

• 指南与解读 •

CSCO 胆道系统肿瘤诊断治疗专家共识(2019 年版)

CSCO 胆道肿瘤专家委员会

【关键词】 胆道系统肿瘤; 诊断; 治疗; 共识

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胆道系统肿瘤(biliary tract carcinoma, BTC)主要包括胆囊癌(gallbladder cancers, GBC)和胆管癌(cholangiocarcinomas, CC) 约占所有消化系统肿瘤的 3%^[1], 绝大多数为腺癌, 侵袭性强, 预后极差, 5 年存活率 < 5%。BTC 全球发病率呈现上升趋势, 其中亚洲国家最为常见。BTC 的诊疗明显有别于肝细胞癌(hepatocellular carcinoma, HCC), 但是目前多数指南或共识将其并入 HCC 一起阐述, 国内尚无广泛接受的 BTC 共识。为了提高对 BTC 的认识, 规范诊疗和研究, 经 CSCO 胆道肿瘤专家委员会充分酝酿讨论, 最终形成本共识, 以供临床医生参考。

1 BTC 的诊断原则

1.1 胆囊癌(GBC) 超声波是 GBC 的首选检查方法, 可用于初步诊断和随访。增强 CT 对于 GBC 的诊断敏感性高达 90% 特别是 T₂ 期及以上的肿瘤。MR 对于胆囊壁增厚的判断比 CT 更准确。PET/CT 对 GBC 诊断的灵敏度优于 MR, 可以发现胆囊癌早期病变, 并可检出直径 ≤ 1.0 cm 的转移淋巴结和转移病灶。ERCP 对胆囊癌常规诊断意义不大。

1.2 胆管癌(CC) 超声波是评价胆道梗阻的最常用初始检查方法。增强 CT 检查可以发现肝内肿块型病灶以及胆管壁增厚和强化, 但对肝外胆管癌的诊断具有局限性, 因为许多肝外胆管癌并不表现为可见的病灶。MR/MRCP 能够清晰、完整地显示胆管系统, 了解胆管梗阻的部位及管周浸润情况, 特别适用于评估管周浸润型胆管癌。血清 CA19-9 在 CC 的诊断、随访期间判断肿瘤是否根治切除和评估进展期的治疗效果中有一定的意义, 特异性为 92.7%, 敏感性为 50%。部分病例 CEA、CA125 亦可作为随访指标。

1.3 活检原则 病理组织学和/或细胞学检查是确诊胆囊癌的唯一依据和金标准。获得病理组织学或细胞学标本的方法包括直视下手术活检、胆汁中脱落细胞学检查以及穿刺活检术等。ERCP 下刷检脱落细胞检查是胆管癌首选的病理学诊断方法, 然而活检和刷片的敏感性较低, 当结果为阴性或者不能明确时, 可以考虑 ERCP 引导的活检或超声内镜引导的细针穿刺。

1.4 鉴别诊断 胆囊癌需要与胆囊息肉、胆囊腺瘤、胆囊结石、肝细胞癌侵犯胆囊以及节段型或局限性腺肌增生症等鉴

别。胆管癌需要与肝细胞癌、肝转移癌、胰头癌、十二指肠乳头癌、胆道良性肿瘤、胆道结石以及胆管炎性狭窄相鉴别。检测血清 IgG4 有助于鉴别 IgG4 相关性胆管炎^[2]。

1.5 BTC 的分子病理学 CK7 和 CK19 表达以及 CK20 缺失可能提示肿瘤的起源, 也是病理组织学鉴别诊断和免疫组化检测中应用较多的指标。胆道肿瘤中有较多的基因突变。目前研究较多的相关分子突变包括 TP53、KRAS、ERBB 家族、PIK3CA/AKT、MET、FGFR2、PTEN、STAT3、NOTCH、SMAD4、ROBO2、PEG3、CDKN2A、RAF 等。目前部分针对上述基因改变的分子靶向药物尚处于临床试验阶段。

2 BTC 的分期

本共识中对于 BTC 的分期采用 UICC/AJCC TNM 分期系统(2017 年第八版)^[2], 肝门部胆管癌(pCCA)可以根据 Bismuth-Corlette 标准进一步划分。

3 BTC 外科治疗

3.1 胆囊癌外科治疗

3.1.1 外科治疗原则 根治性切除是原发性胆囊癌彻底治愈的唯一方法^[3], 胆囊癌术前详尽的检查、评估和 TNM 分期有助于确定手术切除范围, 手术需要经验丰富的胆道外科医师完成(证据等级 1A)。对于术前确诊进展期胆囊癌或术中活检确诊胆囊癌者, 建议行开放胆囊癌根治术^[4]。

3.1.2 手术方式的选择 T_{1a} 和 T_{1b} 的胆囊癌进行单纯胆囊切除术即可, 大多为意外胆囊癌^[5]。T_{1b} 期的胆囊癌应行胆囊癌根治术, 手术范围包括胆囊及胆囊床周围 2 cm 的肝实质, 肝脏切缘必须阴性; T₂ 期和 T₃N₀ 期行 S4b+S5 肝切除术; 对于肿瘤浸润肝实质超过 2 cm、位于胆囊颈部、侵犯胆囊三角或合并肝十二指肠韧带淋巴结转移者(T₃N₁ 期), 需行右半肝或右三叶肝切除术; 未远处转移的 T₄ 期胆囊癌患者可行包括右半肝或右三叶肝切除的联合脏器切除, 合并远处转移者不建议胆囊癌根治术^[6-10](证据等级 2A)。

3.1.3 淋巴结清扫范围 T_{1a} 或 T_{1b} 期胆囊癌无需行区域淋巴结清扫。T_{1b} 期以上清扫范围包括肝十二指肠韧带(12 组)、肝动脉(8 组)和胰头周围(13 组)。术中第 8 组或第 13 组淋巴结活检阳性, 可扩大清扫腹腔干周围淋巴结^[11-12], 第

16 组淋巴结阳性不建议进行手术。胆囊癌淋巴结的清扫数目至少 6 个^[13](证据等级 2A)。

3.1.4 肝外胆管处理 不建议为了增加淋巴结清扫数目而联合肝外胆管切除,因为并不能提高生存率^[14]。胆囊管癌或胆囊颈部癌累及肝外胆管伴有梗阻性黄疸,可以联合肝外胆管切除,术中切缘必须阴性,争取达到 R₀ 切除,行肝门胆管空肠吻合术^[14-18](证据等级 2A)。

3.1.5 联合脏器切除及血管重建 没有远处转移的 T₄ 期胆囊癌已经侵犯周围器官者,可以行扩大根治术,包括联合切除肝外胆管,右三叶肝切除,门静脉切除重建,右半结肠切除和胰十二指肠切除等^[19-22]。门静脉累及是胆囊癌 R₀ 切除的唯一障碍,可以考虑联合门静脉切除重建的胆囊癌根治术,否则建议手术胆道引流^[23-24](证据等级 2A)。

3.1.6 意外胆囊癌 术中发现的意外胆囊癌应进行胆囊病灶和可疑淋巴结的冰冻切片检查,根据冰冻结果进行 TNM 分期,再制定相应的手术范围(证据等级 2A)。术后病理报告证实为 T_{is} 或 T_{1a} 期胆囊癌,切缘阴性者建议密切观察; T_{1b} 期以上者,再次术前需行增强腹盆腔 CT/MRI 和胸部 CT,依据分期行胆囊癌根治术(证据等级 2A)。

3.2 肝内胆管癌外科治疗

3.2.1 手术指征和术前探查 排除肝脏多发病灶及远处转移,可切除的肝内胆管癌建议行手术切除。分期不明者可术中腹腔镜探查,依据探查结果确定手术方式^[25-26](证据等级 2A)。

3.2.2 手术治疗原则 根治性切除是肝内胆管癌获得治愈的唯一方法, R₀ 切除可以改善患者的预后并降低复发风险,肝脏和胆管切缘均要求阴性^[27-34]。胆管切缘距离尚无定论^[32,34](证据等级 2A)。

3.2.3 淋巴结清扫 肝内胆管癌淋巴结转移率超过 30%,淋巴结转移是预测患者预后的重要指标,建议常规行区域淋巴结清扫(包括肝十二指肠、肝动脉和胰头周围)^[32,35]。检出淋巴结数目建议不得少于 6 枚(证据等级 2A)。

3.2.4 肝内胆管癌复发的手术 肝内胆管癌复发部位仍以肝内为主^[36-43],其中约 10% 复发者可以再次手术,建议二次手术切除,仍有生存获益^[44](证据等级 2A)。

3.2.5 肝移植选择 符合移植指征同时残余肝体积不足或者肝功能异常者,肝移植是最有潜力的治疗手段^[45],但需严格排除淋巴结转移、血管侵犯、肝外胆管侵犯等^[46-47]。极早期(肿瘤 < 2 cm)合并肝硬化的肝内胆管癌患者,肝移植治疗效果颇佳^[48](证据等级 2A)。

3.3 肝门部胆管癌外科治疗

3.3.1 手术治疗原则 根治性 R₀ 切除手术是肝门部胆管癌患者获得治愈可能的唯一方法^[49-57]。建议术中胆管切缘常规冰冻检查以确认切缘阴性^[58-59]。大范围肝切除合并肝外胆管切除可提高 R₀ 切除率^[60-62](证据等级 1A)。

3.3.2 手术方式选择 需根据不同肿瘤分型选择合适的手术方式。Bismuth I 型、肿瘤未侵犯尾状叶胆管开口的 II 型

患者可行围肝门部胆管肿瘤切除。位于肝管分叉部的 Bismuth II 型患者需联合肝脏 S4b 段切除或左、右半肝切除; IIIa 型建议行右半肝切除^[63], IIIb 型建议行左半肝切除; IV 型建议行肝中叶切除或扩大左、右半肝切除^[64],以上分期均同时全尾状叶切除^[65-71](证据等级 2A)。

3.3.3 淋巴结清扫范围 淋巴结转移是影响患者预后的重要因素。淋巴结阴性的患者 5 年生存率 30%,局部淋巴结转移者仅 15%,腹主动脉旁淋巴结转移者下降至 12%。淋巴结清扫范围包括:肝十二指肠韧带内淋巴结(12 组)、胰头后方淋巴结(13 组)和肝总动脉旁淋巴结(8 组)^[72]。如果腹主动脉旁淋巴结阳性,则无手术指征(证据等级 2A)。

3.3.4 胆道重建方式 胆道重建方式建议采用经典的胆管-空肠 Roux-en-Y 吻合。肝切除术后如果出现多个胆管断端开口,建议尽可能通过胆管成形术将各胆管开口整合,减少吻合口数量,既可防治胆漏,也可预防胆肠吻合口狭窄。管径较细的胆管可置入支撑引流管。

3.3.5 血管切除重建 术中门静脉或肝动脉的切除重建可以提高 R₀ 切除率^[73-74]。对于肝动脉或门静脉的切除能达到 R₀ 切除者,手术可考虑联合切除重建(证据等级 2A)。

3.3.6 肝移植选择 肝移植能提高肝门部胆管癌患者的总体生存率^[75-78]。如果肿瘤相对局限、没有远处淋巴结转移和远处转移,患者条件允许可考虑行肝移植^[79-80](证据等级 2A)。

3.3.7 术前减黄和门静脉栓塞选择 术前是否需要放置胆道引流管减黄治疗还存在争议。支持者认为术前胆道引流减黄能够改善肝肾功能、凝血功能,缓解胆管炎,提高预留肝脏的储备功能^[81-84]。反对者认为术前胆道引流减黄不能降低手术并发症和病死率,反而增加腹腔出血、胆道感染和肿瘤播散的风险,并且推迟了手术时间,导致肿瘤的进展^[83,85](证据等级 2A)。

只有当出现胆管炎、长时间的胆道梗阻、营养较差及血清总胆红素 > 200 μmol/L 以及需要做大范围肝切除而残余肝体积小于 < 40% 的时候才主张胆道引流^[86]。胆道引流的方法包括经皮经肝胆管引流(PTCD)、内镜逆行鼻胆管引流/支架(ENBD/ERBD)。ENBD 对于 III 型以上肝门部胆管癌需多支引流的患者操作较困难,且长时间引流患者较难耐受,胆管下段炎症水肿严重,对后期的手术造成较大影响,因而 PTCD 引流较为常用。对于引流部位首先穿刺保留健侧肝脏的胆管引流,对肝功能差、黄疸指数高的患者可实施多支胆管引流(证据等级 2A)。为了行扩大的肝脏切除,避免肝脏切除术后肝功能不全的发生,当剩余肝体积小于 30%~40% 时,可行患侧的门静脉栓塞(PVE)^[87-89]。门静脉栓塞前需先行预留侧肝叶的胆道引流以利于预留肝脏再生,一般建议在减黄或栓塞后 4~6 周手术(证据等级 2A)。

3.3.8 腹腔镜手术选择 随着医学影像学检查的发展,腹腔镜探查用于评估分期已基本摒弃。腹腔镜下行门静脉结扎可代替门静脉栓塞,可以更精确的阻断门静脉血流,避免异位栓塞^[90-91]。部分 I 型和 II 型的肝门部胆管癌可在腹腔

镜下行胆管切除、部分肝脏切除、胆肠吻合、肝门淋巴结清扫。腹腔镜手术治疗肝门部胆管癌对于术者的要求较高,手术难度较大,暂时未被广泛接受(证据等级 3)。

3.4 远端胆管癌外科治疗

3.4.1 手术治疗原则 根治性的 R₀ 切除是患者唯一获得治愈的有效手段,术中对于胆管切缘、胰管切缘需进行术中冰冻病理检查,确认切缘未见肿瘤累及^[92](证据等级 1A)。

3.4.2 手术方式选择 对于远端胆管癌,建议行胰十二指肠切除术,切缘保证阴性(证据等级 2A)。标准的 Whipple 术和保留胃幽门的胰十二指肠切除术(PPPD)的治疗效果和并发症发生率无明显差别。早期远端胆管癌腹腔镜及机器人手术与开放手术相比远期疗效无明显差别,但是在术后的快速康复方面有明显的优势^[93-94](证据等级 2A)。

3.4.3 对可切除性的判断 胸部、腹部及盆腔多层螺旋 CT(MDCT)是目前公认的评估有无转移的有效手段。推荐同时进行 MDCT 和 MRCP,以评估有无血管侵犯(主要是门静脉和肝动脉)^[95-96](证据等级 2A)。PET/CT 特异性较高,可以在 CT 或磁共振结果模棱两可的情况下用于评估患者有无转移^[97](证据等级 2A)。当有证据表明肿瘤侵犯肝总动脉、门静脉主干、同时侵犯肝左右动脉、同时侵犯门脉左右支、远处淋巴结转移(胸腔、颈部、肠系膜根部、主动脉旁)或者有明显的远处占位性病变可疑转移时,肿瘤无法根治性切除。对于远端胆管癌或者壶腹部癌,胆管扩张但 CT/MR 未见病灶,可以用 EUS 来评估,必要时可以在 EUS 引导下对可疑病灶或者淋巴结进行穿刺活检(证据等级 2A)。

3.4.4 淋巴结清扫范围 区域淋巴结清扫范围包括胰十二指肠韧带内淋巴结、胰十二指肠前方和后方的淋巴结,以及肠系膜上动脉右侧淋巴结。为了准确判断 N 分期,建议最少检出淋巴结数目为 12 枚,当淋巴结检出数目少于 12 枚且未发现转移时,应标注为 pN₀(证据等级 2A)。

3.4.5 肝移植选择 远端胆管癌不建议行肝移植手术^[98-102]。

3.4.6 术前减黄选择 目前术前减黄治疗仍存在较大争议,多项研究表明术前减黄与否在术后并发症率、病死率上并无显著性差异,但术前减黄可以减轻黄疸带来的瘙痒和疼痛,改善患者的术前状态使之更易耐受手术^[103]。目前支持者建议综合考虑患者的全身情况和拟定的手术方式,包括年龄、黄疸持续时间、凝血功能、营养状态、肿瘤的生长方式和拟行手术方式等。在胰十二指肠切除术患者中,认为“减黄指标=年龄×3+总胆红素值(μmol/L)”,若减黄指标>380,建议行术前减黄^[104]。由于肝外胆管癌和壶腹部癌引起低位恶性梗阻,引流优先选择 ERBD,用最少的支架起到最好的引流效果。若 ERBD 失败,则用 ENBD;若 ENBD 失败,则选择 PTCD,PTCD 尽量选择单侧引流达到减黄效果^[105-106]。术前减黄的时间和手术时机方面也存在较大争议,目前支持者建议减黄时间以使肝功能显著改善或基本恢复正常为宜,不

应当设置具体的减黄时限^[107](证据等级 2A)。

3.4.7 姑息性治疗 对于无法切除的胆管肿瘤患者往往伴有梗阻性黄疸,除辅助治疗外,应当对于患者进行胆汁的引流,建议优先使用 ERBD(金属支架或者塑料支架)内引流,若 ERBD 失败,可行 PTCD 外引流(证据等级 2A)。姑息性胆肠内引流术是解决梗阻性黄疸的另一重要手段,因其无胆汁丢失,明显改善生活质量,如有十二指肠梗阻要加行胃空肠吻合。晚期 BTC 的营养治疗,包括肠内(ONS 或 EN)、肠外营养治疗(PN)。由于晚期 BTC 患者常伴有比较严重的营养不良,影响其对治疗的耐受性和依从性。因此,对 BTC 患者进行营养评估和干预、改善一般状况、提高生活质量,是姑息治疗的重要内容(证据等级 2A)。

4 BTC 放射治疗

放射治疗在术后辅助以及局部晚期病灶的姑息治疗上占据重要地位^[108-109]。根据肿瘤的侵袭范围,以及是否可手术切除,放射治疗可分为三类:可手术切除的术后辅助放疗、术前局部晚期新辅助放化疗、不可手术切除的以及转移性 BTC 的姑息放疗。

4.1 肝内胆管癌

4.1.1 术后辅助放化疗 目前并不推荐对手术时达到 R₀ 切除、N⁻的患者行辅助放疗。而仅对 R_{1/2} 或 N⁺者推荐进行术后辅助放疗(证据等级 2A)。

注释:(1)放疗剂量:推荐辅助放疗的剂量为:45~50.4Gy,1.8~2.0Gy/F;R₁ 切除则瘤床区和切缘再增量至 54~59.4Gy;R₂ 切除可补量至 66~70Gy,但需考虑正常器官的受量。(2)放疗靶区范围:放疗靶区需包括原发肿瘤瘤床以及区域淋巴结(胆管周围淋巴结、胰十二指肠淋巴结、肝门淋巴结、胰头后淋巴结、肠系膜上淋巴结以及腹主动脉旁淋巴结区域;对于原发灶位于左侧肝叶的尚需考虑胃小弯及胃左动脉淋巴引流区)^[110-113]。(3)放疗开始时间:目前对于术后应该开始行放射治疗的最佳时间尚无定论,基于现有回顾性研究以及前瞻性 II 期临床研究 SWOG S0809 结果,建议术后同步放化疗可在术后 8 周以后开始,而且如果与术后辅助化疗联合,可先行术后辅助化疗 2~4 周期后行同步放化疗^[108-109]。(4)同步化疗方案:与放疗同步的化疗药物目前首选推荐为氟尿嘧啶类(5-FU 或含卡培他滨方案),可考虑吉西他滨同步放疗,但未被广泛接受^[110-111]。

4.1.2 术前新辅助放化疗 相较于肝外胆管癌,肝内胆管癌新辅助放疗的作用及意义存在更高的争议性,目前研究多来自小样本回顾性研究。基于现有研究结论,建议在如下情况下可以考虑进行新辅助放疗:①肝内病灶长径≤6 cm;②肝内病灶及淋巴结转移在手术切除范围内;③无肝内及肝外播散转移^[114]。新辅助放疗模式可参考肝外新辅助治疗方案,也可采用 SBRT 技术,参考剂量模式为 40Gy/5F^[109](证据等级 3)。

4.1.3 局部晚期姑息治疗可参见肝外胆管癌治疗部分

4.2 肝外胆管癌(包括肝门部及远端胆管癌)

4.2.1 术后辅助放化疗 基于部分回顾性研究和前瞻性 II 期临床研究 SWOG S0809 结果^[108-109],局部进展期可手术切除的肝外胆管癌术后采取吉西他滨联合卡培他滨的辅助化疗,以及卡培他滨为基础同步放化疗,能带来局控及生存的获益^[108]。因此目前推荐:①对于可手术切除的肝外胆管癌,若为 R₀ 切除但 pT_{3/4} 或 N⁺;② R_{1/2} 术后,推荐进行以 5-FU 或卡培他滨为基础的放化疗(证据等级 2A)。

注释:(1)放疗剂量:瘤床及淋巴引流区放疗剂量为 45~50.4Gy,单次 1.8~2.0Gy, R₁ 切除则瘤床区和切缘再增量至 54~59.4Gy, R₂ 切除可补量至 66~70Gy,但需考虑正常器官的受量;如果采用 IMRT 技术,可在放射治疗中予瘤床同步补量 52.5 Gy/25F, R₁ 切除则剂量可达到 55 Gy/25F^[108,110]。(2)放射靶区的确定:术后放疗靶区需包括:原发肿瘤床、对肝门区肿瘤尚需包括肝脏切缘、吻合口以及区域淋巴结。基于肿瘤部位对应不同区域淋巴引流区,如对于肝门胆管癌,淋巴引流区包括肝十二指肠淋巴结、肝门淋巴结、腹腔干、上腹主动脉旁淋巴结、胰头后方淋巴结,并需考虑胃左动脉及胃小弯侧淋巴引流区^[112-113];对远端胆管癌,淋巴引流区包括肝门淋巴结、肝十二指肠、胰头后淋巴结、肠系膜淋巴结以及腹主动脉引流区,而对于腹腔干淋巴结由于转移风险率低,建议结合影像学评估考虑是否勾画^[112-113]。计划靶区是基于体内脏器移动及摆位误差,于临床靶区外放 5~10 mm 范围^[108]。(3)放疗开始时间:目前对于术后应该开始行放射治疗的最佳时间尚无定论,基于现有回顾性研究以及前瞻性 II 期临床研究 SWOG S0809 结果,建议术后同步放化疗可在术后 8 周开始,而且如果与术后辅助化疗联合,可先行术后辅助化疗 2~4 周期后行同步放化疗^[108,115]。(4)同步化疗方案:主体推荐为氟尿嘧啶类(5-FU 持续静脉滴注,或卡培他滨),而吉西他滨同步放化疗仅见于小样本或回顾性研究,尚未被广泛接受^[109]。

4.2.2 术前新辅助放化疗 术前新辅助放化疗在局部晚期 BTC 中的临床使用价值尚有待考量。现有部分研究显示,对可能切除的 BTC 行术前新辅助放化疗可以达到降期,提高 R₀ 切除率,延长生存的作用,但尚缺乏高级别循证医学证据。建议对 T₃ 以上或者 N⁺ 的局部进展期病灶可考虑行术前放化疗,可能降低分期,提高手术切除率(证据等级 2B)^[116-120]。

注释:(1)放疗靶区及剂量:治疗前影像学所确定的可视肿瘤(原发及转移淋巴结等),可适当外扩包括高危的淋巴结引流区。术前放疗剂量:DT 40~45Gy,单次 1.8~2.0Gy,评估疗效后再决定后续治疗。(2)同步化疗方案为:推荐首选以氟尿嘧啶类(5-FU 持续输注或含卡培他滨方案)为主^[116-117],吉西他滨同样可考虑与放疗同步应用,但要注意防止骨髓抑制^[118-119]。

4.2.3 不可手术切除及转移性胆管癌的姑息放疗 对于不能切除的局部晚期 BTC,如体能状态良好,无阻塞性黄疸,常

规剂量放疗联合同步化疗,相较于单纯化疗或放疗已显示出在缓解症状和延长生存上的优势^[121-123],因此是目前被广泛接受的姑息性放疗方式。除此以外,现有的临床数据已显示大分割放疗方式如 SBRT,已给肝内胆管癌以及病变局限的肝外及胆囊癌带来明显局控及生存的获益^[124-125],而其他放疗方式如质子治疗等,尚缺乏充足的临床研究数据支持^[126]。因此,目前对姑息性放疗的推荐:①对于 BTC 存在广泛淋巴结转移,放疗靶区范围较大者,优先考虑常规剂量放疗联合同步化疗(证据等级 2A);②对于局限的肝内胆管癌,优先考虑 SBRT 治疗(证据等级 2B),而肝外胆管及胆囊癌尽管存在淋巴结转移,但病变较局限者,或仅针对局限病灶行减症放疗,同样可考虑 SBRT 治疗,但需严格考量放疗剂量及正常组织的耐受性(证据等级 3)。

注释:(1)放疗靶区及剂量:基于影像学结果,如增强 CT、MRI 等确定治疗靶区。放疗靶区包括原发肿瘤区、转移淋巴结及可适当外扩包括高危区域淋巴结。放射剂量在肿瘤区域及淋巴引流区为 45~50.4Gy,单次 1.8~2.0Gy,依据患者耐受情况,可将肿瘤区域增量至 60Gy 或更高剂量,治疗中需考虑危及器官受量^[127]。对于高剂量少分割放射治疗如 SBRT,推荐仅照射原发肿瘤和转移淋巴结,不建议包括高危淋巴结引流区。目前对 SBRT 尚无统一剂量模式作为标准推荐,可参考的剂量分割为 30~50Gy/3~5F,单次分割剂量与分割次数的确定有赖于靶区与危及器官的距离及危及器官受量^[109]。(2)化疗方案:与放疗同步的化疗方案可采用吉西他滨或氟尿嘧啶类(5-FU 持续静脉滴注,或卡培他滨),联合化疗方案可采用吉西他滨或氟尿嘧啶类为基础的方案^[109]。

4.3 胆囊癌 术后辅助、新辅助以及局部晚期放射治疗参照肝外胆管癌(肝门部胆管癌)治疗部分,仅放射治疗淋巴结靶区需包括肝门淋巴结、肝十二指肠、腹腔干淋巴结、胰头后淋巴结、肠系膜淋巴结以及腹主动脉引流区。

5 BTC 的系统治疗

5.1 辅助化疗 BTC 具有较高的复发率和远处转移率,因此有必要进行术后辅助化疗。根据已发表的 III 期临床研究结果,综合专家共识,作如下推荐:(1)基于 III 期随机对照 BILCAP 研究结果,推荐口服卡培他滨半年为肝内外胆管癌及肌层浸润性胆囊癌患者术后标准辅助化疗方案^[128](证据等级 1A)。(2)基于一项日本多中心 III 期研究结果,胆囊癌患者术后采用 5-FU 联合丝裂霉素 C(MMC)方案辅助化疗可提高 5 年无疾病生存率和 5 年总生存率^[129],因此亦可选用该方案(证据等级 2B)。(3)基于 III 期随机对照 PRODIGE-12 研究结果,吉西他滨联合奥沙利铂方案辅助化疗并不能提高 BTC 术后的 RFS 和 OS,故不推荐该方案用于 BTC 术后的辅助治疗^[130](证据等级 2B)。因 BTC 辅助治疗的循证医学证据较少,根据部分 II 期临床研究结果以及晚期 BTC 的常用治疗方案,综合专家共识,也可选用以 5-FU 或吉西他滨为基础的方案用于 BTC 术后辅助化疗,如吉西他滨

联合顺铂、吉西他滨联合卡培他滨、吉西他滨联合替吉奥,以及卡培他滨联合奥沙利铂等方案^[131-134](证据等级 2A)。建议继续开展相关临床试验以优化 BTC 的辅助治疗策略。

5.2 新辅助化疗 目前新辅助化疗在 BTC 治疗中的作用尚缺乏高质量临床研究结果支持。鉴于 ABC-02 研究中吉西他滨联合顺铂方案化疗在晚期 BTC 中的作用,综合专家共识,可考虑将该方案用于 BTC 的新辅助化疗^[135](证据等级 2A)。对于部分拟接受肝移植的肝门部胆管癌患者而言,有研究表明肝移植术前接受新辅助治疗可显著提高生存率^[136](证据等级 2B),可考虑选用。鉴于 BTC 新辅助治疗的循证医学证据极少,建议开展相关临床研究以明确新辅助治疗在 BTC 治疗中的作用。

5.3 晚期系统治疗 晚期 BTC 以系统性药物治疗为主。根据已发表的 III 期临床研究结果,综合专家共识,作如下推荐:(1) 基于 III 期随机对照 ABC-02 研究结果,推荐吉西他滨联合顺铂为晚期 BTC 的一线标准治疗方案^[135](证据等级 1A),该方案可将晚期 BTC 患者的 OS 从 8.1 个月提高到 11.7 个月。(2) 基于 III 期随机对照 JCOG1113/FUGA-BT 研究结果^[137],吉西他滨联合替吉奥方案用于晚期 BTC 的一线治疗,其疗效不劣于吉西他滨联合顺铂方案,因此亦推荐该方案作为晚期 BTC 的一线治疗选择(证据等级 1A)。(3) 对于肾功能不全的晚期 BTC 患者,可选用吉西他滨联合奥沙利铂方案,以替代顺铂,减少肾毒性(证据等级 2A)。基于部分 II 期研究结果,其他可选择的两药联合一线治疗方案包括吉西他滨联合 5-FU、吉西他滨联合卡培他滨、吉西他滨联合白蛋白紫杉醇、奥沙利铂联合 5-FU、奥沙利铂联合卡培他滨、顺铂联合卡培他滨,以及白蛋白紫杉醇联合替吉奥等,可根据各医疗中心的使用经验及患者的具体情况选用^[138-144](证据等级 2B)。对于 PS2 的患者,可考虑吉西他滨单药治疗(证据等级 1B)。鉴于两药联合方案治疗晚期 BTC 的 OS 仍较短,目前亦有部分研究初步探索了三药方案一线治疗 BTC 的有效性和安全性。吉西他滨/顺铂/白蛋白紫杉醇方案获得了 11.8 个月的 PFS 及 19.2 个月的 OS^[145];吉西他滨/亚叶酸钙/卡培他滨方案获得了 13 个月的 OS^[146];奥沙利铂/伊立替康/替吉奥方案获得了 12.5 个月的 OS^[147];这些研究均表明三药联合方案化疗在晚期 BTC 治疗中可能带来更高的有效率和进一步的生存获益,但三药方案的毒性较为明显。根据以上临床研究结果,综合专家共识,推荐在有经验的中心,筛选体能状况较好的 BTC 患者使用三药方案一线治疗,并严密监测毒副反应(证据等级 2B)。鉴于晚期 BTC 药物治疗的循证医学证据仍较少,建议继续开展相关临床试验以优化晚期 BTC 的治疗策略。晚期 BTC 二线化疗的循证医学依据较少。基于 III 期随机对照 ABC-06 研究结果,在积极控制症状的基础上,奥沙利铂联合 5-FU (mFOLFOX) 方案二线化疗可将 OS 从 5.3 个月提高到 6.2 个月^[148],因此推荐该方案为晚期 BTC 二线治疗的标准方案(证据等级 I A);根据一项随机 II 期研究结果,使用伊立替康联合卡培他

滨方案二线化疗可较伊立替康单药二线化疗提高 1.3 个月的 PFS,耐受性良好^[149],也可选用(证据等级 2A)。根据一项 II 期单臂研究结果,奥沙利铂/伊立替康/5-FU 三药联合方案获得了 10.7 个月的 OS^[150],亦可作为体能状况较好患者的治疗选择。鉴于晚期 BTC 二线治疗的循证医学证据极少,建议继续开展相关临床研究以优化晚期 BTC 的二线治疗策略。

5.4 BTC 的免疫治疗 免疫检查点抑制剂在 BTC 的治疗中做了许多探索。目前尚无辅助治疗证据。对于晚期 BTC 一线治疗,免疫检查点抑制剂与化疗或靶向药物联合治疗仍处于临床试验阶段。鉴于纳武利尤单抗联合 GC 方案有效率达 36.7%,中位 OS15.4 个月,故该方案可作为一线治疗的选择(证据等级 2A)。对于晚期二线及以上且 MSI-H 的患者,可选择应用帕博利珠单抗治疗^[151-152](证据等级 2A)。由于晚期 BTC 难治,而现阶段免疫治疗证据尚不充分,鼓励患者积极参加临床试验。其他常用的免疫治疗方法包括胸腺肽类药物、干扰素、免疫细胞治疗、肿瘤疫苗、溶链菌素及免疫核糖核酸等,均无较高级别临床研究证据,不作为常规治疗推荐,鼓励患者参加临床试验。

6 BTC 的随访

BTC 的随访目前尚无统一的标准,一般根据疾病的不同阶段具体安排。随访内容一般包括:临床检查、血液检测,包括血常规、生化、肿瘤标志物(CEA、CA19-9)及胸腹盆腔 CT 或胸部 CT、腹部 MR 扫描。根治性术后的患者,两年以内每 3 个月随访 1 次;2~5 年期间 6 个月随访 1 次;5 年后随访时间可以延长至一年一次。对术前 CEA 和(或) CA19-9 升高的患者,若实验室检查发现二者或单一指标升高,可以随时安排临床检查,包括血液检测[包括血常规、生化、肿瘤标志物(CEA、CA19-9 等)]及胸腹盆腔 CT 或胸部 CT、腹部 MR 扫描。晚期患者在接受全身或局部治疗期间,按评价疗效要求或根据并发症,8~12 周随访一次。CA19-9 和(或) CEA 可用于病情监测。

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参考文献

[1] Benavides M , Anton A , Gallego J , et al. Biliary tract cancers: SEOM clinical guidelines [J]. Clin Transl Oncol ,2015 ,17(12) : 982-987.

[2] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) [J]. Hepatobiliary Cancers. Version 1. 2018.

[3] Wernberg JA , Lucarelli DD. Gallbladder cancer [J]. Surg Clin North Am , 2014 , 94(2) : 343-360.

[4] Duffy A , Capanu M , Abou-Alfa GK , et al. Gallbladder cancer (GBC) : 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC) [J]. J Surg Oncol , 2008 , 98(7) : 485-489.

[5] Wakai T , Shirai Y , Yokoyama N , et al. Early gallbladder carcinoma does not warrant radical resection [J]. Br J Surg , 2001 , 88(5) : 675-678.

[6] Yoshikawa T , Araida T , Azuma T , et al. Bisubsegmental liver resection for gallbladder cancer [J]. Hepatogastroenterology , 1998 , 45(19) : 14-19.

[7] Sasaki R , Takeda Y , Hoshikawa K , et al. Long-term results of central inferior (S4a+SS) hepatic subsegmentectomy combined with extended lymphadenectomy for gallbladder carcinoma with subserous or mild liver invasion (pT2-3) and nodal involvement: a preliminary report [J]. Hepatogastroenterology , 2004 , 51(55) : 215-218.

[8] Miyazaki M , Shimizu H , Ohtsuka M , et al. Hepatic S4a+S5 and bile duct resection for gallbladder carcinoma [J]. J Hepatobiliary Pancreatic Sci , 2012 , 19(3) : 225-229.

[9] Ohtsuka M , Miyazaki M , Itoh H , et al. Routes of hepatic metastasis of gallbladder carcinoma [J]. Am J Clin Pathol , 1998 , 109(1) : 62-68.

[10] Horiguchi A , Miyakawa S , Ishihara S , et al. Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma [J]. J Hepatobiliary Pancreat Sci , 2013 , 20(5) : 518-524.

[11] Goetze TO , Paolucci V. The prognostic impact of positive lymph nodes in stages T1 to T3 incidental gallbladder carcinoma: results of the German registry [J]. Surg Endosc , 2012 , 26(5) : 1382-1389.

[12] Shirai Y , Wakai T , Sakata J , et al. Regional lymphadenectomy for gallbladder cancer: rational extent , technical details , and patient outcomes [J]. World J Gastroenterol , 2012 , 18(22) : 2775-2783.

[13] Negi SS , Singh A , Chaudhary A. Lymph nodal involvement as

prognostic factor in gallbladder cancer: location , count or ratio? [J]. J Gastrointest Surg , 2011 , 15(6) : 1017-1025.

[14] Birnbaum DJ , Viganò L , Russolillo N , et al. Lymph node metastases in patients undergoing surgery for a gallbladder cancer. Extension of the lymph node dissection and prognostic value of the lymph node ratio [J]. Ann Surg Oncol , 2015 , 22(3) : 811-818.

[15] Sasaki K , Matsuda M , Hashimoto M , et al. Early cystic duct carcinoma of new classification [J]. Int J Surg Case Rep , 2011 , 2(8) : 246-249.

[16] Nishio H , Ebata T , Yokoyama Y , et al. Gallbladder cancer involving the extrahepatic bile duct is worthy of resection [J]. Ann Surg , 2011 , 253(5) : 953-960.

[17] Fuks D , Regimbeau JM , Le Treut YP , et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group [J]. World J Surg , 2011 , 35(8) : 1887-1897.

[18] Nakata T , Kobayashi A , Miwa S , et al. Impact of tumor spread to the cystic duct on the prognosis of patients with gallbladder carcinoma [J]. World J Surg , 2007 , 31(1) : 155-163.

[19] Agarwal AK , Mandal S , Singh S , et al. Gallbladder cancer with duodenal infiltration: is it still resectable? [J]. J Gastrointest Surg , 2007 , 11(12) : 1722-1727.

[20] Ebata T , Yokoyama Y , Igami T , et al. Review of hepato-pancreato-duodenectomy for biliary cancer: an extended radical approach of Japanese origin [J]. J Hepatobiliary Pancreat Sci , 2014 , 21(8) : 550-555.

[21] Miwa S , Kobayashi A , Akahane Y , et al. Is major hepatectomy with pancreato-duodenectomy justified for advanced biliary malignancy? [J]. J Hepatobiliary Pancreat Surg , 2007 , 14(2) : 136-141.

[22] Ota T , Araida T , Yamamoto M , et al. Operative outcome and problems of right hepatic lobectomy with pancreatoduodenectomy for advanced carcinoma of the biliary tract [J]. J Hepatobiliary Pancreat Surg , 2007 , 14(2) : 155-158.

[23] Maker AV , Butte JM , Oxenberg J , et al. Is port site resection necessary in the surgical management of gallbladder cancer [J]. Ann Surg Oncol , 2012 , 19(2) : 409-417.

[24] Kurosaki I , Hatakeyama K , Minagawa M , et al. Portal vein resection in surgery for cancer of biliary tract and pancreas: special reference to the relationship between the surgical outcome and site of primary tumor [J]. J Gastrointest Surg , 2008 , 12(5) : 907-918.

[25] Goere D , Waghholikar GD , Pessaux P , et al. Utility of staging laparoscopy in subsets of biliary cancers: laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma [J]. Surg Endosc , 2006 , 20(5) : 721-725.

[26] Joseph S , Connor S , Garden OJ. Staging laparoscopy for cholangiocarcinoma [J]. HPB (Oxford) , 2008 , 10: 116-119.

[27] Nakagohri T , Asano T , Kinoshita H , et al. Aggressive surgical resection for hilar-invasive and peripheral intrahepatic cholangiocarcinoma [J]. World J Surg , 2003 , 27(3) : 289-293.

[28] Konstadoulakis MM , Roayaie S , Gomatos IP , et al. Fifteen-year ,

- single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome [J]. *Surgery*, 2008, 143(3): 366-374.
- [29] Paik KY, Jung JC, Heo JS, et al. What prognostic factors are important for resected intrahepatic cholangiocarcinoma? [J]. *J Gastroenterol Hepatol*, 2008, 23(5): 766-770.
- [30] Lang H, Sotiropoulos GC, Sgourakis G, et al. Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients [J]. *J Am Coll Surg*, 2009, 208(2): 218-228.
- [31] Murakami Y, Uemura K, Sudo T, et al. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma [J]. *Ann Surg Oncol*, 2011, 18(3): 651-658.
- [32] Ribero D, Pinna AD, Guglielmi A, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: A multi-institutional analysis of 434 patients [J]. *Arch Surg*, 2012, 147(12): 1107-1113.
- [33] Carpizo DR, D'Angelica M. Management and extent of resection for intrahepatic cholangiocarcinoma [J]. *Surg Oncol Clin N Am*, 2009, 18(2): 289-305.
- [34] Farges O, Fuks D, Boleslawski E, et al. Influence of surgical margins on outcome in patients with intrahepatic cholangiocarcinoma: a multicenter study by the AFC-IHCC-2009 study group [J]. *Ann Surg*, 2011, 254(5): 824-829, 830.
- [35] de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment [J]. *J Clin Oncol*, 2011, 29(23): 3140-3145.
- [36] Casavilla FA, Marsh JW, Iwatsuki S, et al. Hepatic resection and transplantation for peripheral cholangiocarcinoma [J]. *J Am Coll Surg*, 1997, 185(5): 429-436.
- [37] Pichlmayr R, Lamesch P, Weimann A, et al. Surgical treatment of cholangiocellular carcinoma [J]. *World J Surg*, 1995, 19(1): 83-88.
- [38] Weber SM, Jarnagin WR, Klimstra D, et al. Intrahepatic cholangiocarcinoma: Resectability, recurrence pattern, and outcomes [J]. *J Am Coll Surg*, 2001, 193(4): 384-391.
- [39] Inoue K, Makuuchi M, Takayama T, et al. Long-term survival and prognostic factors in the surgical treatment of mass-forming type cholangiocarcinoma [J]. *Surgery*, 2000, 127(5): 498-505.
- [40] Harrison LE, Fong Y, Klimstra DS, et al. Surgical treatment of 32 patients with peripheral intrahepatic cholangiocarcinoma [J]. *Br J Surg*, 1998, 85(8): 1068-1070.
- [41] Roayaie S, Guarrera JV, Ye MQ, et al. Aggressive surgical treatment of intrahepatic cholangiocarcinoma: Predictors of outcomes [J]. *J Am Coll Surg*, 1998, 187(4): 365-372.
- [42] Weimann A, Varnholt H, Schlitt HJ, et al. Retrospective analysis of prognostic factors after liver resection and transplantation for cholangiocellular carcinoma [J]. *Br J Surg*, 2000, 87(9): 1182-1187.
- [43] Ohtsuka M, Ito H, Kimura F, et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival [J]. *Br J Surg*, 2002, 89(12): 1525-1531.
- [44] Spolverato G, Kim Y, Alexandrescu S, et al. Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection [J]. *Ann Surg Oncol*, 2016, 23(1): 235-243.
- [45] Petrowsky H, Hong JC. Current surgical management of hilar and intrahepatic cholangiocarcinoma: The role of resection and orthotopic liver transplantation [J]. *Transplant Proc*, 2009, 41(10): 4023-4035.
- [46] Fu BS, Zhang T, Li H, et al. The role of liver transplantation for intrahepatic cholangiocarcinoma: A single-center experience [J]. *Eur Surg Res*, 2011, 47(4): 218-221.
- [47] Hu XX, Yan LN. Retrospective analysis of prognostic factors after liver transplantation for intrahepatic cholangiocarcinoma in China: A single-center experience [J]. *Hepatogastroenterology*, 2011, 58(109): 1255-1259.
- [48] Sapisochin G, Facciuto M, Rubbia-Brandt L, et al. Liver transplantation for "very early" intrahepatic cholangiocarcinoma: International retrospective study supporting a prospective assessment [J]. *Hepatology*, 2016, 64(4): 1178-1188.
- [49] Geng ZM, Noor H, Zheng JB, et al. Advances in diagnosis and treatment of hilar cholangiocarcinoma—a review [J]. *Med Sci Monit*, 2013, 19: 648-656.
- [50] Cho MS, Kim SH, Park SW, et al. Surgical outcomes and predicting factors of curative resection in patients with hilar cholangiocarcinoma: 10-year single-institution experience [J]. *J Gastrointest Surg*, 2012, 16(9): 1672-1679.
- [51] Nuzzo G, Giuliani F, Ardito F, et al. Improvement in perioperative and long-term outcome after surgical treatment of hilar cholangiocarcinoma: results of an Italian multicenter analysis of 440 patients [J]. *Arch Surg*, 2012, 147(1): 26-34.
- [52] Cannon RM, Brock G, Buell JF. Surgical resection for hilar cholangiocarcinoma: experience improves resectability [J]. *HPB (Oxford)*, 2012, 14(2): 142-149.
- [53] Lian ZR, You HB, Chen X, et al. Resection and drainage of hilar cholangiocarcinoma: an 11-year experience of a single center in mainland China [J]. *Am Surg*, 2011, 77(5): 627-633.
- [54] Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma [J]. *Ann Surg*, 2001, 234(4): 507-517, 517-519.
- [55] Schiffman SC, Reuter NP, McMasters KM, et al. Overall survival peri-hilar cholangiocarcinoma: R1 resection with curative intent compared to primary endoscopic therapy [J]. *J Surg Oncol*, 2012, 105(1): 91-96.
- [56] Rocha FG, Matsuo K, Blumgart LH, et al. Hilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center experience [J]. *J Hepatobiliary Pancreat Sci*, 2010, 17(4): 490-496.
- [57] Miyazaki M, Ito H, Nakagawa K, et al. Aggressive surgical approaches to hilar cholangiocarcinoma: hepatic or local resection? [J]. *Surgery*, 1998, 123(2): 131-136.

- [58] Burke EC, Jamagin WR, Hochwald SN, et al. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system [J]. *Ann Surg*, 1998, 228(3): 385-394.
- [59] Tsao JI, Nimura Y, Kamiya J, et al. Management of hilar cholangiocarcinoma: comparison of an American and a Japanese experience [J]. *Ann Surg*, 2000, 232(2): 166-174.
- [60] Ito F, Agni R, Rettammel RJ, et al. Resection of hilar cholangiocarcinoma: concomitant liver resection decreases hepatic recurrence [J]. *Ann Surg*, 2008, 248(2): 273-279.
- [61] de Jong MC, Marques H, Clary BM, et al. The impact of portal vein resection on outcomes for hilar cholangiocarcinoma: a multi-institutional analysis of 305 cases [J]. *Cancer*, 2012, 118(19): 4737-4747.
- [62] Shi Z, Yang MZ, He QL, et al. Addition of hepatectomy decreases liver recurrence and leads to long survival in hilar cholangiocarcinoma [J]. *World J Gastroenterol*, 2009, 15(15): 1892-1896.
- [63] Ikeyama T, Nagino M, Oda K, et al. Surgical approach to bismuth Type I and II hilar cholangiocarcinomas: audit of 54 consecutive cases [J]. *Ann Surg*, 2007, 246(6): 1052-1057.
- [64] Soares KC, Kamel I, Cosgrove DP, et al. Hilar cholangiocarcinoma: diagnosis, treatment options, and management [J]. *Hepatobiliary Surg Nutr*, 2014, 3(1): 18-34.
- [65] Rea DJ, Munoz-Juarez M, Farnell MB, et al. Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients [J]. *Arch Surg*, 2004, 139(5): 514-523, 523-525.
- [66] Gazzaniga GM, Filauro M, Bagarolo C, et al. Surgery for hilar cholangiocarcinoma: an Italian experience [J]. *J Hepatobiliary Pancreat Surg*, 2000, 7(2): 122-127.
- [67] Parikh AA, Abdalla EK, Vauthey JN. Operative considerations in resection of hilar cholangiocarcinoma [J]. *HPB (Oxford)*, 2005, 7(4): 254-258.
- [68] Cheng QB, Yi B, Wang JH, et al. Resection with total caudate lobectomy confers survival benefit in hilar cholangiocarcinoma of Bismuth type III and IV [J]. *Eur J Surg Oncol*, 2012, 38(12): 1197-1203.
- [69] Kow AW, Wook CD, Song SC, et al. Role of caudate lobectomy in type III A and III B hilar cholangiocarcinoma: a 15-year experience in a tertiary institution [J]. *World J Surg*, 2012, 36(5): 1112-1121.
- [70] Dinant S, Gerhards MF, Busch OR, et al. The importance of complete excision of the caudate lobe in resection of hilar cholangiocarcinoma [J]. *HPB (Oxford)*, 2005, 7(4): 263-267.
- [71] Jang JY, Kim SW, Park DJ, et al. Actual long-term outcome of extrahepatic bile duct cancer after surgical resection [J]. *Ann Surg*, 2005, 241(1): 77-84.
- [72] Kitagawa Y, Nagino M, Kamiya J, et al. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection [J]. *Ann Surg*, 2001, 233(3): 385-392.
- [73] Neuhaus P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma [J]. *Ann Surg*, 1999, 230(6): 808-818, 819.
- [74] Lee SG, Song GW, Hwang S, et al. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience [J]. *J Hepatobiliary Pancreat Sci*, 2010, 17(4): 476-489.
- [75] Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients [J]. *Transplantation*, 2000, 69(8): 1633-1637.
- [76] Robles R, Figueras J, Turrión VS, et al. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma [J]. *Ann Surg*, 2004, 239(2): 265-271.
- [77] Ghali P, Marotta PJ, Yoshida EM, et al. Liver transplantation for incidental cholangiocarcinoma: analysis of the Canadian experience [J]. *Liver Transpl*, 2005, 11(11): 1412-1416.
- [78] Heimbach JK, Gores GJ, Haddock MG, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma [J]. *Semin Liver Dis*, 2004, 24(2): 201-207.
- [79] Jonas S, Mittler J, Pascher A, et al. Extended indications in living-donor liver transplantation: bile duct cancer [J]. *Transplantation*, 2005, 80(1 Suppl): 101-104.
- [80] Shimoda M, Farmer DG, Colquhoun SD, et al. Liver transplantation for cholangiocellular carcinoma: analysis of a single-center experience and review of the literature [J]. *Liver Transpl*, 2001, 7(12): 1023-1033.
- [81] Pitt HA, Gomes AS, Lois JF, et al. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? [J]. *Ann Surg*, 1985, 201(5): 545-553.
- [82] Hochwald SN, Burke EC, Jamagin WR, et al. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma [J]. *Arch Surg*, 1999, 134(3): 261-266.
- [83] Nimura Y, Kamiya J, Kondo S, et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience [J]. *J Hepatobiliary Pancreat Surg*, 2000, 7(2): 155-162.
- [84] Celotti A, Solaini L, Montori G, et al. Preoperative biliary drainage in hilar cholangiocarcinoma: Systematic review and meta-analysis [J]. *Eur J Surg Oncol*, 2017, 43(9): 1628-1635.
- [85] Sakata J, Shirai Y, Wakai T, et al. Catheter tract implantation metastases associated with percutaneous biliary drainage for extrahepatic cholangiocarcinoma [J]. *World J Gastroenterol*, 2005, 11(44): 7024-7027.
- [86] Laurent A, Tayar C, Cherqui D. Cholangiocarcinoma: preoperative biliary drainage (Con) [J]. *HPB (Oxford)*, 2008, 10(2): 126-129.
- [87] Belghiti J, Ogata S. Preoperative optimization of the liver for resection in patients with hilar cholangiocarcinoma [J]. *HPB (Oxford)*, 2005, 7(4): 252-253.
- [88] Yokoyama Y, Nagino M, Nishio H, et al. Recent advances in the treatment of hilar cholangiocarcinoma: portal vein embolization

- [J]. *J Hepatobiliary Pancreat Surg*, 2007, 14(5) : 447-454.
- [89] Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial [J]. *Ann Surg*, 2003, 237(2) : 208-217.
- [90] Are C, Iacovitti S, Prete F, et al. Feasibility of laparoscopic portal vein ligation prior to major hepatectomy [J]. *HPB (Oxford)*, 2008, 10(4) : 229-233.
- [91] Ayiomamitis GD, Low JK, Alkari B, et al. Role of laparoscopic right portal vein ligation in planning staged or major liver resection [J]. *J Laparoendosc Adv Surg Tech A*, 2009, 19(3) : 409-413.
- [92] Nagorney DM, Donohue JH, Farnell MB, et al. Outcomes after curative resections of cholangiocarcinoma [J]. *Arch Surg*, 1993, 128(8) : 871-877.
- [93] Tran KT, Smeenk HG, van Eijck CH, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors [J]. *Ann Surg*, 2004, 240(5) : 738-745.
- [94] Chen S, Chen JZ, Zhan Q, et al. Robot-assisted laparoscopic versus open pancreaticoduodenectomy: a prospective, matched, mid-term follow-up study [J]. *Surg Endosc*, 2015, 29(12) : 3698-3711.
- [95] Blechacz B, Gores GJ. Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment [J]. *Hepatology*, 2008, 48(1) : 308-321.
- [96] Masselli G, Manfredi R, Vecchioli A, et al. MR imaging and MR cholangiopancreatography in the preoperative evaluation of hilar cholangiocarcinoma: correlation with surgical and pathologic findings [J]. *Eur Radiol*, 2008, 18(10) : 2213-2221.
- [97] Lee SW, Kim HJ, Park JH, et al. Clinical usefulness of 18F-FDG PET-CT for patients with gallbladder cancer and cholangiocarcinoma [J]. *J Gastroenterol*, 2010, 45(5) : 560-566.
- [98] Duignan S, Maguire D, Ravichand CS, et al. Neoadjuvant chemoradiotherapy followed by liver transplantation for unresectable cholangiocarcinoma: a single-centre national experience [J]. *HPB (Oxford)*, 2014, 16(1) : 91-98.
- [99] Hong JC, Jones CM, Duffy JP, et al. Comparative analysis of resection and liver transplantation for intrahepatic and hilar cholangiocarcinoma: a 24-year experience in a single center [J]. *Arch Surg*, 2011, 146(6) : 683-689.
- [100] Kaiser GM, Sotiropoulos GC, Jauch KW, et al. Liver transplantation for hilar cholangiocarcinoma: a German survey [J]. *Transplant Proc*, 2008, 40(9) : 3191-3193.
- [101] Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma [J]. *Ann Surg*, 2005, 242(3) : 451-458.
- [102] Becker NS, Rodriguez JA, Barshes NR, et al. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period [J]. *J Gastrointest Surg*, 2008, 12(1) : 117-122.
- [103] Jethwa P, Breuning E, Bhati C, et al. The microbiological impact of pre-operative biliary drainage on patients undergoing hepato-biliary-pancreatic (HPB) surgery [J]. *Aliment Pharmacol Ther*, 2007, 25(10) : 1175-1180.
- [104] 田伏洲, 石力, 汤礼军, 等. 胰头癌术前减黄指征的前瞻性研究 [J]. *中华外科杂志*, 2006, 44(23) : 1614-1616.
- [105] Saiki S, Chijiwa K, Komura M, et al. Preoperative internal biliary drainage is superior to External biliary drainage in liver regeneration and function after hepatectomy in obstructive jaundiced rats [J]. *Ann Surg*, 1999, 230(5) : 655-662.
- [106] Abdullah S, Gupta T, Jaafar KA, et al. Ampullary carcinoma: effect of preoperative biliary drainage on surgical outcome [J]. *World J Gastroenterol*, 2009, 15(23) : 2908-2912.
- [107] van der Gaag NA, de Castro SM, Rauws EA, et al. preoperative biliary drainage for periampullary tumors causing obstructive jaundice: drainage vs (direct) operation (DROP-trial) [J]. *BMC Surg*, 2007, 7(3) : 1-9.
- [108] Ben-Josef E, Guthrie KA, El-Khoueiry AB, et al. SWOG S0809: A Phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma [J]. *J Clin Oncol*, 2015, 33(24) : 2617-2622.
- [109] Sahai P, Kumar S. External radiotherapy and brachytherapy in the management of extrahepatic and intrahepatic cholangiocarcinoma: available evidence [J]. *Br J Radiol*, 2017, 90(1076) : 20170061.
- [110] Williams TM, Majithia L, Wang SJ, et al. Defining the role of adjuvant therapy: cholangiocarcinoma and gall bladder cancer [J]. *Semin Radiat Oncol*, 2014, 24(2) : 94-104.
- [111] Weber SM, Ribero D, O'Reilly EM, et al. Intrahepatic cholangiocarcinoma: expert consensus statement [J]. *HPB (Oxford)*, 2015, 17(8) : 669-680.
- [112] Socha J, Michalak M, Wołakiewicz G, et al. Nodal areas of potential geographic error in adjuvant radiotherapy for biliary tract cancer [J]. *Radiother Oncol*, 2017, 125(2) : 365-373.
- [113] Marinelli I, Guido A, Fuccio L, et al. Clinical Target Volume in Biliary Carcinoma: A Systematic Review of Pathological Studies [J]. *Anticancer Res*, 2017, 37(3) : 955-961.
- [114] Rana A, Hong JC. Orthotopic liver transplantation in combination with neoadjuvant therapy: a new paradigm in the treatment of unresectable intrahepatic cholangiocarcinoma [J]. *Curr Opin Gastroenterol*, 2012, 28(3) : 258-265.
- [115] Lim KH, Oh DY, Chie EK, et al. Adjuvant concurrent chemoradiation therapy (CCRT) alone versus CCRT followed by adjuvant chemotherapy: which is better in patients with radically resected extrahepatic biliary tract cancer?: a non-randomized, single center study [J]. *BMC Cancer*, 2009, 27, 9: 345.
- [116] McMasters KM, Tuttle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma [J]. *Am J Surg*, 1997, 174(6) : 605-608.

- [117] Nelson JW , Ghafoori AP , Willett CG , et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma [J]. *Int J Radiat Oncol Biol Phys* , 2009 , 73(1) : 148-153.
- [118] Katayose Y , Nakagawa K , Morikawa T , et al. Neoadjuvant chemoradiation therapy with gemcitabine for cholangiocarcinoma—three-years results after phase I study and interim analysis of phase II study [J]. *Eur J Cancer* , 2011 , 47(1) : 448-449.
- [119] Kobayashi S , Tomokuni A , Gotoh K , et al. Evaluation of the safety and pathological effects of neoadjuvant full-dose gemcitabine combination radiation therapy in patients with biliary tract cancer [J]. *Cancer Chemother Pharmacol* , 2015 , 76(6) : 1191-1198.
- [120] Jung JH , Lee HJ , Lee HS , et al. Benefit of neoadjuvant concurrent chemoradiotherapy for locally advanced perihilar cholangiocarcinoma [J]. *World J Gastroenterol* , 2017 , 23(18) : 3301-3308.
- [121] Autorino R , Mattiucci GC , Ardito F , et al. Radiochemotherapy with gemcitabine in unresectable extrahepatic cholangiocarcinoma: Long-term results of a phase II study [J]. *Anticancer Res* , 2016 , 36(2) : 737-740.
- [122] Lee KJ , Yi SW , Cha J , et al. A pilot study of concurrent chemoradiotherapy with gemcitabine and cisplatin in patients with locally advanced biliary tract cancer [J]. *Cancer Chemother Pharmacol* , 2016 , 78(4) : 841-846.
- [123] Jackson MW , Amiri A , Jones BL , et al. Treatment selection and survival outcomes with and without radiation for unresectable , localized intrahepatic cholangiocarcinoma [J]. *Cancer J* , 2016 , 22(4) : 237-242.
- [124] Gkika E , Hallauer L , Kirste S , et al. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma [J]. *BMC Cancer* , 2017 , 17(1) : 781.
- [125] Brunner TB , Blanck O , Lewitzki V , et al. Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma [J]. *Radiother Oncol* , 2019 , 132: 42-47.
- [126] Hong TS , Wo JY , Yeap BY , et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized , unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma [J]. *J Clin Oncol* , 2016 , 34(5) : 460-468.
- [127] Brunner TB , Seufferlein T. Radiation therapy in cholangiocellular carcinomas [J]. *Best Pract Res Clin Gastroenterol* , 2016 , 30(4) : 593-602.
- [128] Primrose JN , Fox R , Palmer DH , et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP) : a randomised , controlled , multicentre , phase 3 study [J]. *Lancet Oncol* , 2019 , 20(5) : 663-673.
- [129] Takada T , Amano H , Yasuda H , et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma [J]. *Cancer* , 2002 , 95(8) : 1685-1695.
- [130] Edeline J , Benabdelghani M , Bertaut A , et al. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (PRODIGE 12-ACCORD 18-UNICANCER GI) : A randomized phase III study [J]. *J Clin Oncol* , 2019 , 37(8) : 658-667.
- [131] Kobayashi S , Nagano H , Tomokuni A , et al. A prospective , randomized phase II study of adjuvant gemcitabine versus S-1 after major hepatectomy for biliary tract cancer (KHBO 1208) : Kansai Hepato-Biliary Oncology Group [J]. *Ann Surg* , 2019 , 270(2) : 230-237.
- [132] Siebenhüner AR , Seifert H , Bachmann H , et al. Adjuvant treatment of resectable biliary tract cancer with cisplatin plus gemcitabine: A prospective single center phase II study [J]. *BMC Cancer* , 2018 , 18(1) : 72.
- [133] Kim YS , Jeong CY , Song HN , 等. 氟嘧啶为基础的辅助化疗对胆道癌 R0 切除术后疗效的观察 [J]. *癌症* , 2018 , 37(2) : 56-64.
- [134] 陈向东 , 李仁锋 , 陈昆仑 , 等. 肝外胆道恶性肿瘤根治术后替吉奥单药辅助化疗的临床研究 [J]. *中华外科杂志* , 2019 , 57(4) : 271-276.
- [135] Valle J , Wasan H , Palmer DH , et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer [J]. *N Engl J Med* , 2010 , 362(14) : 1273-1281.
- [136] Darwish MS , Kim WR , Harnois DM , et al. Efficacy of neoadjuvant chemoradiation , followed by liver transplantation , for perihilar cholangiocarcinoma at 12 US centers [J]. *Gastroenterology* , 2012 , 143(1) : 88-98.
- [137] Mizusawa J , Morizane C , Okusaka T , et al. Randomized phase III study of gemcitabine plus S-1 versus gemcitabine plus cisplatin in advanced biliary tract cancer: Japan Clinical Oncology Group Study (JCOG1113 , FUGA-BT) [J]. *Jpn J Clin Oncol* , 2016 , 46(4) : 385-388.
- [138] Alberts SR , Al-Khatib H , Mahoney MR , et al. Gemcitabine , 5-fluorouracil , and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial [J]. *Cancer* , 2005 , 103(1) : 111-118.
- [139] Knox JJ , Hedley D , Oza A , et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial [J]. *J Clin Oncol* , 2005 , 23(10) : 2332-2338.
- [140] Sahai V , Catalano PJ , Zalupski MM , et al. Nab-paclitaxel and gemcitabine as first-line treatment of advanced or metastatic cholangiocarcinoma: A phase 2 clinical trial [J]. *JAMA Oncol* , 2018 , 4(12) : 1707-1712.
- [141] Nehls O , Klump B , Arkenau HT , et al. Oxaliplatin , fluorouracil and leucovorin for advanced biliary system adenocarcinomas: a prospective phase II trial [J]. *Br J Cancer* , 2002 , 87(7) : 702-704.
- [142] Nehls O , Oettle H , Hartmann JT , et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary sys-

tem adenocarcinoma: a prospective multicentre phase II trial [J]. Br J Cancer ,2008 ,98(2) : 309-315.

[143] Kim TW ,Chang HM ,Kang HJ , et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer[J]. Ann Oncol ,2003 ,14(7) : 1115-1120.

[144] Sun Yk ,Zhou AP. Nab-paclitaxel plus S-1 as first line treatment for advanced or metastatic biliary tract adenocarcinoma: A phase 2 study [J/OL]. J Clin Oncol ,2019 [2019-08-11]. <http://abstracts.asco.org/239/AbstView-239-265953.html>.

[145] Shroff RT ,Javle MM ,Xiao L , et al. Gemcitabine , cisplatin , and nab-paclitaxel for the treatment of advanced biliary tract cancers: A phase 2 clinical trial [J/OL]. JAMA Oncol ,2019 [2019-08-11]. <https://jamanetwork.com/journals/jamaoncology/article-abstract/2730639>.

[146] 李 嵘 ,秦叔逵 ,刘秀峰 ,等. GLX 方案一线治疗晚期转移性胆系肿瘤的临床观察 [J]. 临床肿瘤学杂志 ,2015 ,20(7) : 629-632.

[147] Yoo C ,Han B ,Kim HS , et al. Multicenter phase II study of oxaliplatin , irinotecan , and S-1 as first-line treatment for patients with recurrent or metastatic biliary tract cancer [J]. Cancer Res Treat ,2018 ,50(4) : 1324-1330.

[148] Lamarca A ,Palmer DH ,Wasan HS , et al. A randomised phase III , multi-centre , open-label study of Active Symptom Control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy (ASC + mFOLFOX) for patients with locally advanced/metastatic biliary tract cancers (ABC) previously treated with cisplatin/gemcitabine (CisGem) chemotherapy [J/OL]. J Clin Oncol ,2019 [2019-08-11]. <http://abstracts.asco.org/239/AbstView-239-248927.html>.

[149] Zheng Y , Tu X , Zhao P , et al. A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin [J]. Br J Cancer ,2018 ,119(3) : 291-295.

[150] Belkouz A , de Vos-Geelen J , Eskens F , et al. Efficacy and safety of FOLFIRINOX in advanced biliary tract cancer after failure of gemcitabine plus cisplatin: A phase II trial [J/OL]. J Clin Oncol ,2019 [2019-08-11]. <http://abstracts.asco.org/239/AbstView-239-263653.html>.

[151] Diaz LA Jr , Le DT. PD-1 blockade in tumors with mismatch-repair deficiency [J]. N Engl J Med ,2015 ,373(20) : 1979.

[152] Le DT , Uram JN , Wang H , et al. PD-1 blockade in tumors with mismatch-repair deficiency [J]. N Engl J Med ,2015 ,372(26) : 2509-2520.

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附录 1 CSCO 诊疗指南证据类别(2018)

证据特征			CSCO 专家共识度
类别	水平	来源	
1A	高	严谨的 Meta 分析、大型随机对照临床研究	一致共识(支持意见 ≥80%)
1B	高	严谨的 Meta 分析、大型随机对照临床研究	基本一致共识 ,但争议小(支持意见 60% ~ 80%)
2A	稍低	一般质量的 Meta 分析、小型随机对照研究、设计良好的大型回顾性研究、病例-对照研究	一致共识(支持意见 ≥80%)
2B	稍低	一般质量的 Meta 分析、小型随机对照研究、设计良好的大型回顾性研究、病例-对照研究	基本一致共识 ,但争议小(支持意见 60% ~ 80%)
3	低	非对照的单臂临床研究、病例报告、专家观点	无共识、且争议大(支持意见 <60%)