleeding	PT(s/INR)/ Platelet count (100000s/µl)	Bleeding time after ERCP (days) /type	No. of units of blood transfusions/ Hg drop (g/dl)	Attempted treatments	Duration of stenting (days)/ FCSEMS length (cm)	Follow up/ control ERCP (weeks)
91/ F	stones	Atrial fibrillation anticoagulation therapy*	17.6/1.4/195	7 /clot, oozing	2/NA	Epinephrine injection, balloon tamponade	3/4	20/14
37/ M	stones	Hepatitis C; no evidence of cirrhosis	10.8/1.0/239	3/clot, oozing	0/2,4	Epinephrine injection, endoclips	6/6	16/14
80/ F	stones	Periampullary diverticulum	12.4/1.2/231	Immediate/ pulsatile	0/1.3	Epinephrine injection, balloon tamponade	6/6	14/12
40/ M	Ampullary tumor	Hepatitis B AIDS Mycobacterium avium complex	11.0/1.0/207	2/clot, oozing	10/NA	Epinephrine injection	15/6	NA #

F female, M Male, PT Prothrombin time, INR International Normalized Ratio, Hg Hemoglobin, ES endoscopic sphincterotomy, ERCP endoscopy retrograde cholangiopancreatography, ICU Intensive Care Unit, NA not available.*Patient was receiving anticoagulant therapy within 4 days of procedure. Anticoagulants were held for 5 days post-procedure and for more five days after stent removal. # patient was submitted to surgery for ampullary tumor and died 5 days post-surgery.

Table 3 Characteristics, treatment and outcome data of patients with perforations

Age/Sex	Indication	Motive of perforation*	Perforation diagnosis	Number of days in ICU	Duration of stenting (days)/ FCSEMS length (cm)	Follow up (weeks)/control ERCP (weeks)/ choledochoscopy (Yes/NA)
55/F	Stones	Zipper cut ES with bleeding and attempted balloon tamponade	Subcutaneous emphysema Extravasation of contrast Retroperitoneal air on CT scan	4	21/4	108/66/Yes
29/F	Stones	Zipper cut ES	Extravasation of contrast Retroperitoneal air on CT scan	1	30/6	72/48/Yes
31/M	Stones	Large balloon dilatation followed by attempted stones removal	Extravasation of contrast Retroperitoneal air on CT scan	2	30/6	160/58/NA
76/F	Stones	Zipper cut ES	Subcutaneous emphysema Extravasation of contrast Retroperitoneal air on CT scan	3	29/6	156/48/NA

F female, M Male, ES endoscopic sphincterotomy, ERCP endoscopy retrograde cholangiopancreatography, ICU Intensive Care Unit, NA not available, *according to the endoscopist who performed the procedures

Figures

Fig. 1 Use of a fully covered self-expandable metal stent (FCSEMS) for the treatment of difficult-to-control bleeding immediately after sphincterotomy

(A) Endoscopic image of active bleeding after biliary sphincterotomy in a patient with a periampullary diverticulum

(B) Endoscopic lateral view of a fully deployed FCSEMS that resulted in mechanical tamponade and hemostasis. Note the blue tone of the papilla of Vater after epinephrine injection

(C) Inside view of a FCSEMS across the ampullary orifice showing the immediate tamponade of the bleeding site

(D) Fluoroscopic image of a FCSEMS removal through the scope

Fig. 2 Images of a CT scan following post-sphincterotomy perforation

(A) CT scan of the chest. Axial view showing bilateral pneumothorax, pneumomediastinum and subcutaneous emphysema

(B) CT scan of the abdomen. Axial view showing significant pneumoperitoneum and retroperitoneal air. The fully-covered self-expandable metal stent that was used to seal the perforation can be seen in the bile duct.

Video 1 Normal cholangiography and normal cholangioscopy 24 weeks after fully covered self-expandable metal stent removal, used to treat a cystic stump leak after unsuccessful endoscopic treatment with sphincterotomy and plastic stent placement. Note clear endoscopic image of cystic-stump after visualization of hilar bifurcation

Video 2 Cholangiography and cholangioscopy 90 weeks after fully covered self-expandable metal stent removal, used to treat a common bile duct/common hepatic duct leak with associated stricture. Note the endoscopic appearance of a minor stricture (fibrous ring) and the normality of the bile duct above the stricture.

Fig 1 (A)

Fig 1 (B)

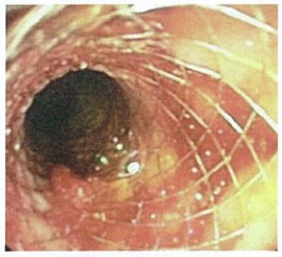

Fig 1 (C)

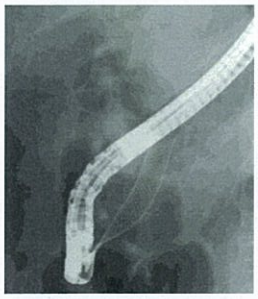

Fig 1 (D)

Fig 2 (A)

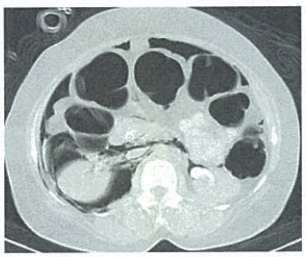

Fig 2 (B)

ARTIGO 7

Liberato M, Canena J.

Endoscopic stenting for hilar cholangiocarcinoma: Efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients

[enviado para publicação]

Title:

Endoscopic stenting for hilar cholangiocarcinoma: Efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients

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Abstract

Background:

Endoscopic biliary drainage of hilar cholangiocarcinoma is controversial with respect to the optimal types of stents and the extent of drainage. This study evaluated endoscopic palliation in patients with hilar cholangiocarcinoma using self-expandable metallic stents (SEMS) and plastic stents (PS).We also compared unilateral and bilateral stent placement according to the Bismuth classification.

Methods

Data on 480 patients receiving endoscopic biliary drainage for hilar cholangiocarcinoma between September 1995 and December 2010 were retrospectively reviewed to evaluate the following outcome parameters: technical success (TS), functional success (FS), early and late complications, stent patency and survival. Patients were followed from stent insertion until death or stent occlusion. Patients were divided into 3 groups according to the Bismuth classification (Group 1, type I; Group 2, type II; Group 3, type>III).

Results

The initial stent insertion was successful in 450 (93.8%) patients. TS was achieved in 204 (88.3%) patients treated with PS and in 246 (98.8%) patients palliated with SEMS ($p<0.001$). In the intention-to-treat (ITT) analysis, the FS in patients treated with SEMS (97.9%) was significantly higher than in patients treated with PS (84.8%) ($p<0.001$). Late complications occurred in 115 (56.4%) patients treated with PS and 60 (24.4%) patients treated with SEMS ($p<0.001$). The median duration of stent patency in weeks (w) were as follows: 20 w in patients palliated with PS and 27 w in patients treated with SEMS ($p<0.0001$). In Group 2, the median duration of PS patency was 17 w and 18 w for unilateral and bilateral placement, respectively ($p=0.0004$); the median duration of SEMS patency was 24 w and 29 w for unilateral and bilateral placement, respectively ($p<0.0001$).

Conclusions

SEMS insertion for the palliation of hilar cholangiocarcinoma offers higher technical and clinical success rates in the ITT analysis as well as lower complication rates and a superior cumulative stent patency when compared with PS placement in all Bismuth classifications. The cumulative patency of bilateral SEMS or PS stents was significantly higher than that of unilateral SEMS or PS stents, with lower occlusion rates in Bismuth II patients.

Background

Cholangiocarcinoma (CCA) is the primary cancer of the bile ducts and it arises from the malignant transformation of cholangiocytes, which are the epithelial cells that line the biliary apparatus. Although it comprises only 10-15% of hepatobiliary neoplasms, the incidence of CCA has increased during the past 3 decades [1]. Hilar CCA was first recognized as a distinct clinical entity in 1965 when Klatskin [2] reported on a series of 13 patients. Malignancies of the biliary hilum have an extremely poor prognosis, with a 5-year survival rate of less than 10% [3]. In the majority of cases, curative resection is not a therapeutic option, and palliation is the main goal of therapy [3, 4]. The relief of biliary obstruction not only reduces jaundice and associated pruritus but also improves related symptoms such as anorexia and disturbed sleep patterns and leads to an improved quality of life [5]. Endoscopic biliary drainage is preferable to percutaneous or surgical procedures and has become the standard of care because of its low invasiveness [4, 5, 6, 7].

Endoscopic palliative bile duct drainage was first reported by Soehendra et al [8]. Currently, two types of endoscopic stents are available. With the introduction of duodenoscopes with 4.2-mm working channels in 1982, the endoscopic insertion of large-bore plastic biliary stents (PS) became possible [9]. The main disadvantage of plastic endoprostheses is a relatively high occlusion rate caused by biliary sludge, which occurs at a median interval of 3 to 4 months after placement [3]. First described in 1989 [10, 11], self-expandable metal stents (SEMS) are available with different lengths, diameters and delivery devices. SEMS with a maximum diameter of 10 mm theoretically offer the optimal conditions for long-term drainage; however, only one prospective randomized trial has compared PS with SEMS in the management of patients with hilar biliary obstruction [12]. In that study, Wagner et al. reported that SEMS placement resulted in higher long-term patency rates and higher technical success rates with diminished costs. One study [13] reviewed a small number of consecutive patients who underwent SEMS or PS placement for hilar obstruction and also reported that SEMS yielded better outcomes. A recent paper [14] comparing the clinical effectiveness of SEMS and plastic stents in patients with inoperable hilar CCA showed a significantly better stent patency for all Bismuth classifications [15] when metal stents were used. However, few comparative data are available from a large number of patients to address whether PS or SEMS is preferable for palliating malignant hilar obstruction, and it remains unclear whether or not SEMS placement is superior to plastic stent drainage.

The benefit of bilateral versus unilateral stenting continues to be debated [16, 17, 18, 19, 20, 21]. Only one randomized controlled study using PS has compared unilateral with bilateral drainage [19], and the authors concluded that the insertion of more than one endoprostheses did not appear to be justified as a routine procedure and that single-stent insertion was effective. However Deviére et al [20] using two or more PS to achieve complete drainage of the biliary system showed that this approach improves survival and reduces procedure-related mortality and the incidence of early and late cholangitis when compared to incomplete drainage. Thus far, no prospective randomized study has compared the unilateral and bilateral placement of SEMS. A recent study suggested more favorable cumulative stent patency with bilateral over unilateral SEMS placement in cases of hilar obstruction, especially in cases of CCA [21]. The endoscopic deployment of bilateral SEMS is technically challenging, even for experienced endoscopists. Various techniques have been described for bilateral SEMS placement [5, 16, 21, 22, 23, 24, 25, 26, 27]. The most commonly used technique is the stent-within-stent method, in which a wide mesh SEMS (although a stent with a closed-cell configuration can also be used) is inserted into one side of the hepatic duct, and a second SEMS is positioned on the contralateral side across the mesh [22, 23]. Recently, SEMS with extra-wide open mesh designs in the central portion to facilitate bilateral placement have been described, and the initial trials have shown encouraging results [24, 25]. Other studies have described techniques to place the SEMS in a side-by-side configuration, with good results [5, 16, 21]. Recently, a novel SEMS was developed with a 6 French delivery system to allow a side-by-side pre-deployment insertion of bilateral SEMS [26].

The aim of this article is to report on the experience of our single tertiary-level center in the endoscopic palliation of hilar CCA during the last 15 years. In this study, we compared the technical success, functional success, early complications, late complications, stent patency and survival for patients treated with PS and SEMS. We also compared unilateral and bilateral stent placement according to the Bismuth classification.

Material and Methods

Patients and study design

This was a retrospective review of cases of endoscopically inserted plastic and metal stents in patients with unresectable hilar CCA over a period of 15 years (September 1995 to December 2010). Data were retrospectively reviewed from a dedicated prospective computerized endoscopy database at a tertiary referral academic center (Center of Gastroenterology, Cuf Infanto Santo Hospital, Lisbon, Portugal). The diagnosis was based on ultrasound, computed

tomography, magnetic resonance cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), clinical history and histologic or cytologic confirmation by pathologists. Patients were considered to have an unresectable malignancy based on their medical fitness or disease extent. The follow-up continued from stent insertion until patient death or stent occlusion. The endoscopic and medical reports of these patients were reviewed together with the radiological findings to determine the outcome in terms of the following parameters: technical success, functional success, early and late complications, stent patency and survival. Hilar obstructions were characterized by the Bismuth classification [15].

Patients were divided into 3 groups: Group 1 included patients with a type I malignant stricture, Group 2 included patients with a Bismuth type II cancer and Group 3 included patients with Bismuth type III or IV strictures. Patients in Group 1 were further divided into Group 1A if they were palliated with PS or Group 1B if they underwent SEMS placement. Patients in Group 2 had unilateral or bilateral placement of PS or SEMS and were divided in 4 subgroups: Group 2A was palliated with 1 PS, Group 2B was palliated with bilateral PS, Group 2C underwent 1 SEMS placement and Group 2D underwent bilateral SEMS placement. Patients in Group 3 were divided into Group 3A if they underwent PS placement or Group 3B if they received an SEMS. The intention-to-treat (ITT) and per protocol (PP) methods were used in this analysis. The ITT analysis was based on the original total cohort of patients enrolled. The PP analysis was based on the subset of patients with successful unilateral or bilateral stent placement. Patient characteristics and stent insertions were evaluated by the ITT analysis. Stent patency, complications and survival were evaluated by the PP analysis. All patients provided full, informed written consent prior to their procedures. The study was approved by our institutional review board.

Definition of events

Technical success (TS) or successful stent insertion was defined as the passage of the stent across the stricture along with the flow of contrast medium and/or bile through the stent. Functional success (FS) or successful drainage was defined as a decrease in bilirubin to less than 75% of the pre-treatment level within the first month. Early and late complications were defined as those occurring within 30 days and after 30 days of stent placement, respectively, according to the criteria of Cotton et al. [28]. Occlusion of the stent was considered if patients had recurrent jaundice with cholestasis or cholangitis (fever, increase in serum bilirubin, leucocytosis) and dilatation of intrahepatic bile duct, revealed by imaging. Stent patency was defined as the period between stent insertion and stent occlusion or patient death.

Technique

A prophylactic treatment with broad-spectrum antibiotics was initiated before the procedure and continued for 10 days after. All procedures were performed by 2 experienced pancreatobiliary endoscopists (M.L. and J.C.). ERCP procedures were performed with the patient in the prone position under sedation, with propofol administered by an anaesthesiologist. All endoscopic examinations were performed using a therapeutic duodenoscope (TJF-145, TJF-160R, TJF-160VR, TJF-Q180V, Olympus, Tokyo, Japan). The strategy used for biliary decompression was selected at the discretion of the endoscopist, based on the location and complexity of the strictures as well as the expected time of survival of the patient. Plastic stents were not changed routinely, and patients were treated if occlusion of the stent or cholangitis developed. Unilateral PS stenting was done with 10 French stents. If the patient had bilateral PS placed, at least one of the stents had a diameter of 10 French. Biliary sphincterotomy was performed in all cases to facilitate single or bilateral stent placement.

For bilateral SEMS placement, we routinely use a previously described stent-within-stent technique (Figure 1) [22, 23]. In a small subset of patients, bilateral drainage with SEMS was achieved using 2 different side-by-side techniques. In the first technique, as described in detail elsewhere [26], we used a novel non-foreshortening metal stent with a 6 French delivery system (Zilver 635; Cook Medical, Winston-Salem, NC) to enable side-by-side bilateral hilar deployment because duodenoscopes with 4.2-mm working channels allow the simultaneous delivery of both stents. After bilateral guidewire placement, the Zilver 635 biliary uncovered metal stent deployment system was sequentially introduced over the guidewires into the left and right hepatic ducts in a side-by-side fashion. Biliary dilatation was performed as needed to facilitate stent placement. The stents were then carefully deployed across the strictures in alternating/sequential fashion between the left and right sides until full deployment was achieved (Figure 2). All SEMS used had a 10-mm luminal diameter and an 80-mm length. In the second technique, we also performed placement of bilateral stents in a sequential fashion [5, 16, 21]. After the insertion of bilateral guidewires, we performed bilateral balloon dilatation of the stenosis. The first SEMS was usually placed in the left hepatic duct. The second SEMS was advanced to the right hepatic duct after the expansion of the initial stent. Stents are usually placed with their distal ends at the same level intraductally, i.e, not in a transpapillary position (Figure 3). Special care was taken to place both SEMS at the same level to facilitate re-entry in future if needed.

Follow-up

Follow-up continued from stent insertion to the death of the patient or to the stent occlusion for all patients. Only patients in whom the stent occlusion was reviewed in our center were included in the study. Follow-up was obtained by reviewing clinical notes provided by regular clinic visits or by medical assistant reports, lab results, imaging, data on our prospective database and structured telephone interviews with medical assistants or family during follow-up or at the time of manuscript preparation. Patients with incomplete follow-up were excluded from the study. All of the patients were dead at the time of manuscript preparation.

Statistical analysis

Student's *t* test and the χ^2 test were used to calculate the statistical significance of different demographic and clinical variables when appropriate. Cumulative stent patency and cumulative patient survival were calculated by the Kaplan-Meier method, and groups were compared by the log-rank test. All reported *P*-values were for two-sided test and a *P*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 18 (SPSS Inc., Chicago, Illinois).

Results

Patients

A total of 12850 records for ERCP procedures that occurred between September 1995 and December 2010 were identified in the endoscopy database. In total, 528 records for patients with hilar CCA who underwent endoscopic insertion of plastic and metal stents were selected in the endoscopy database. Forty-eight of these patients were excluded for the following reasons: incomplete data concerning endoscopic procedures and follow-up (37 patients) and further surgery after the initial stenting (11 patients).

In total, 480 patients (249 male and 231 female) with a mean age of 74.6 years (range: 45-96) were enrolled in the study. There were 231 and 249 patients palliated with PS and SEMS, respectively. The characteristics of the patients are shown in Table 1. There were no significant differences in the demographics between patients treated with PS and those treated with SEMS or for unilateral and bilateral stenting, overall and among the groups defined earlier in the Methods section.

Stent insertion

The outcomes of the stent insertion are shown in Tables 2 and 3. The initial stent insertion (Table 2) was successful in 450 (93.8%) patients. TS was achieved in 204 (88.3%) and 246 (98.8%) patients palliated with PS and SEMS, respectively. There were 30 patients with failed endoscopic endoprostheses placement. Among these patients, 10 received percutaneous drainage, 4 underwent surgery and the remaining 16 were considered unfit for further interventions and transferred to palliative care. FS was achieved in 440 patients (ITT = 91.6%; PP = 97.8%). All patients with failed successful drainage were in Group 3 (8 in Group 3A and 2 in Group 3B). These patients showed no improvement of bilirubin after the stent placement because of extensive hepatic involvement. Five of these patients underwent bilateral percutaneous biliary drainage without significant reductions in the bilirubin level. The remaining 5 patients had significant comorbidities and very advanced disease, and they were not candidates for further intervention. SEMS comparison with PS provided significantly different degrees of technical success, overall ($p < 0.001$) and in Group 1 ($p = 0.036$), Group 2 ($p = 0.008$) and Group 3 ($p < 0.001$). In the ITT analysis, the FS in patients treated with SEMS was significantly higher than that in patients treated with PS overall ($p < 0.001$) and in Group 1 ($p = 0.036$), Group 2 ($p = 0.008$) and Group 3 ($p < 0.001$). In the PP analysis, the functional success in patients treated with SEMS was significantly higher than that in patients treated with PS both overall ($p = 0.026$) and in Group 3 ($p < 0.001$).

Stent insertion outcomes for Group 2 are shown in Table 3. Bilateral stenting was performed in 38 patients with PS and in 42 patients with SEMS. Bilateral PS was attempted in 40 patients, and stents were successfully placed in 38 patients (95%). The remaining 2 patients had unilateral PS placement. Failure to place the guidewire in the contralateral duct was the reason for failure in these 2 patients. Bilateral SEMS placement was attempted in 45 patients, and successful bilateral drainage was achieved in 42 (93.3%) patients. The remaining 3 patients were treated with unilateral SEMS. The main reason for unsuccessful bilateral SEMS insertion was a failure to place the guidewire into the contralateral hepatic duct through the interstices of the initial SEMS. There were no significant differences in the ITT and PP analyses of TS and FS in patients with unilateral vs. bilateral PS and SEMS placement.

Complications

Early complications

Early complications (Table 4) occurred in 17 (8.3%) patients treated with PS and in 5 (2.0%) patients who underwent SEMS placement ($p = 0.002$). Early complications included pancreatitis, bleeding and stent failure (occlusion and migration). There was no procedure-related mortality.

Late complications

Late complications (Table 4) occurred in 115 (56.4%) patients treated with PS and in 60 (24.4%) patients treated with SEMS, and these differences were significant ($p < 0.001$). All late complications were stent-related and included migration (only in PS patients), occlusion and cholangitis. There were significant differences in occlusion and cholangitis when comparing patients treated with PS and those treated with SEMS. Repeat endoscopic biliary drainage because of stent failure was required in 56.4% of patients with PS. In the group of patients with SEMS, 75.6% did not require any further intervention. In Group 2, 17/21 (80.9%) patients with unilateral PS placement and 13/38 (34.2%) patients treated with bilateral PS stenting ($p < 0.001$) had stent occlusion, respectively. Repeat endoscopic biliary drainage because of stent occlusion was required for 11/35 (31.4%) patients treated with one SEMS versus 5/42 (11.9%) patients with bilateral SEMS placement ($p = 0.036$).

Stent patency

Patients treated with PS and SEMS had a median time to occlusion of 20 weeks (range: 3-25; mean: 18.9) and 27 weeks (range: 8-54; mean: 27.1), respectively. Kaplan-Meier analysis showed that the cumulative stent patency times were significantly longer in patients treated with SEMS than in those treated with PS ($p < 0.0001$); the estimated relative risk of occlusion (hazard ratio-HR) was 2.6731-fold higher in the PS group than in the SEMS group, (95% CI 2.1416-3.3365) (Figure 4). The median stent patency time was 22 weeks (range: 14-25; mean: 22) in Group 1A and 35 weeks (range: 25-54; mean: 35) in Group 1B. These differences were significant ($p < 0.0001$); the HR was 4.6219 higher in Group 1A than in Group 1B, (95% CI 3.2799-6.5129). In Group 3A, stent occlusion occurred after a median time of 12 weeks (range: 3-14; mean: 11), whereas in Group 3B, the median time to occlusion was 17 weeks (range: 8-20; mean: 16) ($p < 0.0001$). The HR was 3.8195-fold higher in Group 3A than in Group 3B, (95% CI 1.9186-7.6037). The median stent patency time was 17 weeks (range: 7-18; mean: 15) in Group 2A (PS, unilateral) and 18 weeks (range: 12-22; mean: 18) in Group 2B (PS, bilateral). The median stent patency time was 24 weeks (range: 18-26; mean: 23) in Group 2C (SEMS, unilateral) and 29 weeks (range: 22-28; mean: 30) in Group 2D (SEMS, bilateral). Kaplan-Meier analysis showed a significant difference in the cumulative stent patency time for bilateral and

unilateral plastic stenting (p = 0.0004), and the HR was 2.2355-fold higher in Group 2A than in Group 2B (95% CI 1.1787-4.2399) (Figure 3). The cumulative stent patency time for bilateral SEMS stenting was significantly longer than that for unilateral SEMS stenting (p < 0.0001), with an HR that was 3.6934 higher in Group 2C than in Group 2D (95% CI 2.0755-6.5724) (Figure 5).

Survival

The median survival time was 46 weeks (range: 9-61; mean: 46.1) and 45 weeks (range: 7-59; mean: 44.9) in patients treated with PS and SEMS, respectively. Kaplan-Meier analysis showed no differences in the cumulative survival between the 2 groups (p = 0.18), with an HR 1.1777-fold higher in the SEMS group than in the PS group (95% CI 0.9104-1.5236) (Figure 6).

Discussion

According to our findings, in a retrospective review of 480 patients, the palliation of hilar CCA with SEMS was associated with successful stent insertion and successful drainage in the ITT analysis as well as a lower complication rate and increased cumulative stent patency compared with PS placement for all Bismuth classifications. The outcome in terms of FS after PS insertion in patients with advanced disease (Group 3) was very poor. In a subset of patients with Bismuth type II hilar strictures, the cumulative stent patency of bilateral SEMS or PS placement was significantly higher than that of unilateral SEMS or PS stenting, with lower occlusion rates. In this group of patients, bilateral SEMS placement offered the best results in terms of cumulative stent patency and occlusion rates.

Our data results from a single academic tertiary center which is a referral center for ERCPs especially difficult cases and tumors. It is the largest center in the country receiving patients from 20-30 hospitals all over the southern part of the country. We perform an average of 850 ERCPs per year, thus having a huge inclusion potential as far as hilar CCAs are concerned. Furthermore our center is the main referral center for endoscopic palliation of malignancies, coming from oncology, gastroenterology and surgical centers.

There have been few comparative studies regarding PS and SEMS placement in hilar CCA, and because such data are scarce, no clear consensus has been reached regarding the optimal approach in these patients. Wagner et al. [12] reported the only prospective randomized study comparing SEMS and PS placement in hilar obstruction. Twenty patients with type II-IV hilar malignancies were randomly assigned to PS (n = 9) or SEMS (n = 11), which were placed by a combined endoscopic-percutaneous technique. Although the sample size was small, and most of the stents were placed by the percutaneous route, the authors observed a higher long-term

patency with a decreased incidence of cholangitis, higher technical success rates, significantly lower re-intervention rates for stent failure and diminished costs with reduced hospital stay for patients who received SEMS. One study [13] prospectively assessed the 30-day outcomes of endoscopic palliation with PS (n = 28) and SEMS (n = 34) performed for malignant hilar obstruction in 62 consecutive patients. Adverse outcomes included stent occlusion, cholangitis, migration and the need for re-intervention. By logistic regression, PS placement was associated with short-term adverse outcomes (odds ratio: 6.32; 95% confidence interval: 1.23-32.56), independent of disease severity, Bismuth class or drainage quality. Raju et al. [14] recently presented a retrospective review of 100 patients who underwent PS (n=52) and SEMS (n=48) placement for inoperable hilar CCA. Patients were followed to death, re-intervention or for at least one year. Stent patency and patient survival were the main end-points examined. Patients were divided into 3 groups according to the Bismuth classification, similarly to our study, and there was a high percentage of type III and type IV patients (65%). The TS was high in both groups (95.8% vs. 94.2% in favor of SEMS). The number of bilateral stents was too low for a statistical comparison. The SEMS group demonstrated a significantly higher patency (5.56 vs. 1.86 months) and required fewer re-interventions for stent obstruction. The authors concluded that the patency of metallic stents was superior to that of PS in all Bismuth classifications, although a clear comparison between the groups was not presented in the paper.

Our study suggests that patency of SEMS is significantly longer with lower occlusion rates when compared with PS. In our paper, the duration of patency in the plastic stent group was longer than previously reported [14, 29]. This finding may be due to the result of the high number of patients with Bismuth type I strictures enrolled in our study, as PS placed in patients with more advanced disease tend to have shorter patency times [14, 29]. The use of SEMS in hilar CCA has multiple theoretical advantages, including a small and flexible delivery system that allows for better technical success and flexibility and a mesh network that enables not only a more stable conformation with the tortuous hilar anatomy but also drainage of subsegmental ducts. In our study, we found better TS when using SEMS, which could be related to the inherent characteristics of the stents, as long and inflexible large-bore plastic stents are difficult to place in complex strictures. Overall, the TS was high in both groups (88.3% in the PS group and 98.8% in the SEMS group), and these differences were significant. More complex strictures showed greater differences in TS when comparing PS with SEMS. Even in Group 1, there were significant differences between the two stent types (95.7% versus 100%), and this finding reflects our large sample size. As expected, the FS of PS placement in

patients with more advanced disease (Group 3) was lowest, not only in the ITT analysis but also in the PP analysis. This finding could be the result of the lack of side holes in this type of stent, which can result in reduced drainage from secondary branch ducts. In our study, PS were not routinely changed, which was the main cause of the significantly higher rate of late complications associated with stent failure in patients treated with PS. Overall, our study suggests that PS stenting is associated with worse outcomes than SEMS placement; therefore, endoscopic palliation with PS should be reserved for pre-surgical biliary drainage when needed and for patients with a short expected survival time.

The optimal technique for endoscopic palliative metal placement and the benefits of bilateral versus unilateral stenting are still controversial and highly debated. De Palma et al. [19] reported the only prospective randomized controlled study comparing unilateral and bilateral drainage using plastic stents. In that study, 157 consecutive patients with hilar obstruction caused by several malignancies were randomly assigned to unilateral (n=79) or bilateral (n=78) stent placement and followed prospectively. In the ITT analysis, unilateral placement had a significantly higher rate of stent insertion (88.6% vs. 76.9%) and a lower rate of complications and early cholangitis than bilateral placement. The authors concluded that the routine insertion of more than one stent would not be justified and that single stent insertion avoids the risk of further procedure-related complications and mortality. However these results need to be interpreted with caution because of some study biases. Information about stent patency and occlusion rates in both groups was not available. Furthermore subgroup analysis of patients was not done and there was a high number of patients with Bismuth type I stricture included for which placement of one stent is sufficient; thus it is impossible to find out how results might have been affected by their inclusion. A recent retrospective review of 46 patients with hilar malignant obstruction compared unilateral (n = 17) and bilateral (n = 29) SEMS stenting [21] and found no significant differences in TS (100% vs. 90%), FS (100% vs. 96%), early (0% vs. 10%) or late complications (65% vs. 54%). Cumulative stent patency was significantly increased with bilateral stenting (median patency of 488 days vs. 210 days, p = 0.009), especially in cases of CCA.

Endoscopic bilateral metal drainage poses particular challenges for endoscopists and has been considered to be more technically challenging than unilateral stenting [5, 16, 18, 21, 22, 23, 24, 25, 26, 27, 30]. Various techniques have been described for bilateral SEMS placement, and in the absence of a truly Y-shaped SEMS, the creation of a Y-shaped stent configuration across the hilar bifurcation requires the placement of straight SEMS in either a nested or parallel configuration. Most endoscopists use the stent-within-stent technique previously described

[22, 23] in this paper. Theoretically, stent-within-stent deployment may prevent bile influx into the area of stent overlap, leading to sludge formation. Furthermore, tumor ingrowth can occur more easily through an expanded stent mesh in the area of overlap. In addition, a nested SEMS configuration can be difficult to revise when cancer ingrowth obstructs the stents. To facilitate nested Y-shaped SEMS placement across the biliary confluence, SEMS placement with an extra-large open mesh in the central portion of the stent has been described. Kim et al. [24] reported their experience in 34 patients, in which TS was achieved in 85.3% patients, and the FS in the PP analysis was noted to be 100%. Stent obstruction occurred in 31% of the patients, and the median duration of stent patency was 239 days. To overcome the theoretical vulnerability of the wide mesh stent to tumor ingrowth, Park et al. [25] described a new stent for nested bilateral stenting without the wide-wire mesh design. They reported a TS rate of 94.3% and an FS rate in the PP analysis of 100%. Interestingly, the re-intervention rate for stent occlusion was only 6%. The median stent patency was 150 days.

Endoscopic bilateral metal stenting can also be accomplished using a parallel arrangement known as side-by-side deployment [5, 16, 21]. It has been reported that this technique occasionally causes portal vein occlusion and increases the rate of cholangitis because of the excessive expansion of the bile duct by parallel stents [21]. Dumas et al. [16] reported a TS of 88% (22/25 patients) for bilateral metal stenting with side-by-side deployment. In some cases, this technique is impossible once one SEMS has been deployed, even if a second guidewire is already in the contralateral duct, because the first stent may press into the bile-duct wall and prevent passage of the delivery system for the second SEMS. One solution for this problem [5] is to place a temporary plastic stent in a sub-hilar position, with 2 guidewires placed in the right and left hepatic ducts, before deployment of the first SEMS. After the placement of the first SEMS beside the plastic stent, the delivery catheter for the second SEMS is advanced into the contralateral duct, with the plastic stent maintaining the passage. Following the deployment of the second SEMS, the plastic stent is removed. Another solution to side-by-side SEMS placement is to use the novel SEMS with a 6F delivery system. Using this technique, Chennat et al. [26] reported a TS of 100% (10/10 patients) and a median stent patency of 130 days. The side-by-side approach may facilitate subsequent endoscopic access to both drained ductal segments. Overall, these different techniques have similar results. There is no consensus regarding the best technique for bilateral metal stenting, and no study has compared the outcome of the various techniques in terms of TS, stent patency, complications and the need for re-intervention.

In our study, bilateral stenting was only reported in patients with Bismuth type II strictures because in our retrospective review, patients with Bismuth type III and IV strictures who underwent bilateral stenting were short in numbers and had an incomplete follow-up with important data missing; therefore, they could not be included in the study. Furthermore we avoid attempting bilateral stenting in very advanced disease because in cases of complex hilar strictures bilateral stenting may not be sufficient for complete drainage. In these patients complete drainage is achieved by 3 or more metal stents and even successful bilateral stenting in advanced disease can leave some ducts filled with contrast undrained [31]. Injection of contrast into intrahepatic ducts that cannot be adequately drained should be avoided, as this practice is associated with worse outcomes [18]. A recent study by Costamagna group suggests that multiple SEMS can be placed in hilar malignant strictures with promising results and that SEMS malfunctions can be easily managed [32]. In our study using metal stents, bilateral placement was successful in 42/45 (94.3%) patients, and these results are comparable to those of other reports that found a TS rate between 80-100% [16, 21, 23, 24, 25, 26]. The median stent patency time of our bilateral metal stenting was 29 weeks, which was similar to the 130 to 239 day range [16, 21, 23, 24, 25, 26] reported by other authors, except for Naitoh et al. [21], who reported a median stent patency of 488 days. We found that bilateral metal stenting was significantly better than unilateral placement in patients with Bismuth type II strictures, which was similar to the results of Naitoh et al. [21] obtained in a group of patients with hilar CCA, and we did not experience higher complication rates (such as early cholangitis) in patients with bilateral stenting. These authors suggested that better results with bilateral stenting were associated with the side-by-side technique; however, we used a stent-within-stent technique in up to 90% of our patients, and our results were similar in terms of better bilateral patency, which suggests that no particular endoscopic technique for bilateral metal stent placement is more effective than another in terms of patency and occlusion rates. We also found a significantly lower occlusion rate with bilateral metal stenting (11.9% versus 31.4%) compared with unilateral SEMS placement. Our bilateral stent occlusion rate compares favorably to previously reported values of between 23 and 40% [21, 23, 24, 25, 26], although a recent study reported an occlusion rate of 6% [25].

We also found that bilateral PS stenting was significantly better than unilateral PS placement in terms of patency and occlusion rates. The differences in patency were small (median 17 weeks; mean 15 weeks for unilateral versus median 18 weeks; mean 18 weeks for bilateral) but statistically significant. In contrast to the present study, De Palma et al. [19] did not report stent patency and occlusion rates. Furthermore, in the study of De Palma et al., the poor

results of bilateral stenting from the ITT analysis with high rates of cholangitis and lower TS suggest that the opacification of both lobes was performed even in patients with advanced disease. As mentioned earlier in this paper we did not attempt to place 2 PS stents in patients with advanced disease (Bismuth III and IV strictures) where bilateral stenting may not be sufficient for complete drainage, leaving ducts undrained with associated cholangitis. Taken together, these findings suggest that bilateral stenting is better than unilateral stenting, and the best results are produced with bilateral metal placement especially in patients with Bismuth type II strictures.

We did not find significant differences in survival, although some of the patients with bilateral metal stenting had improved survival time especially those free from re-intervention and occlusion with cholangitis. Although cholangitis has a negative impact on survival time, survival depends mainly on the disease stage and we had more patients (49 vs. 72) with advanced disease (Group 3) in the SEMS group, favoring survival in the PS group, although without statistical significance.

Several limitations of our study should be taken into account. This was a retrospective study from a single tertiary center. Bilateral stenting was only reported in patients with Bismuth type II hilar strictures. The study was performed over 15 years using different materials, guidewires, stents and techniques, and this variation could have affected the rates of TS and FS, especially considering the plastic stents used in the 1990s. We suggest that further studies with a prospective randomized controlled design are needed in which bilateral and multiple metal stenting (in complex hilar strictures and advanced disease) can be compared with unilateral placement of SEMS across all Bismuth classifications of hilar CCA in terms of TS, stent patency, need for re-intervention, complications and improvement of the quality of life. In these proposed studies, different techniques for bilateral metal stent placement should also be compared.

The strengths of our study are the large number of patients included, both overall and in the different Bismuth classifications, when comparing plastic with metal stents, as well as the examination of bilateral stenting using both plastic and metal stents in a large subset of patients, which allowed comparisons between the outcomes. To our knowledge, this is the largest series of endoscopic palliation of hilar CCA ever reported.

In conclusion, our data suggest that endoscopic palliation of hilar CCA with SEMS should be considered the standard of care, as it offers higher technical and clinical success rates in an ITT analysis as well as lower complication rates and superior cumulative stent patency when

compared with PS placement for all Bismuth classifications. The cumulative stent patency of bilateral SEMS or PS stenting was significantly higher than that of unilateral SEMS or PS stenting, with lower occlusion rates in Bismuth type II patients. In this group of patients, bilateral SEMS placement offered the best results in terms of cumulative stent patency and the need for repeat endoscopic biliary drainage resulting from stent occlusion.

Acknowledgments

The authors are indebted to Maria Filipa Costa Neves Santos Silva, MBA for her critical revision of the statistical analysis

References

1 – Lazaridis KN, Gores GJ. **Cholangiocarcinoma**. *Gastroenterol* 2005; **128**: 1655-1667

2 – Klatskin G. **Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis: an usual tumor with distinctive clinical and pathologic features**. *Am J Med* 1965; **38**: 241-247

3 – Cheng JL, Bruno MJ, Bergman JJ, Rauws EA, Tytgat GN, Huibregtse K. **Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents**. *Gastrointest Endosc* 2005; **56**: 33-39

4 – Gerges C, Schumacher B, Terheggen G, Neuhaus H. **Expandable metal stents for malignant hilar biliary obstruction.** *Gastrointest Endosc Clin N Am* 2011; **21**: 481-97

5 – Hookey LC, Le Moine O, Deviere J. **Use of a temporary plastic stent to facilitate the placement of multiple self-expanding metal stents in malignant biliary hilar strictures.** *Gastrointest Endosc* 2005; **62**: 605-609

6 – Speer AG, Cotton PB, Russell RC, Mason RR, Hatfield AR, Leung JW, MacRae KD, Houghton J, Lennon CA. **Randomized trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice**. *Lancet* 1987; **2**: 57-62

7 – Andersen JR, Sorensen SM, Kruse A, Rokkjaer M, Matzen P. **Randomized trial of endoscopic endoprostheses versus operative bypass in malignant obstructive jaundice**. *Gut* 1989; **30**: 1132-1135

8 – Soehendra N, Reynders-Frederix V. **Palliative Bile Duct Drainage – A new endoscopic method of introducing a transpapillary drain**. *Endoscopy* 1980; **12**: 8-11

9 - Huibregtse K, Tytgat GN. **Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis**. *Gut* 1982; **23**: 371-375.

10 - Huibregtse K, Cheng J, Coene PP, Fockens P, Tytgat GN. **Endoscopic placement of expandable metal stents for biliary strictures-a preliminary report on experience with 33 patients**. *Endoscopy* 1989; **21**: 280–282

11 - Neuhaus H, Hagenmuller F, Classen M. **Self-expanding biliary stents: preliminary clinical experience**. *Endoscopy* 1989; **21**: 225–228

12 - Wagner HJ, Knyrim K, Vakil N, Klose KJ. **Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial.** *Endoscopy* 1993; **25**: 213–18.

13 – Perdue DG, Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Overby CS, Ryan ME, Bochna GS, Snady HW, Moore JP. **Plastic versus self-expanding metallic stents for malignant hilar obstruction: a prospective multicenter observational cohort study.** *J Clin Gastroenterol* 2008; 42: 1040-1046

14 - Raju RP, Jaganmohan SR, Ross WA, Davila ML, Javle M, Raju GS, Lee JH. **Optimum palliation of inoperable hilar cholangiocarcinoma: comparative assessment of the efficacy of plastic and self-expanding metal stents.** *Dig Dis Sci* 2011; **56**: 1557-1564

15 - Bismuth H, Castaing D, Traynor O. **Resection or palliation: priority of surgery in the treatment of hilar cancer.** *World J Surg* 1988; **12**: 39–47

16 - Dumas R, Demuth N, Buckley M, Peten EP, Manos T, Demarquay JF, Hastier P, Caroli-Bosc FX, Rampal P, Delmont JP. **Endoscopic bilateral metal stent placement for malignant hilar stenoses: identification of optimal technique**. *Gastrointest Endosc* 2000; **51**: 334–338

17 - Polydorou AA, Chisholm EM, Romanos AA, Dowsett JF, Cotton PB, Hatfield AR, Russell RC. **A comparison of right versus left hepatic duct endoprosthesis insertion in malignant hilar biliary obstruction.** Endoscopy 1989; **21**: 266–271

18 - *Chang WH, Kortan P, Haber GB.* **Outcome in patients with bifurcation tumors who undergo unilateral versus bilateral hepatic duct drainage.** *Gastrointest Endosc* 1998; **47**: 354–362

19 - De Palma GD, Galloro G, Siciliano S, Iovino P, Catanzano C. **Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study**. *Gastrointest Endosc* 2001; **53**: 547–53

20 – Deviere J, Baize M, Toeuf J, Cremer M. **Long-term follow-up of patients with hilar malignant strictures treated by endoscopic internal biliary drainage**. *Gastrointest Endosc* 1988; **34**: 95-101

21 – Naitoh I, Ohara H, Nakazawa T, Ando T, Hayashi K, Okumura F, Okayama Y, Sano H, Kitajima Y, Hirai M, Ban T, Miyabe K, Ueno K, Yamashita H, Joh T. **Unilateral versus bilateral**

endoscopic metal stenting for malignant hilar biliary obstruction. *J Gastroenterol Hepatol* 2009; **24**: 552-557

22 – Neuhaus H, Gottlieb K, Classen M. **The "stent through wire mesh technique" for complicated biliary strictures.** *Gastrointest Endosc* 1993; **39**: 553-556

23 – Chahal P, Baron T. **Expandable metal stents for endoscopic stent-within-stent placement for malignant hilar biliary obstruction**. *Gastrointest Endosc* 2010; **71**: 195-199

24 - Kim JY, Kang DH, Kim HW, Choi CW, Kim ID, Hwang JH, Kim DU, Eum JS, Bae YM. **Usefulness of slimmer and open-cell-design stents for endoscopic bilateral stenting and endoscopic revision in patients with hilar cholangiocarcinoma (with video)**. *Gastrointest Endosc* 2009; **70**: 1109-1115

25 – Park DH, Lee SS, Moon JH, Choi HJ, Cha SW, Kim JH, Seo DW, Lee SK, Park SH, Lee MS, Kim SJ, Kim MH. **Newly designed stent for endoscopic bilateral stent-in-stent placement of metallic stents in patients with malignant hilar biliary strictures: multicenter prospective feasibility study (with videos).** *Gastrointest Endosc* 2009; **69**: 1357-1360

26 – Chennat J, Waxman I. **Initial performance profile of a new 6F self-expanding metal stent for palliation of malignant hilar biliary obstruction**. *Gastrointest Endosc* 2010; **72**: 632-636

27 – Liberato M, Pontes J: **Tumores de las Vias Biliares y del Pancreas.** In Endoscopia Digestiva Diagnóstica y Terapéutica. Edited by Vázquez-Iglesias J, Aguirre P. Madrid: Editorial Medica Panamericana; 2008: 551-572

28 - Cotton P, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. **Endoscopic sphincterotomy complications and their management: An attempt at consensus.** *Gastrointest Endosc* 1991; **37**: 383–393.

29 – Rerknimitr R, Kladcharoen N, Mahachai V, Kullavanijaya P. **Results of endoscopic biliary drainage in hilar cholangiocarcinoma.** *J Clin Gastroenterol* 2004; **38**: 518-523

30 – Kawamoto H, Ishida E, Ogawa T, Okamoto Y, Okazaki H, Kato J, Okada H, Shiratori Y. **Multiple Stenting in Hilar Bile Duct Carcinoma: Three-Branched Partial Stent-in-Stent Deployment with the JOSTENT SelfX**. *Endoscopy* 2004; **36**: 829-830

31 – Larghi A, Tringali A, Lecca P, Giordano M, Costamagna G. **Management of hilar strictures.** *Am J Gastroenterol* 2008; **103**: 458-473

32 – Boskoski I,Ttringali A, Familiari P, Mutignani M, Costamagna G. **Multiple self-expandable metal stents for malignant hilar strictures: patient survival and stent patency [abstract].** *Endoscopy* 2011; **43** (Suppl 1) A13

Figures

Figure 1 Bilateral self-expandable metal stents (SEMS) placement using a stent-within-stent technique.

(A) After deployment of the first stent across the hilar stricture, the guidewire was inserted, under fluoroscopic guidance, into the contralateral hepatic duct trough the interstices of the initial SEMS.

(B) Dilatation of the interstices of the first SEMS with a hydrostatic balloon to facilitate the passage of a second SEMS into the contralateral hepatic duct.

(C) Bilateral SEMS placement obtaining a Y-shaped configuration.

Figure 2 Bilateral metal stenting using side-by-side deployment.

Figure 3 Bilateral metal stenting using the novel 6 French delivery system.

(A) Side-by-side bilateral hilar predeployment.

(B) Bilateral hilar postdeployment to form a Y-shaped configuration.

Figure 4 Kaplan-Meier analysis showing that cumulative stent patency was significantly longer in patients treated with self-expandable metal stents (SEMS) than in patients palliated with plastic stents (PS) ($p < 0.0001$).

Figure 5 Cumulative Stent Patency curves by Kaplan-Meier analysis in patients treated using unilateral (Uni) and bilateral (Bil) plastic stents (PS) and self-expandable metal stents (SEMS). Uni PS versus Bil PS ($p = 0.0004$). Uni versus Bil SEMS ($p < 0.0001$).

Figure 6 Kaplan-Meier analysis of cumulative survival shows no differences between patients treated with plastic stents (PS) and self-expandable metal stents (SEMS).

Table 1 Patient characteristics.

	Plastic Stent	Metal Stent	*P* value	Total
Group 1	N=115	N=99		N=214
Sex (%)	60M (52.2), 55F (47.8)	50M (50.5), 49F (49.5)	0.8081	110M (51.4), 104F (48.6)
Age (years)	73.9 (45-88)	74.3 (50-91)	0.7462	74.1 (45-91)
Group 2	N=67	N=78		N=145
Sex (%)	30M (44.8), 37F (55.2)	39M (50), 39F (50)	0.5301	69M (47.6), 76F (52.4)
Age (years)	74.9 (49-93)	74.7 (51-95)	0.8912	74.8 (49-96)
Unilateral	N= 29	N=36		
Sex (%)	13M (44.8), 16F (55.2)[a]	17M (47.2), 19F (52.8)[c]		
Age (years)	74.8 (49-90)[b]	74.8 (53-95)[d]		
Bilateral	N=38	N=42		
Sex (%)	17M (44.7), 21F (55.3)	22M (52.4), 20F (47.8)		
Age (years)	75.0 (50-93)	74.6 (51-92)		
Group 3	N=49	N=72		N=121
Sex (%)	30M (61.2), 19F (38.8)	40M (55.6), 32F (44.4)	0.5351	70M (57.9), 51F (42.1)
Age (years)	75.4 (58-94)	75.1 (56-90)	0.8402	75.2 (56-94)
Total	N=231	N=249		N=480
Sex (%)	120M (51.9), 111F (48.1)	129H (51.8), 120M (48.2)	0.9751	249M (51.9), 231F (48.1)
Age (years)	74.5 (45-94)	74.7 (50-95)	0.8262	74.6 (45-96)

M, male; F, female; Group 1, patients with Bismuth type I malignant strictures; Group 2, patients with Bismuth type II malignant strictures, Group 3, patients with Bismuth type III and IV malignant strictures; Age in mean (range). [a] sex PS unilateral vs. bilateral p = 0.9941. [b] age PS

unilateral vs. bilateral p = 0.9922. [c]sex SEMS unilateral vs. bilateral p = 0.6496. [d]age SEMS unilateral vs. bilateral p = 0.9366

Table 2 Stent insertion outcome.

		Plastic			Metal			*P*		Total		
		n	**TS**	**FS**	**n**	**TS**	**FS**	**TS**	**FS**	**n**	**TS**	**FS**
Group 1	n	115	110	110	99	99	99			214	209	209
	ITT (%)		(95.7)	(95.7)		(100)	(100)	0.036	0.036		(97.7)	(97.7)
	PP (%)			(100)			(100)		-			(100)
Group 2	n	67	59	59	78	77	77			145	136	136
	ITT (%)		(88.1)	(88.1)		(98.7)	(98.7)	0.008	0.008		(93.8)	(93.8)
	PP (%)			(100)			(100)		-			(100)
Group 3	n	49	35	27	72	70	68			121	105	95
	ITT (%)		(71.4)	(55.1)		(97.2)	(94.4)	<0.001	<0.001		(86.8)	(78.5)
	PP (%)			(77.1)			(97.1)		0.001			(90.5)
Total	n	231	204	196	249	246	244			480	450	440
	ITT (%)		(88.3)	(84.8)		(98.8)	(97.9)	<0.001	<0.001		(93.8)	(91.6)
	PP (%)			(96.1)			(99.2)		0.026			(97.8)

ITT, intention-to-treat; PP, per protocol; TS, technical success; FS, functional success; Group 1, patients with Bismuth type I malignant strictures; Group 2, patients with Bismuth type II malignant strictures; Group 3, patients with Bismuth type III and IV malignant strictures.

Table 3 Stent insertion outcome in Group 2.Unilateral and bilateral stenting with SEMS and PS.

		Plastic Stent	Metal Stent
Group 2 (n) 59	Unilateral (n)	21	35
	Bilateral (n)	38	42

Group 2, patients with Bismuth type II malignant strictures.

Table 4 Complications.

	Plastic (n=204)		Metal (n=246)		*P* value	Total	
	n	%	n	%		n	%
Early Complications	17	8.3	5	2	0.002[a]	22	4.9
Stent failure	12	5.9	0	0	<0.001[a]	12	2.7
- occlusion	8	3.9	0	0	0.017[a]	8	1.8
- migration	4	2.0	0	0	0.027[a]	4	0.9
Pancreatitis	4	2.0	3	1.2	0.534	7	1.6
Bleeding	1	0.5	2	0.8	0.670	3	0.7
Late Complications	115	56.4	60	24.4	<0,001[a]	175	38.9
Stent failure	115	56.4	60	24.4	<0,001[a]	175	38.9
- occlusion	106	52.0	60	24.4	<0,001[a]	166	36.9
with cholangitis	68/106	33.3	14/60	5.7	<0,001[a]	83/166	18.2
- migration	9	4.4	0	0	0,001[a]	9	2.0

[a]Statistically significant

Fig 1 (A)

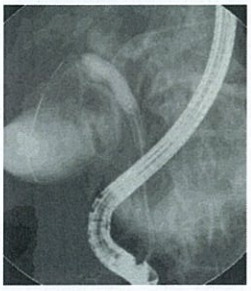

Fig 1 (B)

Fig 1 (C)

Fig 2 (A)

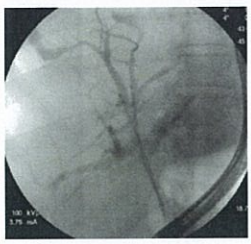

Fig 3 (A)

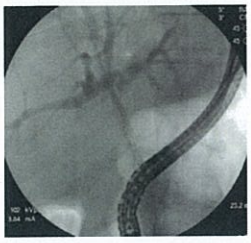

Fig 3 (B)

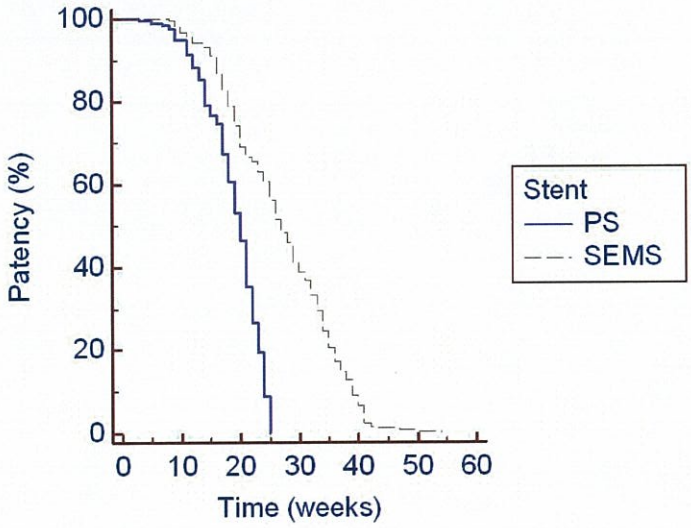

Fig 4

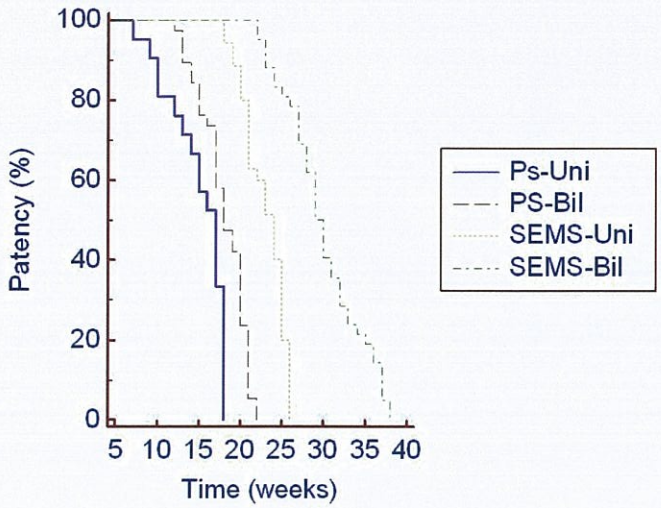
100
80
60
40
20
0
Patency (%)
5 10 15 20 25 30 35 40
Time (weeks)
Ps-Uni
PS-Bil
SEMS-Uni
SEMS-Bil

Fig 5

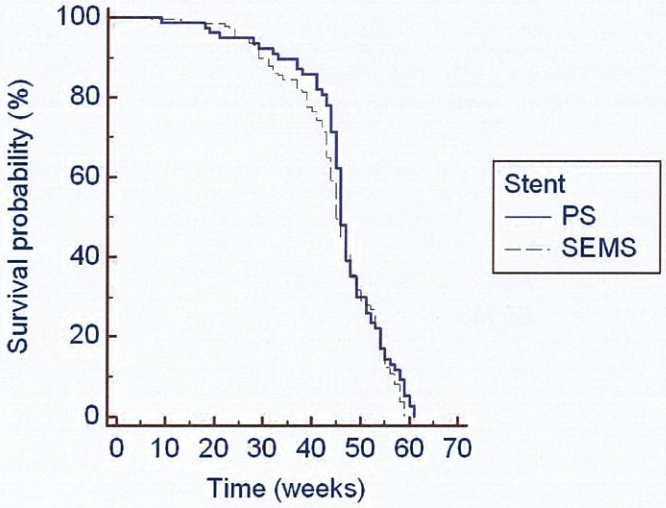
100
80
60
40
20
0
Survival probability (%)
0 10 20 30 40 50 60 70
Time (weeks)
Stent
PS
SEMS

Fig 6

DISCUSSÃO

DISCUSSÃO

O objectivo principal desta dissertação é contribuir para o esclarecimento de vários focos de controvérsia que envolvem a colocação de próteses expansíveis em situações benignas e malignas em vários segmentos do tubo digestivo.

Quando no início se definiram os objectivos colocaram-se várias questões:

1) Papel das próteses metálicas auto-expansíveis na terapêutica paliativa de estenoses malignas gastro-duodenais, desde a sua colocação até à morte dos doentes.

Apesar de múltiplos trabalhos na literatura colocarem em evidência a eficácia clínica das próteses entéricas na obstrução maligna gastro-duodenal, estudos recentes sugerem que essa eficácia perde-se ao longo do tempo[50,51]. Doentes com sobrevidas superiores a 2 meses deviam ser operados, procedimento associado, num estudo, a baixa taxa de morbilidade. A literatura é escassa em grandes grupos de doentes seguidos até à morte após a colocação das próteses. No estudo 1, um ensaio preliminar, procuramos mostrar, recorrendo a próteses esofágicas cobertas, que a eficácia a longo prazo era uma realidade. Este estudo sugeria que o uso de próteses cobertas era um caminho a explorar. Contudo, relatos posteriores de próteses entéricas TTS (de morfologia, concepção e força radial diferentes das esofágicas por nós utilizadas) sugeriram que o uso de dispositivos cobertos era limitado pela sua elevada taxa de migração. Para consubstanciar a utilidade das próteses a muito longo-prazo, no nosso estudo 2, seguimos uma larga população até à morte. A primeira constatação é que, tal como sugerido na literatura, a obstrução maligna gastro-duodenal é um evento pré-terminal em doentes com uma sobrevida expectável muito limitada. No estudo 2 a população apresentou uma sobrevida mediana e média de 8 semanas e 16.4 semanas respectivamente (intervalo 1-104). Perante uma sobrevida curta, estão criadas as condições para a colocação de próteses. Neste estudo obteve-se uma elevada taxa de sucesso técnico e clínico (100% e 97.2% respectivamente), semelhante aos valores da literatura, tornando evidente o consenso geral que esta técnica apresenta elevada taxa de sucesso técnico e permite, de imediato (24-96H), que os doentes restabeleçam a sua alimentação oral. Mas a grande vantagem do nosso trabalho é apresentar evidência que cerca de 95% dos doentes mantiveram a alimentação oral durante o resto das suas vidas e que desses ¾ não necessitaram de intervenção adicional. E dos que necessitaram de reintervenção por obstrução da prótese (cerca de 10%), a

generalidade voltou a alimentar-se após colocação de uma segunda e por vezes terceira prótese. E o que é mais interessante é que 2/3 dos doentes consegue manter uma dieta sólida (mole/pastosa ou mesmo geral) até ao fim das suas vidas após a colocação de uma prótese entérica. Para além disso esta técnica está associada a uma morbilidade aceitável e onde as complicações graves são muito pouco frequentes. Em virtude da baixa sobrevida dos doentes e da morbilidade associada aos procedimentos cirúrgicos, bem como da evidência da sua eficácia a longo prazo, parece-nos que a colocação de próteses metálicas é o caminho a seguir e este trabalho fornece evidência razoável.

2) Valor da utilização, a longo prazo, de próteses metálicas no tratamento paliativo de estenoses malignas colo-rectais

Nos últimos 3 anos ocorreu um intenso debate sobre o valor das próteses metálicas como tratamento paliativo na obstrução maligna colo-rectal. Existem trabalhos referindo um número elevado de complicações a curto e longo prazo, limitando o uso deste dispositivos e sugerindo que o tratamento de escolha é a cirurgia apesar de estar associada a um número importante de colostomias e degradação da qualidade de vida em doentes que apresentam uma esperança de vida curta[55,73]. Existem, na literatura, poucos estudos que seguiram um número importante de doentes até à morte, estando os dados limitados por seguimentos incompletos. No estudo 3, um estudo inicial, seguimos prospectivamente 28 doentes e 71.4% dos casos mantiveram-se livres de obstrução sem intervenção até á morte. O benefício inicial obtido com a colocação das próteses foi acrescido em 4 doentes, a quem a obstrução da prótese, por crescimento tumoral, foi resolvida pela colocação de nova prótese. Isto permitiu elevar para 85.7% a taxa de doentes que se mantiveram livres de obstrução e sem necessidade de cirurgia, através da colocação de próteses. Este trabalho foi dos primeiros a apresentar a sugestão que lesões obstrutivas a montante do ângulo esplénico podiam ser tratadas com a mesma taxa de sucesso das lesões do cólon esquerdo. Estes resultados preliminares foram solidificados com o estudo 4, um estudo retrospectivo em que 89 doentes foram seguidos até à morte. Neste estudo obtivemos uma taxa de sucesso técnico e clínico (95.5% e 91.0% respectivamente), semelhantes aos referidos na literatura. A taxa de sucesso técnico foi idêntica no cólon esquerdo e direito. No total 76.4% dos doentes mantiveram-se livres de obstrução sem intervenção adicional e esses números foram ampliados em mais 8 doentes (no total uma taxa de 85.4%) se considerarmos os doentes em que foi colocado uma segunda prótese após obstrução da primeira. Da nossa população inicial apenas 13.5% dos doentes foram submetidos a colostomia definitiva. Se reparamos com atenção os nossos dois estudos, separados pelo tempo e com diferentes populações apresentam resultados similares. Dois

trabalhos retrospectivos recentes parecem defender os nossos resultados[52,74]: a) um estudo com 168 doentes apresenta, aos 6 meses, uma taxa de sucesso clínico estimado (doentes sem reintervenção) de 77.2%. neste trabalho, foi possível, com a utilização de próteses, manter uma larga percentagem de doentes (88.5%) livres de sintomas obstrutivos até à morte[74]; b) um estudo comparativo entre tratamento endoscópico e cirúrgico refere que a taxa de sucesso clínico sem intervenção adicional do grupo endoscópico foi de 66.2%, enquanto que a taxa de sucesso da cirurgia foi de 87.7%[52]; contudo com a estratégia de colocação de nova prótese nos doentes com reobstrução tumoral foi possível aumentar o sucesso clínico para números a rondar os 85% o que é sobreponível à eficácia cirúrgica. No nosso estudo a taxa de complicações foi aceitável e a mortalidade mínima. Juntamente com estes relatos recentes, o nosso trabalho, com uma larga casuística de doentes seguidos até à morte parece sugerir que a colocação de próteses na paliação de estenoses malignas colo-rectais é uma terapêutica eficaz e de primeira linha.

3) Esclarecimento do papel de diferentes próteses expansíveis no tratamento de estenoses benignas do esófago, refractárias aos tratamentos convencionais.

As estenoses benignas do esófago resultam de várias agressões como a doença do refluxo, ingestão de agentes cáusticos, cirurgia e radioterapia. O tratamento de escolha é a dilatação seriada com velas ou balões, com ou sem injecção intra-lesional de corticosteróides como a triancinolona. O grande problema é que numa percentagem importante de doentes se verifica recidiva das suas estenoses e da disfagia, após as dilatações. Num grupo de doentes com poucas opções terapêuticas e onde a cirurgia poderá não ser a melhor escolha, a colocação temporária de próteses expansíveis, com um efeito dilatador permanente, tem emergido como uma possibilidade terapêutica. O grande entusiasmo inicial, relacionado com a utilização de próteses plásticas, tem vindo a ser moderado com os relatos recentes associados a resultados pouco animadores[93-97]. Surgiram, recentemente, duas outras opções: as próteses biodegradáveis e as metálicas totalmente cobertas, com resultados conflituosos e de difícil interpretação. Não são claras as vantagens das diferentes próteses e quais as complicações associadas. O nosso trabalho (estudo 5) é o primeiro estudo prospectivo a comparar, numa série de factores, as 3 próteses disponíveis em doentes com verdadeiras estenoses refractárias, o que não é o caso em muitos trabalhos da literatura. Comparamos, de uma forma prospectiva e não randomizada, 3 grupos de 10 doentes e verificamos que a eficácia clínica das próteses biodegradáveis e totalmente cobertas é semelhante, rondando os 30-40%. As próteses plásticas estiveram associadas a uma baixa taxa de sucesso, a longo prazo (10%), e a elevadas taxas de migrações e intervenções adicionais. O nosso estudo parece evidenciar

que a taxa de sucesso, a longo prazo, é baixa (habitualmente inferior a 50%), embora seja obtida num grupo de doentes de difícil manuseamento. Para além do mais, após um período inicial de permanência de uma prótese, a segunda colocação de uma nova prótese por um período de tempo adicional, sobretudo em doentes sem história de migração pode aumentar as taxas de sucesso. O nosso trabalho parece abrir as portas a um estudo multicêntrico, randomizado e prospectivo entre próteses biodegradáveis e metálicas totalmente cobertas em que esteja em análise a taxa de sucesso a longo prazo, a satisfação dos doentes e qualidade de vida, bem como a avaliação da melhor duração do tempo de colocação das próteses metálicas.

4) Avaliação da importância, eficácia e tempo de colocação de próteses metálicas totalmente cobertas no tratamento de condições benignas das vias biliares.

Existe um conjunto de condições benignas das vias biliares que são habitualmente tratadas através da CPRE, sejam elas consequência ou não da própria CPRE. Neste grupo estão englobadas as fugas biliares pós-colecistectomia, as hemorragias pós-ETE e as perfurações pós-ETE ou durante a execução do exame. A colocação de próteses de plástico de largo calibre é um elemento fundamental na terapêutica destas situações. Contudo, existe uma pequena percentagem destas condições benignas onde a endoscopia se revelava infrutífera, obrigando ao recurso à terapêutica cirúrgica, opção associada a morbilidade não negligenciável. Nos últimos 4 anos assistiu-se a alguns relatos de colocação de próteses metálicas totalmente cobertas para a resolução destas condições biliares benignas refractárias ao tratamento endoscópico convencional. A grande maioria dos relatos é unânime ao referir uma taxa de sucesso próxima dos 100%, embora em muitos casos o excessivo tempo de permanência das próteses na via biliar esteja associado a complicações[114,119,120]. No nosso estudo avaliámos, não só a eficácia da colocação das próteses como terapêutica de recurso em várias condições benignas, bem como procuramos determinar a duração adequada da permanência das próteses na via biliar de forma a haver sucesso clínico e não se registarem complicações. Este trabalho é o primeiro relato onde existe a sugestão que a colocação temporária de próteses totalmente cobertas por um período inferior a 30 dias é eficaz (em 100% dos casos na nossa série) no tratamento de fugas biliares pós-colecistectomia, hemorragias pós-ETE e perfurações. Adicionalmente observámos que o tempo de permanência da prótese na via biliar deve variar consoante a condição benigna. Além do mais este trabalho sugere, através de seguimento a longo prazo com recurso à colangioscopia, um perfil de segurança elevado, após a permanência das próteses por um período inferior a um mês. Este trabalho original abre um espaço para um estudo prospectivo onde se possa detalhar a duração mais adequada do

tempo de colocação das próteses de forma a evitar as complicações descritas na literatura e que nós não observámos.

5 – Abordagem da importância e eficácia da colocação unilateral e bilateral de próteses plásticas e metálicas no tratamento do colangiocarcinoma hilar.

O colangiocarcinoma hilar é uma entidade com mau prognóstico, onde menos de 10% dos doentes estão vivos aos 5 anos. Na grande generalidade dos casos a terapêutica paliativa é a única opção e recentemente a drenagem por via endoscópica afirmou-se como o procedimento de escolha quando comparado com a cirurgia ou com a drenagem percutânea devido à sua eficácia e menor morbilidade[133-136]. Quando pesquisamos a literatura existe escassa informação comparativa entre a colocação de próteses metálicas e plásticas em doentes com obstrução maligna do hilo biliar. Os estudos disponíveis parecem sugerir um maior sucesso técnico e clínico, associado a menos custos e maiores tempos de patência das próteses metálicas quando comparadas com os resultados das próteses plásticas[139-141]. Contudo, falta um estudo comparativo com larga casuística e em que as diferentes classes de Bismuth sejam analisadas. Por outro lado, existe um debate infindável sobre o valor da colocação unilateral e bilateral de próteses (metálicas ou plásticas) em lesões que apresentam uma classificação de Bismuth $\geq$ II. O nosso estudo analisa, retrospectivamente, 480 doentes com colangiocarcinoma hilar submetidos a terapêutica unilateral e bilateral com próteses metálicas e plásticas. Apresenta a maior casuística jamais publicada e fornece evidência que o tratamento paliativo de escolha do colangiocarcinoma hilar é a colocação de uma prótese metálica, uma vez que em comparação com as próteses plásticas os dispositivos metálicos estão associados a um maior sucesso técnico e clínico, menor taxa de complicações, menor taxa de reintervenções e maior tempo de patência das próteses. Finalmente, e ao sugerir que em doentes com lesões com Bismuth II existe vantagem na colocação bilateral de próteses metálicas em termos de patência e taxa de intervenção adicional, este estudo abre caminho a um ensaio randomizado que possa comparar a colocação unilateral com a bilateral de próteses metálicas na paliação das lesões malignas do hilo.

Do que se disse e em função da investigação efectuada, cinco conclusões principais podem ser tiradas desta dissertação:

- Em doentes com obstrução maligna gastro-duodenal e intolerância alimentar, as próteses metálicas auto-expansíveis permitem a manutenção da alimentação oral, seja com uma ou mais próteses em mais de 90% dos

doentes, evitando o recurso à cirurgia de derivação em doentes com esperança de vida muito limitada.

- A paliação de estenoses malignas colo-rectais em doentes com lesões inoperáveis pode ser feita com próteses metálicas auto-expansíveis. Esta abordagem permite que cerca de 75% dos doentes se mantenham livres de obstrução sem intervenção adicional e que as vantagens da colocação de próteses possam ser prolongadas até cerca de 85% dos doentes com a colocação de duas ou mais próteses. O procedimento está associado a uma taxa de complicações aceitável e a uma mortalidade mínima. A cirurgia é necessária em 10 a 15% dos doentes e deve ser reservada para situações de falência da terapêutica endoscópica.

- Estenoses benignas do esófago refractárias podem ser tratadas pela colocação temporária de próteses metálicas totalmente cobertas ou próteses biodegradáveis. Esta abordagem permite que cerca de 30-40% dos doentes fique sem disfagia a longo prazo. Este tratamento é associado a baixa taxa de complicações e afirma-se como uma terapêutica a considerar num grupo de doentes com opções muito limitadas.

- Próteses metálicas totalmente cobertas devem ser usadas como tratamento de recurso em algumas condições benignas das vias biliares (fugas refractárias, hemorragias de difícil controlo e perfurações), após falências dos tratamentos endoscópicos convencionais. A colocação temporária das próteses por períodos inferiores a 30 dias deve ser orientada (em termos de duração temporal) consoante o tipo de condição benigna e o procedimento é eficaz (próximo dos 100% de sucesso) e seguro a curto e longo prazo.

- Estenoses malignas do hilo devem ser paliadas com próteses metálicas que oferecem uma taxa de sucesso técnico e clínico superior a 90% dos casos, em todas os tipos da classificação de Bismuth. Sempre que tecnicamente possível em lesões hilares do tipo II a colocação bilateral de próteses metálicas deve ser recomendada pois está associada a um maior tempo de patência das próteses e a uma menor necessidade de intervenções adicionais.

BIBLIOGRAFIA

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1. van Hooft JE, Uitdehaag MJ, Bruno MJ, *et al*. Efficacy and safety of the new WallFlex enteral stent in palliative treatment of malignant gastric outlet obstruction (DUOFLEX study): a prospective multicenter study. *Gastrointest Endosc* 2009; **69**: 1059-1066
2. Watt AM, Faragher IG, Griffin TT, *et al*. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg 2007;246:24-30
3. Sterioff S. Etimology of the word "stent". Mayo Clin Proc 1997; 72:377-379.
4. Esser JF. Studies in plastic surgery of the face: I. Use the skin of the neck to replace face defects. II. Plastic operations about the mouth. III. The epidermic inlay. Ann Surg 1917; 65:297-315.
5. ReMine WH, Grindlay JH. Skinlined omentum and plastic sponge tubes for experimental choledochoduodenostomy. AMA Arch Surg 1954; 69:255-262.
6. Chenoweth AI. Discussion [The fate of free grafts in common bile duct]. Ann Surg 1960; 151:781-782.
7. Firlit CF, Brown JL. Ureteral stents: a device for removal. J Urol 1972; 108:954.
8. Weldon CS, Ameli MM, Morovati SS, *et al*. A prosthetic stented aortic homograft for mitral valve replacement. J Surg Res 1966; 6:548-552.
9. Dotter CT. Transluminally-placed coilspring endarterial tube grafts: long-term patency in canine popliteal artery. Invest Radiol 1969; 4:329-332.
10. Dotter CT, Buschmann RW, McKinney MK, *et al*. Transluminal expandable nitinol coil stent grafting: preliminary report. Radiology 1983; 147:259-260.
11. Molnar W, Stockum AE. Relief of obstructive jaundice through percutaneous trans-hepatic catheter-a new therapeutic method. Am J Roentgenol Radium Ther Nucl Med 1974; 122:356-367.
12. Soehendra N. Reyders-Frederix V. Palliative biliary duct drainage. A new method for endoscopic introduction of a new drain. Dtsch Med Wochenschr 1979; 104:206-207 [in German].
13. Song HY, Choi KC, Kwon HC, *et al*. Esophageal strictures: treatment with a new design of modified Gianturco stent. Work in progress. Radiology 1992; 184:729-734
14. Bethge N, Sommer A, Vakil N. A prospective trial of self-expanding metal stents in the palliation of malignant esophageal strictures near the upper esophageal sphincter. Gastrointest Endosc 1997; 45:300-303
15. Bethge N, Sommer A, Gross U, *et al*. Human tissue response to metal stents implanted in vivo for the palliation of malignant stenosis. Gastrointest Endosc 1996; 43:596-602

16. Vakil N, Gross U, Bethge N. Human tissue response to metal stents. Gastrointest Endosc Clin N Am 1999; 9:359-365
17. Baron T. Covered self-expandable metal stents for benign biliary tract diseases. Curr Opin Gastroenterol 2011; 2:262-267
18. Hair CS, Devonshire DA. Severe hyperplastic tissue stenosis of a novel biodegradable esophageal stent and subsequent successful management with high-pressure balloon dilatation. Endoscopy 2010; 42(S 02):E132-133
19. Adler DG, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: Experience in 36 patients. Am J Gastroenterol 2002; 97:72-78
20. Kim JH, Song HY, Shin JH, *et al*. Metallic stent placement in the palliative treatment of malignant gastroduodenal obstructions: prospective evaluation of results and factors influencing outcome in 213 patients. Gastrointest Endosc 2007; 66:256-264
21. Piesman M, Kozarek RA, Brandabur JJ, *et al*. Improved oral intake after palliative duodenal stenting for malignant obstruction: A prospective multicenter clinical trial. Am J Gastroenterol 2009; 104:2404-2411
22. Telford JJ, Carr-Locke DL, Baron TH, *et al*. Palliation of patients with malignant outlet obstruction with the enteral Wallstent: outcomes from a multicenter study. *Gastrointest Endosc* 2004; **60**:916-920
23. Costamagna G, Tringali A, Spicak J, *et al*. Treatment of malignant gastroduodenal obstruction with a nitinol self-expanding metal stent: an international prospective multicentre registry. *Dig Liver Dis* 2012; 44:37-43
24. Lopes CV, Pesenti C, Bories E, *et al*. Self-expandable metallic stents for palliative treatment of digestive cancer. *J Clin Gastroenterol* 2008; 42:991-996
25. Grabber I, Dumas R, Filoche B, *et al*. The efficacy and safety of duodenal stenting: a prospective multicenter study. Endoscopy 2007; 39:784-787
26. Maetani I, Isayama H, Mizumoto Y. Palliation in patients with malignant gastric outlet obstruction with a newly designed enteral stent: a multicenter study. Gastrointest Endosc 2007; 66:355-360
27. Garcia-Cano J, Sanchez-Manjavacas N, Chicano MV, *et al*. Palliative management of malignant gastric outlet obstruction with endoscopiccally inserted self-expanding metal stents. Rev Esp Enferm Dig 2008; 100: 320-326
28. Holt AP, Patel M, Ahmed MM. Palliation of patients with malignant gastroduodenal obstruction with self-expanding metal stents: the treatment of choice? Gastrointest Endosc 2004; 60:1010-1017

29. Wilson RG, Varma JS. Laparoscopic gastroenterostomy for malignant duodenal obstruction. Br J Sur 1992;79:1348
30. Brimhall B, Adler DG. Enteral stents for malignant gastric outlet obstruction. Gastrointest Endoscopy Clin N Am 2011;21:389-403
31. Truong S, Bohndorf V, Geller H, *et al*. Self-expanding metal stents for palliation of malignant gastric outlet obstruction. Endoscopy 1992; 24:433-435
32. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Eng J Med 2001; 344:1681-1687
33. Baron TH, Harewood GC. Enteral self-expandable stents. Gastrointest Endosc 2003; 58:421-433
34. Kim J, Yoo B, Lee K, *et al*. Self-expanding coil stent with a long delivery system for palliation of unresectable malignant gastric outlet obstruction: a prospective study. Endoscopy 2001; 33:838-842
35. Maetani I, Tada T, Shimura J, *et al*. Technical modifications and strategies for stenting gastric outlet strictures using esophageal endoprostheses. Endoscopy 2002; 34:402-406
36. Jeong JY, Han JK, Kim AY, *et al*. Fluoroscopically guided placement of a covered self-expandable metallic stent for malignant antroduodenal obstructions. AJR Am J Roentgenol 2002; 178:847-852
37. Jung JS, Song HY, Kang SG, *et al*. Malignant gastroduodenal obstructions: treatment by means of a covered expandable metallic stent-initial experience. Radiology 2000; 216:758-763
38. Park KB, Do YS, Kang WK, *et al*. Malignant obstruction of gastric outlet and duodenum: palliation with flexible covered metallic stents. Radiology 2000; 216:758-763
39. Maetani I, Ukita T, Tada T, *et al*. Metallic stents for gastric outlet obstruction: reintervention rate is lower with uncovered versus covered stents, despite similar outcomes. Gastrointest Endosc 2009; 69:806-812
40. Kim CG, Choi IL, Lee JY, *et al*. Covered versus uncovered self-expandable metallic stent placement for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study. Gastrointest Endosc 2010; 72:25-32
41. Dormann A, Meisner S, Verin N, *et al*. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. Endoscopy 2004; 36:543-550

42. Jeurnink SM, van Eijck CH, Steyeberg EW, *et al*. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18
43. Stawowy M, Kruse A, Mortensen FV, *et al*. Endoscopic stenting for malignant gastric outlet obstruction. Surg Laparosc Endosc Percutan Tech 2007;17:5-9
44. Fiocca E, Ceci V, Donatelli G, *et al*. Palliative treatment of upper gastrointestinal obstruction using self-expansible metal stents. Eur Rev Med Pharmacol Sci 2006;10:179-82
45. Laasch H-U, Martin DF, Maetani I. Enteral stents in the gastric outlet and duodenum. Endoscopy 2005; 37:74-81
46. Mutignani M, Tringali A, Shah SG, *et al.* Combined endoscopic stent insertion in malignant biliary and duodenal obstruction. Endoscopy 2007; 39:440-447
47. Hosono S, Ohtani H, Arimoto Y, *et al*. Endoscopic stenting versus surgical gastroenterostomy for palliation of malignant gastroduodenal obstruction: a meta-analysis. J Gastroenterol 2007; 42:283-290
48. Fiori E, Lamazza A, Volpino P, *et al*. Palliative management of malignant antro-pyloric strictures. Gastroenterostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res 2004; 24:269-271.
49. Mehta S, Hindmarsh A, Cheong E, *et al.* Prospective randomized trial of laparoscopic gastrojejunostomy versus duodenal stenting for malignant gastric outflow obstruction. Surg Endosc 2006 20:239-242.
50. Jeurnink AM, Steyerberg EW, van Hooft JE, *et al.* Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc 2010; 71:490-499
51. Jeurnink SM, Steyerberg EW, Vleggaar FP, *et al*. Predictors of survival in patients with malignant gastric outlet obstruction: a patient-oriented decision approach for palliative treatment. Dig Dis Sci 2011; 43:548-552
52. Lee HJ, Hong SP, Cheon JH, *et al*. Long-term outcome of palliative therapy for malignant colorectal obstruction in patients with unresectable metastatic colorectal cancers: endoscopic stenting versus surgery. Gastrointest Endosc 2011;73:535-542
53. Repici A, Ferreira DP. Expandable metal stents for malignant colorectal strictures. Gastrointest Endoscopy Clin N Am 2011;21:511-533

54. Self-expanding metal stents as non-surgical palliative therapy for malignant colonic obstruction: time to change the standard of care? [editorial]. Gastrointest Endosc 2007;66:928-930
55. Fernández-Esparrach G, Bordas JM, Giráldez MD, *et al*. Severe complications limit long-term clinical success of self-expanding metal stents in patients with obstructive colorectal cancer. Am J Gastroenterol 2010;105:1087-1093
56. Self-expanding metal stents in malignant colonic obstruction: have we covered all angles? [editorial]. Gastrointest endosc 2007:67:937-939
57. Watt AM, Faragher IG, Griffin TT, *et al*. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. Ann Surg 2007;246:24-30
58. Repici A, Fregonese D, Costamagna G, *et al*. Ultraflex precision colonic stent placement for palliation of malignant colonic obstruction: a prospective multicenter study. Gastrointest Endosc 2007;66:920-927
59. Baron TH. Colonic stenting: technique, technology, and outcomes for malignant and benign disease. Gastrointest Endosc Clin N Am 2005;15:757-771
60. Keswani RN, Azar RR, Edmundowicz SA, *et al.* Stenting for malignant colonic obstruction: a comparison of efficacy and complications in colonic versus extracolonic malignancy. Gastrointest Endosc 2009;69:675-680
61. Trompetas V, Saunders M, Gossage J, *et al*. Shortcomings in colonic stenting to palliate large bowel obstruction from extracolonic malignancies. Int J Colorectal Dis 2010;25:851-854
62. Sebastian S, Johnston S, Geoghegan T, *et al*. Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction. Am J Gastroenterol 2004; 99:2051-5
63. Dohmoto M, Rupp KD, Hohlbach G. Endoscopically-implanted prosthesis in rectal carcinoma, Dtsch Med Wochenschr 1990;115:915;[in German]
64. Choi JS, Choo SW, Park KB, *et al*. Interventional management of malignant colo-rectal obstruction: use of covered and uncovered stents. Korean J Radiol 2007;8:57-63
65. Park S, Cheon JH, Park JJ, et al. Comparison of efficacies between stents for malignant colorectal obstruction: a randomized prospective study. Gastrointest Endosc 2010;71:304-310
66. Lee KM, Shin SJ, Hwang JC, *et al.* Comparison of uncovered stents with covered stents for treatment of malignant colorectal obstruction. Gastrointest Endosc 2007;66:931-936

67. Cheung HY, Chung CC, Tsang WW, *et al.* Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. Arch Surg 2009;144:1127-1132
68. Pirlet IA, Slim K, Kwiatkowski F, *et al.* Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc 2011;25:1814-1821
69. Targownik LE, Spiegel BM, Back J, *et al*. Colonic stent vs. emergency surgery for management of acute left-sided malignant colonic obstruction: a decision analysis. Gastrointest Endosc 2004;60:865-874
70. Singh H, Latosinsky S, Spiegel BM, *et al*. The cost-effectiveness of colonic stenting as a bridge to curative surgery in patients with acute left-sided malignant colonic obstruction: a Canadian perspective. Can J Gastroenterol 2006;20:779-785
71. Xinopoulos D, Dimitroulopoulos D, Theodosopoulos T, *et al*. Stenting or stoma creation for patients with inoperable malignant colonic obstructions? Results of a study and cost-effectiveness analysis. Surg Endosc 2004;18:421-426
72. Fiori E, Lamazza A, De Cesare A, *et al*. Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res 2004;24:265-268
73. van Hooft JE, Fockens P, Marinelli AW, *et al*. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy 2008;40:184-91
74. Small AJ, Coelho-Prabhu N, Baron TH. Endoscopic placement of self-expandable metal stents for malignant colonic obstruction: long-term outcomes and complication factors. Gastrointest Endosc 2010;71:560-572.
75. Varadarajulu S, Roy A, Lopes T, *et al*. Endoscopic stenting versus surgical colostomy for the management of malignant colonic obstruction: comparison of hospital costs and clinical outcomes. Surg Endosc 2011; 25:2203-2209.
76. Nagula S, ishill N, Nash C, *et al*. Quality of life and symptom control after stent placement of surgical palliation of malignant colorectal obstruction. J Am Coll Surg 2010;210:45-53
77. Repici A, De Caro G, Luigiano C, *et al*. WallFlex colonic stent placement for management of malignant colonic obstruction: a prospective study at two centres. Gastrointest Endosc 2008;67:77-84
78. Manes G, de Bellis M, Fuccio L, *et al*. Endoscopic palliation in patients with incurable malignant colorectal obstruction by means of self-expanding metal stent: analysis of

results and predictors of outcomes in a large multicenter series. Arch Surg 2011;146:1157-1162.

79. Khot UP, Lang AW, Murali K, *et al*. Effectiveness of stent placement for palliative treatment in malignant colorectal obstruction and predictive factors for stent occlusion. Br J Surg 2002;89:1096-1102
80. Suh JP, Kim SW, Cho YK, *et al*. Effectiveness of stent placement for palliative treatment in malignant colorectal obstruction and predictive factors for stent occlusion. Surg Endosc 2010;24:400-406
81. Ptok H, Meyer F, Marusch F, Steinert R, Gastinger I, Lippert H, et al. Palliative stent implantation in the treatment of malignant colorectal obstruction. Surg Endosc 2006; 20:909-14
82. Datye A, Hersh J. Colonic perforation after stent placement for malignant colorectal obstruction-causes and contributing factors. Minim Invasive Ther Allied Technol 2011;20:133-140.
83. Hapani S, Chu D, Wu S. Risk of perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009;10:559-68
84. Eloubeidi MA, Talreja JP, Lopes TL, et al. Success and complications associated with placement of fully covered removable self-expandable metal stents for benign esophageal diseases (with videos). Gastrointest Endosc 2011; 73:673-681
85. Siersema PD. Stenting for benign esophageal strictures. Endoscopy 2009; 41:363-373
86. Siersema PD, Wijkerslooth LR. Dilatation of refractory benign esophageal strictures. Gastrointest Endosc 2009; 70:1000-1012
87. Kockman ML, McClave SA, Boyce HW. The refractory and the recurrent esophageal stricture: a definition [Letter to Editor]. Gastrointest Endosc 2005; 62:474-475
88. Ackroyd R, Watson DI, Devitt PG, *et al*. Expandable metallic stents should not be used in the treatment of benign esophageal strictures. J Gastroenterol Hepatol 2001; 16:484-487
89. Sanda GS, Marcon NE. Expandable metal stents for benign esopagheal obstruction. Gastrointest Endosc Clin N Am 1999; 9:437-446
90. Sharma P, Kozarek R. Role of esophageal stents in benign and malignant diseases. Am J Gastroenterol 2010; 105:258-273
91. Evrard S, Le Moine O, Lazaraki G, *et al*. Self-expanding plastic stents for benign esophageal lesions. Gastrointest Endosc 2004; 60:894-90

92. Repici A, Conio M, De Angelis C, *et al*. Temporary placement of an expandable polyester silicone-covered stent for treatment of refractory benign esophageal strictures. Gastrointest Endosc 2004; 60: 513-519
93. Holm AN, Levy JG, Goustout CJ, *et al*. Self-expanding plastic stents in treatment of benign esophageal conditions. Gastrointest Endosc 2008; 67:20-25
94. van Boeckel PG, Vleggaar FP, Siersema PD. A comparison of temporary self-expanding plastic and biodegradable stents for refractory benign esophageal strictures. Clin Gastroenterol Hepatol 2011; 9:653-659
95. Dua KS, Vleggaar FP, Santharam R, *et al*. Removable self-expanding plastic esophageal stent as a continuous, non-permanent dilator in treating refractory benign esophageal strictures: a prospective two-center study. Am J Gastroenterol 2008; 103:2988-2994.
96. Oh YS, Kochman ML, Ahmad NA, *et al*. Clinical outcomes after self-expanding plastic stent placement for benign strictures. Dig Dis Sci 2010; 55:1344-48
97. Triester SL, Fleischer DE, Sharma VK. Failure of self-expanding plastic stents in treatment of refractory benign esophageal strictures. Endoscopy 2006; 38: 533-537
98. Barthel JS, Kelley ST, Klapman JB. Management of persistent gastroesophageal anastomotic strictures with removable self-expandable polyester silicon-covered (Polyflex) stents: an alternative to serial dilatation. Gastrointest Endosc 2008; 67:546-552
99. Repici A, Hassan C, Sharma P, *et al*. Systematic review: the role of self-expanding plastic stents for benign esophageal strictures. Alim Pharm Ther 2010; 31:1268-1275
100. Baron TH, Burgart LJ, Pochron NL. An internally covered (lined) self-expanding metal stent: tissue response in a porcine model. Gastrointest Endosc 2006;64:263-267
101. Kim JH, Song HY, Choi EK, *et al.* Temporary metallic stent placement in the treatment of refractory benign esophageal strictures: results and factors associated with outcome in 55 patients. Eur Radiol. 2009; 19: 384-390
102. Eloubeidi MA, Talreja JP, Lopes TL, Al-Awabdy BS, Shami VM, Kahaleh M. Success and complications associated with placement of fully covered removable self-expandable metal stents for benign esophageal diseases (with videos). *Gastrointest Endosc.* 2011; 73: 673-681
103. Liu J, Hu Y, Cui C, *et al*. Removable, fully covered, self-expandable metal stents for the treatment of refractory benign esophagogastric anastomotic strictures. Dysphagia 2011; DOI: 10.1007/s00455-011-9361-1, August 09

104. Saito Y, Tanaka T, Andoh A, *et al.* Novel biodegradable stents for benign esophageal strictures following endoscopic submucosal dissection. Dig Dis Sci 2008; 53:330-333.

105. Saito Y, Tanaka T, Andoh A, *et al.* Usefulness of biodegradable stents constructed of poly-l-lactic acid monofilaments in patients with benign esophageal stenosis. World J Gastroenterol 2007; 13:3977-3980

106. Repici A, Vleggaar FP, Hassan C, *et al.* Efficacy and safety of biodegradable stents for refractory benign esophageal strictures: the BEST (Biodegradable Esophageal Stent) study. Gastrointest Endosc 2010; 72:927-934.

107. van Boeckel PG, Vleggaar FP, Siersema PD. A comparison of temporary self-expanding plastic and biodegradable stents for refractory benign esophageal strictures. Clin Gastroenterol Hepatol 2011; 9:653-659

108. van Hooft JE, Henegouwen MI, Rauws EA, *et al.* Endoscopic treatment of benign anastomotic esophagogastric strictures with a biodegradable stent. Gastrointest Endosc 2011; 73:1043-1047

109. Sandha GS, Bourke MJ, Haber GB, *et al.* Endoscopic therapy for bile leak based on a new classification: results in 207 patients. Gastrointest Endosc 2004; 60:567–574

110. Kaffes AJ, Hourigan L, De Luca N, *et al.* Impact of endoscopic intervention in 100 patients with suspected postcholecystectomy bile leak. Gastrointest Endosc 2005;61:269–275

111. Judah JR, Draganov PV. Endoscopic therapy of benign biliary strictures. World J Gastroenterol 2007; 13:3531-3539

112. Vaira D, D'Anna L, Ainley C, *et al.* Endoscopic sphincterotomy in 1000 consecutive patients. Lancet 1989;2:431-434

113. Andriulli A, Loperfido S, Napolitano G, *et al.* Incidence rates of Post-ERCP complications: a systematic survey of prospective studies. Am J Gastroenterol 2007;102:1781-1788

114. Baron T. Covered self-expandable metal stents for benign biliary tract diseases. Curr Opin Gastroenterol 2011;2:262-267

115. Ho H, Mahajan A, Gosain S, *et al.* Management of complications associated with partially covered biliary metal stents. Dig Dis Sci 2010;55: 516-522

116. Coté GA, Ansstas M, Shah S, *et al.* Findings at endoscopic retrograde cholangiopancreatography after endoscopic treatment of postcholecistectomy bile leaks. Surg Endosc 2010;24:1752–1756

117. Simmons DT, Petersen BT, Goustout CJ, *et al.* Risk of pancreatitis following endoscopically placed large-bore biliary plastic stents with and without biliary sphincterotomy for management of postoperative bile leaks. Surg Endosc 2008;22:1459-1463

118. Baron T, Poterucha J. Insertion and removal of covered expandable metal stents for closure of complex biliary leaks. Clin Gastroenterol Hepatol 2006;4:381-386

119. Wang A, Ellen K, Berg C, *et al.* Fully covered self-expandable metallic stents in the management of complex biliary leaks: preliminary data - a case series. Endoscopy 2009;41:781-786.

120. Phillips MS, Bonatti H, Sauer, *et al.* Elevated stricture rate following the use of fully covered self-expandable metal biliary stents for biliary leaks following liver transplantation. Endoscopy 2011;43:512-517

121. Ferreira LE, Baron TH. Post-sphincterotomy bleeding: who, what, when, and how. Am J Gastroenterol 2007;102:2850–2858

122. Leung J, Chan F, Sung J, *et al.* Endoscopic sphincterotomy-induced hemorrhage: A study of risk factors and the role of epinephrine injection. Gastrointest Endosc 1995;42:550–554.

123. Shah J, Marson F, Binmoeller K. Temporary self-expandable metal stent placement for treatment of post-sphincterotomy bleeding. Gastrointest Endosc 2010;72:1274-1278

124. Itoi T, Yasuda I, Doi S, *et al.* Endoscopic hemostasis using covered metallic stent placement for uncontrolled post-endoscopic sphincterotomy bleeding. Endoscopy 2011;43:369-372

125. Enns R, Eloubeidi M, Mergener K, *et al.* ERCP-related perforations: risk factors and management. Endoscopy 2002;34:293-298

126. Garcia-Cano J, Taberna-Arana L, Jimeno-Ayllón C, et al. Use of fully-covered self-expandable metallic stents for the management of benign biliary conditions. Rev Esp Enferm Dig 2010;102:526-532

127. Larghi A, Tringali A, Lecca P, *et al.* Management of hilar strictures. Am J Gastroenterol 2008;103:458-473

128. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterol 2005;128:1655-1667

129. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress. Part 1:epidemiology and etiology. J Gastroenterol Hepatol 2002;17:1049-1055

130. Klatskin G. Adenocarcinoma of the hepatic duct at its bifurcation within the porta hepatitis: an usual tumor with distinctive clinical and pathologic features. Am J Med 1965;38:241-247

131. Bismuth H, Castaing D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. World J Surg 1988;12:39–47

132. Cheng JL, Bruno MJ, Bergman JJ, *et al*. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents. Gastrointest Endosc 2005;56:33-39

133. Gerges C, Schumacher B, Terheggen G, *et al*. Expandable metal stents for malignant hilar biliary obstruction. Gastrointest Endosc Clin N Am 2011;21:481-497

134. Hookey LC, Le Moine O, Deviere J. Use of a temporary plastic stent to facilitate the placement of multiple self-expanding metal stents in malignant biliary hilar strictures. Gastrointest Endosc 2005;62:605-609

135. Speer AG, Cotton PB, Russell RC, *et al*. Randomized trial of endoscopic versus percutaneous stent insertion in malignant obstructive jaundice. Lancet 1987;2:57-62

136. Andersen JR, Sorensen SM, Kruse A, *et al.* Randomized trial of endoscopic endoprostheses versus operative bypass in malignant obstructive jaundice. Gut 1989; 30:1132-1135

137. Huibregtse K, Cheng J, Coene PP, *et al*. Endoscopic placement of expandable metal stents for biliary strictures-a preliminary report on experience with 33 patients. Endoscopy 1989;21:280–282

138. Neuhaus H, Hagenmuller F, Classen M. Self-expanding biliary stents: preliminary clinical experience. Endoscopy 1989;21:225–228

139. Wagner HJ, Knyrim K, Vakil N, et al. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. Endoscopy 1993;25:213–18.

140. Perdue DG, Freeman ML, DiSario JA, *et al.* Plastic versus self-expanding metallic stents for malignant hilar obstruction: a prospective multicenter observational cohort study. J Clin Gastroenterol 2008;42:1040-1046

141. Raju RP, Jaganmohan SR, Ross WA, *et al*. Optimum palliation of inoperable hilar cholangiocarcinoma: comparative assessment of the efficacy of plastic and self-expanding metal stents. Dig Dis Sci 2011;56:1557-1564

142. De Palma GD, Galloro G, Siciliano S, *et al.* Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. Gastrointest Endosc 2001;53:547–53

143. Deviere J, Baize M, Toeuf J, *et al*. Long-term follow-up of patients with hilar malignant strictures treated by endoscopic internal biliary drainage. Gastrointest Endosc 1988;34:95-101

144. Naitoh I, Ohara H, Nakazawa T, *et al.* Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction. J Gastroenterol Hepatol 2009; 24: 552-557

145. Neuhaus H, Gottlieb K, Classen M. The "stent through wire mesh technique" for complicated biliary strictures. Gastrointest Endosc 1993;39:553-556

146. Chahal P, Baron T. Expandable metal stents for endoscopic stent-within-stent placement for malignant hilar biliary obstruction. Gastrointest Endosc 2010;71:195-199

147. Kim JY, Kang DH, Kim HW, *et al*. Usefulness of slimmer and open-cell-design stents for endoscopic bilateral stenting and endoscopic revision in patients with hilar cholangiocarcinoma (with video). Gastrointest Endosc 2009; 70: 1109-1115

148. Park DH, Lee SS, Moon JH, *et al*. Newly designed stent for endoscopic bilateral stent-in-stent placement of metallic stents in patients with malignant hilar biliary strictures: multicenter prospective feasibility study (with videos). Gastrointest Endosc 2009;69:1357-1360

149. Chennat J, Waxman I. Initial performance profile of a new 6F self-expanding metal stent for palliation of malignant hilar biliary obstruction. Gastrointest Endosc 2010;72:632-636

150. Liberato M, Pontes J: Tumores de las Vias Biliares y del Pancreas. In Endoscopia Digestiva Diagnóstica y Terapéutica. Edited by Vázquez-Iglesias J, Aguirre P. Madrid: Editorial Medica Panamericana; 2008:551-572

151. Hookey LC, Le Moine O, Deviere J. Use of a temporary plastic stent to facilitate the placement of multiple self-expanding metal stents in malignant biliary hilar strictures. Gastrointest Endosc 2005;62:605-609

152. Dumas R, Demuth N, Buckley M, *et al*. Endoscopic bilateral metal stent placement for malignant hilar stenoses: identification of optimal technique. Gastrointest Endosc 2000;51:334–338