·专家述评·

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肝外胆管癌的介入治疗现状与展望

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［摘要］ 肝外胆管癌是指源于肝外胆管包括肝门区至胆总管下端胆管的恶性肿瘤。在美国癌症联合会（American Joint Committee on Cancer，AJCC）第8版指南中，肝外胆管癌被分类分为肝门胆管癌和远端胆管癌两部分。近年来，肝外胆管癌的发病率逐渐升高，且预后较差，手术切除在治疗中的局限性逐渐体现。在胆管癌的诊断方面，癌胚抗原

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（carcinoembryonic antigen，CEA）和糖类抗原19-9（carbohydrate antigen 19-9，CA19-9）均无特异性，仅作为提示患者病情改变的标志，便于及时调整治疗。影像学检查如计算机体层成像（computed tomography，CT）或磁共振成像（magnetic resonance imaging，MRI）可以用来进行多期对比，磁共振胰胆管造影（magnetic resonance cholangiopancreatography，MRCP）在肝外胆管癌的诊断中也具有重要的作用。目前，肝部分切除或胆管切除是肝门部胆管癌的常规外科治疗方式，而针对远端胆管癌可以行胰十二指肠切除术，但对于有转移的肝外胆管癌，手术不能达到根治的效果。随着介入治疗技术的发展，针对不可切除的肝外胆管癌的介入治疗将成为新的趋势。近年来，胆道引流、胆道腔内射频消融术（radio frequency ablation，RFA）、胆道支架、放射性粒子植入以及经肝动脉介入治疗等方法在胆管癌治疗中已广泛应用，研究的热点包括胆管癌的胆道引流以及改善胆汁淤积等，目前临床常用的介入治疗方法包括胆管引流术、RFA以及局部放化疗，其中胆道引流术包括经皮穿肝胆管引流术（percutaneous transhepatic biliary drainage，PTBD）、内镜下鼻胆管引流术（endoscopic nasobiliary drainage，ENBD）以及经皮胆道内支架植入术（percutaneous transhepatic biliary stenting，PTBS），对于缓解病情、治疗胆道梗阻均具有较好的效果。RFA通过高频电流产生热量，达到杀死肿瘤细胞的目的。经动脉化疗栓塞术（transarterial chemoembolization，TACE）已成为肝脏肿瘤主要的治疗方式之一，许多学者在TACE联合放射性粒子植入、TACE联合经动脉灌注化疗（hepatic arterial infusion chemotherapy，HAIC）方面进行尝试，并取得了不同程度的成果；^{125}I粒子近距离放射治疗、立体定向放疗、光动力疗法等在一些小样本的临床试验中也取得了一定的效果，但目前仍旧缺乏大样本的临床数据支持。因此，未来在胆管癌的介入治疗方面，放射性粒子或放射性支架置入病变部位以进行局部放疗，或采用TACE联合HAIC，以及采用分子靶向治疗药物和免疫疗法与介入技术的结合等，有望为肝外胆管癌患者提供更多选择。

［**关键词**］胆管癌；介入治疗；胆道引流术；射频消融术

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Progress in interventional therapy of extrahepatic cholangiocarcinoma　WANG Hongbo, YANG Yefa, GE Naijian　(Eastern Hepatobiliary Intervention Center, the Third Affiliated Hospital of Naval Medical University, Shanghai 201805, China)

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［**Abstract**］ Extrahepatic cholangiocarcinoma refers to a malignant tumor originating from the extrahepatic bile duct, including the bile duct from the hilar area to the lower end of the common bile duct. In the 8th edition of American Joint Committee on Cancer (AJCC) guideline, extrahepatic cholangiocarcinoma is classified into two parts: hilar and distal parts. In recent years, the incidence of extrahepatic cholangiocarcinoma has gradually increased, and the prognosis has been poor. The limitations of traditional surgical resection in treatment have gradually manifested. In the diagnosis of cholangiocarcinoma, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are not specific and are only used as a reminder of changes in the condition for patients, which facilitates timely adjustment of treatment. Imaging examinations such as computed tomography (CT)/magnetic resonance imagining (MRI) can be used for multi-phase comparison to achieve the purpose of diagnosis. MRCP also plays an important role in the diagnosis of extrahepatic cholangiocarcinoma. At present, hepatectomy or cholangioectomy is the conventional surgical treatment for hilar cholangiocarcinoma. For distal cholangiocarcinoma, pancreaticoduodenectomy can be performed to achieve the purpose of treatment. However, due to the limitations of traditional surgery, extrahepatic cholangiocarcinoma with metastasis can not be effectively controlled. Therefore, with the development of interventional technology, interventional therapy for unresectable extrahepatic cholangiocarcinoma will become a new trend. In recent years, biliary drainage, radiofrequency ablation of the biliary tract, biliary stents, radioactive particles implantation and transhepatic artery intervention have become more and more mature in the treatment of cholangiocarcinoma. Recent research hotspots include biliary drainage of cholangiocarcinoma and improving cholestasis. The current commonly used interventional treatment methods include bile duct drainage, radiofrequency ablation and local radiotherapy and chemotherapy. Among them, biliary drainage includes percutaneous transhepatic biliary drainage (PTBD), endoscopic nasobiliary drainage (ENBD) and percutaneous transhepatic biliary stenting (PTBS) are effective in relieving the condition and treating biliary obstruction; in addition, radiofrequency ablation generates heat through high-frequency current, which can achieve the purpose of killing tumors. In recent years, transarterial chemoembolization (TACE) has become one of the main treatment options for liver cancer. Many attempts have been made, and various results have been achieved. In addition, ^{125}I particle brachytherapy, stereotactic radiotherapy, photodynamic therapy, etc. have also achieved certain effects in some small-sample clinical trials, but they are still lack of sufficient clinical data to support. Therefore, in the future interventional treatment

of cholangiocarcinoma, radioactive particles or radioactive stents placed in the lesion for local radiotherapy, TACE combined with hepatic arterial infusion chemotherapy (HAIC), as well as molecular targeted drugs and immunotherapy with combination of interventional technology are hopeful to be effective treatment options for patients with extrahepatic cholangiocarcinoma.

［**Key words**］ Cholangiocarcinoma; Interventional therapy; Biliary drainage; Radiofrequency ablation

肝外胆管癌指源于肝外胆管包括肝门区至胆总管下端胆管的恶性肿瘤，根据其解剖位置的不同，可分为2种亚型：肝门部胆管癌和远端胆管癌。在美国癌症联合会（American Joint Committee on Cancer，AJCC）第8版指南中，肝外胆管癌被分为肝门胆管癌和远端胆管癌两部分，此外考虑到肿瘤浸润深度是远端和肝门部胆管癌患者预后的独立预测因子，肿瘤浸润深度被添加到$T_{1\text{-}3}$期中[1]。胆管癌发病率在全球范围内呈上升趋势，目前约占所有原发性肝癌的15%和胃肠道恶性肿瘤的3%[2]。它经常发生在乙型肝炎病毒感染、肝硬化等患者中[3]。肝外胆管癌属于侵袭性肿瘤，由于早期缺少临床特征，大多数患者在就诊时已是晚期[4]。

近年来，在核医学与传统影像技术的结合之下，对肝外胆管癌患者诊疗计划的制定更加完善[5]。目前，肝外胆管癌主要的介入治疗方法包括射频消融术（radio frequency ablation，RFA）、支架植入、胆管引流术和局部放化疗等，对于伴有恶性胆道梗阻的胆管癌患者可以有效地缓解病情，但对于肝门部胆管梗阻的患者应谨慎，有研究[6]报道胆管引流可能与发病率升高相关，因此在确定引流方式时应进行多学科团队（multi-disciplinary team，MDT）会诊之后再进行选择。

目前，在肝脏肿瘤的介入治疗中，经动脉化疗栓塞术（transarterial chemoembolization，TACE）已成为一线治疗方案，近年来，TACE联合放射性粒子植入、TACE联合经动脉灌注化疗（hepatic arterial infusion chemotherapy，HAIC）等针对肝脏肿瘤的治疗[7]，已取得了不同程度的进展。未来，在肝外胆管癌的介入治疗方面，借助放射性粒子支架［如钇（^{90}Y）树脂微球等］进行局部放疗，以及采用具有针对性的化疗方案的HAIC对局部进行灌注化疗，同时结合分子靶向药物和免疫疗法或也将成为值得探索的方向。本文就肝外胆管癌介入治疗领域的研究现状进行综述并对未来发展趋势予以展望。

1 胆道引流术

胆道引流手术的目的是解除胆汁淤积症状进而改善肝功能，对肿瘤本身的治疗作用尚未经证实。常见的引流方式主要有经皮穿肝胆管引流术（percutaneous transhepatic biliary drainage，PTBD）、内镜下鼻胆管引流术（endoscopic nasobiliary drainage，ENBD）以及经皮胆道内支架植入术（percutaneous transhepatic biliary stenting，PTBS）等。

PTBD是在经皮穿肝胆管造影（percutaneous transhepatic cholangiography，PTC）的基础上发展而来的一种胆道微创引流术，包括外引流和内引流等。在有效减轻胆道梗阻症状的同时，PTBD也会导致较为严重的术后并发症，如血管损伤和癌细胞转移[8]。在Coelen等[9]的研究中，胆管癌患者经PTBD治疗后，含有癌细胞的胆道内容物可溢出到腹腔，并导致腹膜播种。因此，在有选择余地时，对胆管癌患者也可优先考虑ENBD，以减少因经皮穿刺操作而引起的肿瘤种植性转移。

近年来，随着内镜技术的发展与成熟，ENBD在解除胆道梗阻方面的应用也越来越多。Maeda等[10]发现，在接受肝门部胆管癌切除术的患者中，ENBD的耐受性良好，且胆管炎的发生率相对较低，因此推荐在术前进行ENBD胆汁引流。Kawashima等[11]的研究发现，与传统的7-Fr ENBD导管相比，改良的6-Fr ENBD导管可以降低ENBD后胆管炎的发生率，二次引流的情况显著减少。此外，Nakamura等[12]的研究中发现，ENBD联合内支架治疗在恶性胆道梗阻的治

疗中可以有效地减少术后需要二次干预的情况。

此外，PTBS也是解除胆管癌胆道梗阻的选择之一。对于胆管癌引起的恶性胆道梗阻，单纯引流可能会再次堵塞胆管。此种情况下，姑息性胆道支架有助于减轻症状，提高患者生活质量[13]。近年来，Anderloni等[14]的研究指出超声内镜引导下使用管腔对置金属支架（lumen-apposing metal stent，LAMS）进行胆总管十二指肠吻合术（endoscopic ultrasound-guided transmural cyst drainage，EUS-CD），可作为恶性梗阻性黄疸和ERCP失败患者的替代治疗方法，临床成功率为97.7%。

2 RFA

RFA是通过高频电流产生热量，对局部组织造成不可逆的细胞损伤，使肿瘤组织凝固坏死，进而达到杀死肿瘤细胞的目的。现有的RFA技术主要包括经皮射频消融术（percutaneous radiofrequency ablation，PRA）以及内镜下射频消融术（endoscopic radiofrequency ablation，ERA）。RFA现已广泛应用于多种类型肝脏肿瘤的治疗，特别是对于部分小肿瘤，接受RFA治疗患者的无瘤生存率及总生存率与手术治疗相当[15]。并且有研究[16]表明，RFA的住院时间、治疗费用和并发症风险均低于传统手术。其主要并发症包括肝脓肿、胆道狭窄或出血等。Gao等[17]发现，相比于单独的支架置入，RFA联合治疗会改善无法手术的原发性肝外胆管癌患者的生活质量。Qi等[18]在一项对比研究中发现，胆管癌合并恶性梗阻性黄疸患者行PTCD+RFA联合胆道支架置入术后，相对于仅行PTCD联合胆道支架置入术的患者，术后黄疸发生情况减少，患者的肝功能和病情得到改善。但也有学者指出，内镜RFA的生存获益似乎仅限于无远处转移的肝外胆管癌患者[19]。此外，相对于经皮途径的手术，有学者认为，内镜下RFA通过提高支架通畅率和延长总生存期，在不可切除的胆管癌患者中有更好的表现[20]。目前，外科设备改进问题至关重要，Inoue等[21]指出，电极和组织接触点的不充分导致消融深度不均，对预后的影响也需要考虑。不可逆电穿孔（irreversible electroporation，IRE）是一种影像引导下通过短脉冲高压电流破坏细胞膜导致细胞凋亡的技术。IRE的目的是通过逐渐隔离节段性胆管来避免或延迟疾病的局部进展。由于没有冷/热沉降效应，IRE可以减少对邻近结构（即门静脉和肝动脉）的损伤，这是IRE相对于其他消融方法（如微波和RFA）的主要优势[22]。

3 放疗与化疗

目前，胆道粒子支架内照射治疗、普通支架联合外放疗、肝动脉介入灌注化疗、光动力疗法以及创新性胆道支架治疗也是晚期肝外胆管癌重要的治疗方式，并可以有效地改善晚期患者的生存质量并延长生存期。

由于肝外胆管癌的病理学分型大多为腺癌，因此放疗联合支架等介入治疗可取得更好的效果[23]。胆道粒子支架内照射治疗可有效地改善胆管癌患者的肝功能，是一种安全、有效、创伤小的胆管癌治疗方法，可考虑在临床上推广应用[24]。Wang等[25]对比了自膨式金属支架联合导管加载^{125}I粒子近距离放疗与传统姑息性手术治疗晚期胆管癌的效果。结果发现，经过粒子支架内照射治疗后，患者的病情显著改善。此外，在恶性梗阻性黄疸的治疗方面，胆管支架联合^{125}I粒子植入治疗能够有效地推迟支架再狭窄发生的时间，低剂量、近距离的放射源能够有效地灭活靶组织，进而控制病变，延长患者的生存期[26]。立体定向放疗（stereotactic body radio therapy，SBRT）是一种小照射野聚焦式的放射治疗，它可以在保证非靶区的正常组织不被破坏的前提下，通过剂量递增技术使靶区达到消融所需要的程度，进而对病变组织进行有效灭活[27]。一项meta分析[28]结果表明，胆管癌切除术后进行外束放疗联合化疗有一定的益处。Baak等[29]探索了化疗后增加SBRT的可行性和安全性，但由于样本量限制，并未发现增加SBRT后对患者的生存质量带来实质性的影响。目前在评价单侧和双

侧置入放射性支架治疗肝门部胆管癌患者的相关临床疗效方面，也存在争议。Wang等[30]对比了两种支架植入方式下不同患者的术后情况，结果并未显示差异有统计学意义。而Kim等[31]在一项对比研究中指出，在恶性胆道梗阻患者中，双侧支架组在胆管炎发生率和6个月死亡率方面优于单侧支架组。值得一提的是，采用^{90}Y树脂微球的内照射放疗近年来也日益广泛地用于肝胆肿瘤的治疗中，Edeline等[32]在一项针对晚期不可切除的肝内胆管癌的Ⅱ期临床试验中，将化疗联合^{90}Y的SIRT作为无法切除的肝内胆管癌的一线治疗方案，结果显示很多患者被降期至可以手术。Paprottka等[33]进行的另一项研究评估了在73例不可切除的肝内胆管癌患者中使用^{90}Y树脂微球进行103次放射栓塞的安全性，认为多次放射栓塞治疗可能会提高患者的生存率，但是必须通过进一步的研究来证实。

近年来，动脉内治疗联合使用化疗药物也被证明能够取得较好的治疗效果。Gairing等[34]报道，在姑息性化疗中联合经动脉化疗栓塞可延长胆管癌患者的生存期。Yang等[35]的meta分析结果显示，由于传统的全身治疗会导致生存质量下降和显著的不良反应，因此在评估使用化疗药物或放疗的研究后，他们认为经动脉治疗是安全有效的治疗选择。此外，也有学者对比了辅助化疗与传统手术在可切除胆管癌中的治疗效果，对于根治性切除术后的胆管癌患者，尤其是晚期患者，应考虑辅助化疗[36]。

光动力疗法（photodynamic therapy，PDT）是用光敏药物和激光活化治疗肿瘤的一种新方法。作为一种新的胆管癌姑息治疗方法，PDT可以有效地改善不可切除胆管癌患者的胆汁淤积和生活质量。一项前瞻性观察研究显示，PDT可用于替代治疗不可切除肝外胆管癌，对于肝外胆管癌患者，结合PDT的辅助放疗具有早期生存优势[37]。此外，超声引导下PDT治疗局部晚期胆胰恶性肿瘤同样取得了较好的效果[38]。经内镜逆行性胰胆管造影术（endoscopic retrograde cholangiopancretography，ERCP）或经皮穿肝胆道内镜术（percutaneous transhepatic cholangioscopy，PTCS）引导的PDT支架置入可延长不可切除的肝门胆管癌患者的生存期[39]。但也有学者对PDT的治疗方式提出了质疑，一项meta分析[40]结果显示，接受PDT治疗的患者总生存率和30 d死亡率均高于RFA或仅支架姑息治疗。

此外，在支架材料的选择以及支架联合局部治疗方面，许多学者也进行了探索。有学者采用可降解的镁支架作为胆道内支架的新选择[41]。目前针对胆管癌肿瘤微环境和免疫治疗等多项相关临床研究和动物实验正在进行中[42]。

4 总结及展望

肝外胆管癌近年来发病率逐渐升高，且预后较差，由于患者早期症状不明显，大部分患者确诊时已不具备外科切除指征。对于不可切除或转移性的患者，胆道引流、消融等局部治疗能缓解症状，改善预后；而联合放疗、化疗以及新型支架治疗等能有效地抑制肿瘤的进一步发展，延长患者生存期[43]。

除了改进局部治疗手段，更有必要对分子靶向药物和免疫疗法进行深入研究。随着局部治疗手段的发展，局部治疗与系统治疗在选择上已没有先后之分。对于肝内多发病灶或肝内肿瘤较大不适宜手术且不伴有远处转移的患者，可以优先选择局部治疗，而对于出现远处转移的患者，则可考虑系统化疗。因此，肝外胆管癌的局部治疗联合系统治疗以及多种局部治疗间的联合应用，将成为今后探索的方向。

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