

# 胆管癌支架治疗的现状及进展

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## ■背景资料

胆管癌(cholangiocarcinoma, CCA)是最常见的胆道恶性肿瘤。因其起病隐匿、早期诊断困难、治疗方法有限, 预后极差。大多数患者就诊时已失去外科手术机会。胆道支架治疗是晚期胆管癌重要的姑息治疗手段, 可解除胆道梗阻, 改善患者生活质量, 延长生存期。

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## Biliary stenting for cholangiocarcinoma: An update

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## Abstract

Cholangiocarcinoma (bile duct cancer) is the most common malignant tumor of the biliary tree. This devastating malignancy presents late, and is notoriously difficult to diagnose, thus resulting a high mortality. The majority of cholangiocarcinoma patients present with an unresectable disease, and survive less than 12 mo following diagnosis. Biliary stent placement is an effective palliative therapy for malignant biliary obstruction, which can significantly improve the quality of life, and extend the survival time of patients. Different biliary stent placement methods would closely affect the prognosis of patients. The purpose of this article is to review the treatment efficacy, insertion paths and types of biliary stents. This paper also covers emerging

biliary stents including drug stents, and biliary stent combination local therapy.

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**Key Words:** Cholangiocarcinoma; Biliary stent; Photodynamic therapy; Endobiliary radiofrequency ablation

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## 摘要

胆管癌(cholangiocarcinoma)是最常见的胆道恶性肿瘤。因其起病隐匿、早期诊断困难、治疗方法有限, 预后极差。大多数患者就诊时已失去外科手术机会。胆道支架治疗是晚期胆管癌重要的姑息治疗手段, 可解除胆道梗阻, 改善患者生活质量, 延长生存期。不同支架治疗方法的选择与患者的预后密切相关。本文结合最近几年有关文献, 就胆管癌支架治疗效果, 支架植入路径选择, 不同材质支架特点及应用, 载药支架等新兴胆道支架的研究进展, 以及支架联合局部治疗的应用等作一综述, 以供临床参考。

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**关键词:** 胆管癌; 胆道支架; 光动力治疗; 胆道内射频消融

**核心提示:** 不同支架治疗方法的选择与晚期胆管癌患者的预后密切相关。本文比较了不同支架植入路径的选择, 不同材质支架的特点及应用。介绍了近年来研究热点的药物洗脱支架、放射性支架等新兴胆道支架, 以及支架联合光动力治疗或射频消融治疗等局部治疗手段的最新研究进展, 对于临床和研究有重要指导价值。

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## 0 引言

胆管癌(cholangiocarcinoma, CCA)起源于胆管上皮细胞, 是全世界第2大原发性肝胆系肿瘤, 也是最常见的胆道恶性肿瘤<sup>[1,2]</sup>。胆管癌起病隐匿、早期诊断困难、治疗方法有限, 预后极差, 中位生存期不足24 mo<sup>[1]</sup>。胆道脓毒症、肝衰竭、恶病质和营养不良是胆管癌最主要的死因<sup>[3]</sup>。手术切除是唯一有效的治疗手段。然而大多数患者就诊时已失去手术切除机会, 在12 mo之内因恶病质及功能衰竭而死亡<sup>[4]</sup>。根治性手术五年生存率也仅为20%-40%<sup>[5]</sup>。

胆道支架植入术主要用于无法行手术切除的晚期胆管癌患者, 是解除其恶性胆道梗阻的一种有效的姑息性治疗手段。其目的是解除阻塞性胆汁淤积, 减轻黄疸、皮肤瘙痒、腹痛等相关并发症, 预防胆管炎, 避免渐进性胆道梗阻引起的肝衰竭, 通过微创治疗提高生活质量、降低治疗成本、减少手术相关并发症、缩短住院时间<sup>[6-8]</sup>。在晚期胆管癌的姑息性治疗中不同支架的选择及治疗方法至关重要。

## 1 经内镜胆道支架引流和经皮胆道支架引流

经内镜胆道引流比经皮胆道引流更符合生理特点、患者创伤小且舒适<sup>[9]</sup>。相对于经皮肝穿刺胆管造影(percutaneous transhepatic cholangiography, PTC), 内镜下逆行性胰胆管造影术(endoscopic retrograde cholangio-pancreatography, ERCP)有更多的优点: 可直视十二指肠及乳头, 检查肿瘤浸润情况, 可轻松获取细胞及组织样本, 后续放置支架可解除阻塞性胆汁淤积<sup>[10]</sup>。支架内引流可以恢复胆汁正常生理通道, 维持胆汁生理功能。一项美国的研究表明, 对无法行手术切除的患者内镜治疗费用明显低于手术治疗, 且可获得更长的生存期, 内镜下支架置入术可作为姑息性胆道引流的首选方法<sup>[11]</sup>。

经皮支架植入术通常用于内镜治疗失败或不能经内镜治疗的患者(例如胃部分切除史、幽门梗阻), 对于肝门部胆管狭窄的患者, 行经皮引流可避免内镜引流的高失败率和并发症发生率, 且经皮支架植入一枚以上金属支架更为容易<sup>[9]</sup>。在一项韩国的多中心回顾研究中, 经皮胆道引流成功率高于内镜下胆道引流, 两组中胆道引流成功后中位生存时间、支架通畅时间及并发症发生率均无明显差异, 其中胆道引流成功患者的中位生存时间均高于引流失败者<sup>[12]</sup>。经皮引流的主要缺点是经皮管所造成的不适及相关并

发症, 如出血、感染、胆汁瘘、导管阻塞和移动, 应根据恶性胆道狭窄的位置(肝门部或胆总管下段)选择合适的姑息性治疗的手段<sup>[10]</sup>。

## 2 塑料支架和金属支架

塑料支架和金属支架均可用于解除恶性胆道梗阻。塑料支架的直径为7.0-11.5 F, 长度为5-18 cm<sup>[13]</sup>。塑料支架费用较低、操作技术简单、发生阻塞时易于拆除和替换, 然而由于塑料支架直径较小, 更易发生阻塞, 引起胆管炎。有20%-40%单边或双边支架植入术后发生胆管炎, 其原因是支架直径小及胆道细菌感染继发生物膜形成和胆泥淤积, 多数塑料支架治疗恶性胆道梗阻的患者至少需要更换一次支架<sup>[1,2]</sup>。对于极高龄恶性梗阻性黄疸患者Grönroos等<sup>[14]</sup>认为对于应用塑料支架即可。

与塑料支架相比, 金属支架在近年来的研究中显示出更多的优势, 应用也日益增多。一方面, 他增大了支架的直径, 从而增加支架通畅时间、减少梗阻复发。其中自膨式金属支架(self-expanding metal stents, SEMSs)是应用最为广泛的金属支架, 大多数SEMSs的长度在4-10 cm之间, 直径一般为10 mm<sup>[15]</sup>。另一方面, 金属支架的网眼可避免堵塞侧支胆管, 使胆汁得到更好的引流<sup>[16]</sup>。研究表明金属支架通畅时间明显高于塑料支架, 两者通畅时间分别为10-12 mo和3-4 mo<sup>[10]</sup>。对于肝门部胆管癌, SEMSs植入后通畅时间也明显高于塑料支架, 且SEMSs有利于减少再手术的次数, 降低总的治疗费用<sup>[17]</sup>。金属支架的主要缺点在于: 支架本身费用高, 植入后不易移除。

一般认为金属支架主要应用于预期生存时间>3 mo、接受化疗或其他姑息性治疗的不可切除的胆管癌患者, 植入金属支架可减少ERCP次数、缩短住院时间、减少并发症的发生<sup>[2,18,19]</sup>。欧洲胃肠内镜学会指南推荐: 对于肝门部胆管恶性狭窄的患者, 预期生存期>3 mo或并发胆道感染者首选SEMSs; 对于确诊为恶性胆总管梗阻的患者, 如果预期生存期>4 mo或SEMSs本身的成本小于ERCP费用的50%, 应首选直径10 mm的SEMSs<sup>[15]</sup>。

## 3 裸支架和覆膜支架

胆道金属支架可以进一步分为裸支架和覆膜支架。裸支架主要由不锈钢、镍钛合金等制成, 覆膜支架表面由硅橡胶、聚亚安酯、聚四氟乙烯等材质的膜覆盖, 可避免肿瘤向内生长造成支

### ■ 研发前沿

普通支架只能机械性阻止肿瘤生长, 并不能杀伤肿瘤, 作为近年来研究热点的药物洗脱支架和放射性支架克服了以上不足。在机械性解除胆道梗阻的同时具有抑制肿瘤细胞增殖的作用。另外, 支架联合光动力治疗或射频消融治疗也是新兴的肿瘤局部治疗手段, 通过联合治疗的方法局部抑制肿瘤生长, 可延长支架通畅时间, 提高患者生存率, 具有良好的发展前景, 也是胆管癌姑息性治疗具有良好发展前景的新方向。

## ■ 相关报道

《Biliary stents: models and methods for endoscopic stenting》本文献详细介绍了不同胆道支架的分类、材质、规格及特点,胆道支架植入移除的方法技巧,多枚支架植入的应用,以及新型支架的研究等,内容详实具有临床指导意义。

架阻塞,并使支架易于移除。其中膜覆盖整个支架者称为全覆膜支架,覆盖部分支架而两端不覆盖者称为半覆膜支架<sup>[15]</sup>。

覆膜支架会阻塞侧支胆管,且更易发生支架移位,在肝门部胆管癌中应用甚少<sup>[20,21]</sup>。一项多中心实验纳入了400例不可手术切除的胆管远端恶性梗阻患者,应用裸支架和覆膜支架治疗后,患者的生存期、支架通畅时间、并发症发生率均无明显差异,然而应用裸支架者更易发生肿瘤向内生长,应用覆膜支架者更易发生支架移位<sup>[22]</sup>。裸SEMS、半覆膜SEMS、全覆膜SEMS支架移位率分别约为1%、5%、20%<sup>[15]</sup>。近期一项Meta分析则显示,在胆管远端恶性梗阻的患者,与裸支架相比植入覆膜支架可延长的支架通畅时间及患者的生存期<sup>[23]</sup>。

## 4 单侧支架和双侧支架

在胆管癌特别是肝门部胆管癌的姑息性治疗中,胆道引流的程度仍存在争议。单侧支架植入与双侧支架植入相比,操作更简单,费用更低,再介入治疗更容易<sup>[24]</sup>。De Palma等<sup>[25]</sup>认为胆管分叉处的肿瘤不应常规应用一个以上的支架治疗,双侧支架比单侧支架植入的成功率更低,且双侧支架植入会导致更高的并发症发生率。Iwano等<sup>[26]</sup>认为肝脓肿在双侧支架植入术后发病率更高。内镜下双侧支架植入比单侧支架植入操作难度更大,植入后行再介入手术情况也更复杂<sup>[24]</sup>。

然而随着内镜技术的提高,近期的研究则认为肝门部胆管癌双侧引流较单侧引流更有效,双侧引流可获得更长的支架通畅时间,而支架植入的成功率、引流成功率、并发症发生率无明显差别,双侧支架植入的成功率也达到了90%-93%<sup>[27-29]</sup>。双侧支架植入主要有两种方式:并排式和嵌入式。一项纳入52例肝门部恶性梗阻患者的实验显示:并排式双侧支架植入术后并发症发生率高于嵌入式支架植入,然而并排式支架通畅率也更高<sup>[30]</sup>。目前对于两种植入方式比较的研究较少,尚需进一步的研究来阐明两种方法的优劣势。

2013年亚太共识建议:肝门部胆管癌的姑息性胆道支架治疗应引流50%体积以上的肝脏,应根据个人肝脏的解剖特点决定应用单支架、双支架或多支架<sup>[31]</sup>。

## 5 药物洗脱支架和放射性支架

目前无论普通金属支架或塑料支架、裸支架或

腹膜支架都只是机械性的姑息治疗,并无抑制肿瘤细胞增殖的效应。

药物洗脱支架(drug-eluting stents, DESs),广泛应用于冠状动脉疾病,近年来越来越多的研究将非血管性载药支架(non-vascular DESs)应用于胃肠道、胆道、气管、支气管等恶性梗阻的治疗中。支架表面的抗肿瘤药物通过单纯扩散至黏膜及黏膜下层,使肿瘤微环境药物浓度达到最大,减小非肿瘤区域的药物毒性。同时,通过支架表面的抗肿瘤药物抑制肿瘤细胞增殖、黏膜增生,减少肿瘤向内生长的风险,增加支架通畅率<sup>[32,33]</sup>。

紫杉醇洗脱支架研究最为广泛,已在细胞、动物及临床研究中证明其安全有效<sup>[34-36]</sup>。一项前瞻性随机化研究纳入了52例恶性胆道梗阻患者,比较了紫杉醇载药覆膜支架与普通覆膜支架的治疗效果,证实了紫杉醇载药支架安全性,然而该研究中两组中支架通畅时间和患者生存时间均无明显差异<sup>[37]</sup>。近期亦有体内、外研究证实索拉非尼洗脱支架亦具有抑制细胞增殖、侵袭及血管生成的作用<sup>[38]</sup>。

放射性支架目前研究尚少,Guijin等<sup>[39]</sup>和He等<sup>[40]</sup>已在细胞水平证实(103)Pd放射性支架可抑制胆管癌细胞增殖,诱导凋亡。随着进一步的实验室及临床研究,药物洗脱支架及放射性支架将有望成为胆管癌安全有效的局部治疗手段。

## 6 支架联合光动力治疗和胆道内射频消融

光动力治疗(photodynamic therapy, PDT)是一种新兴的恶性肿瘤的姑息治疗方法,其原理是:静脉注射的光敏药物在肿瘤组织中聚集浓度大大高于周围组织,用特定波长的光照射时,光敏剂发生光化学反应产生氧自由基导致肿瘤细胞坏死,而周围正常组织受损很小或几乎不受损伤。多项研究证实支架联合PDT治疗晚期胆管癌安全有效,与单独应用支架治疗相比,可更好的引流胆汁,延长患者生存时间,改善生存质量,延长支架通畅时间<sup>[41,42]</sup>。Lee等<sup>[43]</sup>认为支架联合光动力治疗较单纯支架治疗可提高患者生存期延长支架通畅时间,并不增加并发症的发生率。在一些报道中少数病例会出现胆管炎或光毒性的不良反应<sup>[44-47]</sup>。

传统的射频消融术(radiofrequency ablation, RFA)主要用于治疗心律失常,近年来逐渐成为肿瘤微创治疗新技术,多用于肝癌等实体性肿瘤的治疗<sup>[48,49]</sup>。在肝内胆管癌的治疗中也有应用<sup>[50,51]</sup>。



胆道内射频消融(endobiliary radiofrequency ablation, RFA)是局部抑制胆管癌生长的又一新方法。其原理是通过高频电流使肿瘤组织、血管凝固坏死。近期的研究认为对于肝外胆管癌,采取胆道支架联合RFA的治疗方法安全有效<sup>[52-55]</sup>。患者在植入胆道支架引流之前,首先应用射频消融电极对肿瘤部位进行灼烧,减轻胆道狭窄,也可进行多次射频消融治疗增强抑瘤效果。胆道支架联合RFA可延长支架通畅时间,减少阻塞率,降低治疗成本,提高生存率<sup>[54,55]</sup>。

支架联合PDT或RFA治疗都是新兴的肿瘤局部治疗手段,通过联合治疗的方法克服了普通支架只能机械性阻止肿瘤生长的不足,已于临床证实可增加之间通畅时间,具有良好的发展前景,然而尚需大样本长时间的研究来证实其疗效。

## 7 结论

支架治疗是胆管癌姑息治疗安全有效的手段,在胆管癌的治疗过程中,选择不同的支架植入路径、支架材质、支架类型、支架数量、载药支架以及支架联合局部治疗的应用与患者的预后密切相关。应根据患者的预期生存期、一般情况、并发症、经济状况等具体情况综合考虑,选择最适治疗方案。新技术的发展也将提高胆管癌支架治疗的效果。目前双层支架(double layer stents, DLS)<sup>[56,57]</sup>、抗返流支架<sup>[58,59]</sup>期望通过改善支架材料、去除侧孔、增加支架内表面光滑程度、减少十二指肠中食物返流等方法延长支架通畅时间,也是新型支架发展的有益尝试,其治疗效果尚待进一步的研究。

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## ■创新盘点

目前对于系统性比较胆管癌不同支架治疗技术,尤其是新型胆道支架及胆道支架联合治疗的报道较少。本文系统性论述了晚期胆管癌支架治疗的目前的研究现状及进展,介绍了胆管癌支架治疗的效果,支架植入路径的选择,不同材质支架的特点及应用,准确把握了载药支架、放射性支架等新兴胆道支架,以及支架联合光动力治疗、射频消融术的发展方向,可为临床和研究提供重要的参考。

## ■应用要点

本文详细介绍了支架植入路径的选择,不同材质支架的特点及应用,准确把握了载药支架、放射性支架等新兴胆道支架以及支架联合光动力治疗、射频消融术的发展方向。在临床应用中,为胆管癌患者选择适合治疗方法提供参考依据。

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## ■同行评价

本文系统性论述了晚期胆管癌支架治疗的目前的研究现状及进展,介绍了胆管癌支架治疗的效果,比较了不同支架植入路径,不同材质类型支架的特点及应用,准确把握了载药支架、放射性支架等新兴胆道支架,以及支架联合光动力治疗、射频消融术的发展方向,可为临床和研究提供重要参考。

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