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· 文献综述 ·

肝门部胆管癌的外科治疗现状

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摘要

肝门部胆管癌(HC)虽然发生率低,但预后较差,而外科手术仍是目前的唯一治愈手段。经历半个多世纪的发展,HC的外科治疗获得极大进展,随之而来的争议仍然存在。笔者就HC的术前分期及治疗、手术切除范围、血管切除与重建、淋巴结清扫数目及范围、腹腔镜手术、肝移植应用等方面的现状展开论述,为HC外科治疗提供借鉴。

关键词

胆管肿瘤; Klatskin 肿瘤; 外科手术; 综述文献
中图分类号: R735.8

Current status in surgical management of hilar cholangiocarcinoma

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Abstract

Although the prevalence of hilar cholangiocarcinoma (HC) is relatively low, it is associated with dismal prognosis, and surgical resection remains the only curative treatment for this condition. Over more than half a century, considerable achievements have been made in surgical treatment of HC, meanwhile, the accompanied controversies still exist. The authors, in this paper, discuss the issues concerning the preoperative staging and management, and surgical resection scope, combined vascular resection with reconstruction, number and scope of lymph node dissection, laparoscopic procedure and liver transplantation for HC, so as to provide helpful guidance for surgical management of HC.

Key words

Bile Duct Neoplasms; Klatskin's Tumor; Surgical Procedures, Operative; Review
CLC number: R735.8

胆管癌(cholangiocarcinoma)指来源于胆管上皮细胞的恶性肿瘤,其发生率占全部恶性肿瘤的比例低于1%^[1],占原发性肝胆恶性

肿瘤比例的10%^[2],按照发生的解剖部位不同分为肝内、肝门部及远端胆管癌,其中肝门部胆管癌(hilarcholangiocarcinoma, HC)约占50%~70%^[2],由Klatskin在1965年首次报道,又被称为Klatskin肿瘤,外科手术是唯一治愈手段;半个多世纪以来,随着医学进步,对HC疾病进程、病理生理及肿瘤生物学的认识也不断提高,但是,仍然只有25%的初诊患者有手术切除机会,术后5年生存率仅11%~42%^[3-5]。本文将从术前准备(肿瘤分期、术前治疗)及外科手术(切除范

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围、血管切除与重建、淋巴结清扫数目及范围、腹腔镜技术、肝移植应用)对HC的外科治疗现状进行阐述。

1 目前国际应用的HC分期

Bismuth和Corlette在上世纪70年代提出Bismuth-Corlette分型,其中I型肿瘤位于肝总管、左右肝管汇合部以下,II型肿瘤侵犯汇合部但未侵犯左右肝管,III型侵犯右肝管(IIIa)或左肝管(IIIb),IV型同时侵犯左右肝管^[6],该分型按照胆管受侵犯范围分类,简单实用,能够指导手术方式选择,目前仍然广泛应用于临床,但并未提供其他信息,例如有无血管侵犯、淋巴结转移、远处转移、肝叶萎缩等,因此,无法准确评估患者预后;之后,纪念Sloan-Kettering癌症中心(MSKCC)的Jarnagin等^[7]提出根据胆管受侵犯位置及范围、门静脉有无受侵犯以及有无肝叶萎缩这三个因素将HC分为T₁、T₂及T₃期,在225例HC术前评估准确率达到86%,但该分期较复杂,也未评估淋巴结及远处转移或动脉受侵犯;美国癌症分期联合委员会(American Joint Commission on Cancer, AJCC)制订了HC的TNM分期^[8],这是一个基于术后病理结果的TNM分期,能够评估预后,但有研究^[9]显示其判定预后的价值不及MSKCC中的T分期,也无法指导术后可切除性评估及手术方式选择;为了在全球范围内收集病例、统一评估HC的可切除性及预后,Deoliveira等^[10]提出了综合包括肿瘤侵犯胆管范围(B)、门静脉侵犯(PV)、肝动脉侵犯(HA)、残余肝体积(V)、淋巴结转移(N)、远处转移(M)、以及肿瘤大小(T)、病理类型(F)、肝脏基础疾病(D)等因素的分期方法,但最近研究^[11]显示该方法需要收集大量信息而限制其应用;Boudjema等^[12]提出了根据左外叶胆管汇合部是否受侵犯来判断切除可能性的分型,该分型依据:(1)肝门部的解剖特点,左右肝管汇合部及肝总管位于十二指肠韧带右侧并紧邻肝动脉右支,左肝管比右肝管长,左肝动脉位于十二指肠韧带左侧或肝胃韧带、距离左右肝管汇合部较远;(2)左外叶是术后残余肝体积的最低要求;(3)左外叶肝管汇合部受侵犯时肿瘤通常已经范围较广并侵犯血管,切除可能性较小,即使通过扩大半肝联合血管切除及重建完成手术,但预后在大多数报道中

并未改善。该分型与Bismuth分型的预测性较一致,对于可切除性判断的准确率较高,但是忽略了血管重建技术在门静脉或肝动脉受侵犯病例中的重要作用,因此特异性较低。一些无法切除病例通过血管重建技术能够根治,虽然有研究^[13-15]证实血管切除重建后患者并未获得满意疗效,但仍然有支持患者获益的研究报道^[16-18],对此,将在后文中进一步阐述。

2 术前治疗

目前,HC术前胆道引流(pre-operative biliary drainage, PBD)仍存争议,原因之一是缺乏证据支持PBD能够减少术后病死率及提高生存率^[19-21];另一方面,经皮肝穿刺胆道引流(percutaneous transhepatic biliary drainage, PTBD)存在1.7%~5.2%的穿刺隧道癌细胞种植率^[22],而内镜下鼻胆管引流(endoscopic nasobiliary drainage, ENBD)既能够避免癌细胞种植,又较内镜下胆道支架(endoscopic biliary stenting, EBS)内引流的感染率降低,似乎是最佳的PBD方式,但仍有相当比例的ENBD引流效果不佳而需要再次行PTBD引流^[8, 23-25],同时,ENBD达到减黄预期的时间比PTBD更长^[8, 23]。尽管PBD存在争议,并且引流持续时间及适合手术的最佳胆红素水平仍未达成共识,但是,对于胆管炎,拟行术前抗肿瘤治疗,高胆红素血症引发的营养不良、肝肾功能不全以及行门静脉栓塞(portal vein embolization, PVE)的患者,术前PBD仍是最佳选择^[8, 26]。

正常肝脏可耐受最大切除量为20%的剩余肝体积(future liver remnant, FLR),而慢性肝炎或肝硬化则是40%的FLR,FLR不足将加大术后肝功能衰竭风险。Makuuchi等^[27]首次报道在大范围肝切除术治疗胆管癌的患者术前应用PVE能够增加FLR,之后,大量研究^[17, 28-30]证实术前PVE通过增加FLR减少术后并发症率及病死率;但是,并未见PVE能够增加HC患者R₀切除率或增加生存率的相关报道。除此之外,联合肝脏离断和门静脉结扎的两步肝切除术(associating liver partition and portal vein ligation for staged hepatectomy, ALPPS)也用于因FLR不足而无法手术切除的HC患者。相较于PVE能够在4~8周内增加11.9%的FLR,ALPPS则在一期术后9 d内使FLR增加74%,但33%~64%的并发症率远高于16%的PVE并发症率,

因此, 该项技术还需要进一步评估^[28,31]。

3 手术切除范围

R_0 切除是影响HC预后的重要因素之一^[4-5, 17], 因此, 能否达到 R_0 切除决定了外科手术切除范围。通过对切除组织的病理学检查发现浸润癌在胆管近切缘沿纵轴的粘膜下浸润达到0.6~18.8 mm, 非浸润癌的表浅侵犯长度达到(54±19) mm^[32]; 此外, 术中胆管切缘的冷冻切片检查准确率、敏感性及特异性分别是56.5%、75.0%、46.7%^[33], 近期1篇报道^[34]也证实胆管切缘的冷冻检查存在敏感性较低、假阴性结果的高风险以及阴性切缘的二次获得率低的缺点, 因此, 临床价值有限; 基于此, 在胆肠吻合技术可行及减少潜在并发症的前提下, 尽可能多地获得胆管近端切缘长度才能够保证高的 R_0 切除率。另一方面, 肝门部胆管癌因为胆管壁较薄以及特殊的解剖位置而更容易侵犯胆管周围结构以及向肝实质侵犯, 联合大范围肝切的肝外胆管切除能够提高 R_0 切除率^[4, 17, 35-36]。

对于Bismuth I/II型肿瘤, 有研究^[36-37]认为对乳头型的 T_1 及 T_{is} 期肿瘤行肝外胆管切除加或不加部分肝切除即可, 但是, 外科医师无法在术前及术中准确判断肿瘤TNM分期, 而乳头型只占HC病理组织分型的5%~10%, 其余是>70%的硬化型以及20%的结节型^[8], 因此, 联合大范围肝切除术逐渐成为主流, 其中, 尾状叶(I段)因为紧贴肝门而受肿瘤沿胆管浸润或是直接侵犯肝实质的几率极大, 因此, 大范围肝切除术需要联合I段切除^[17,20,36]。然而, 考虑到大范围肝切除术后肝功能衰竭发生率增加, 有报道^[36,38-39]对于Bismuth I/II型、 T_1 及 T_2 期的III型, 甚至IV型肿瘤, 应用小范围中央区肝切除, 包括I段切除, I段和IV(IVb)段切除, I段、IV(IVb)段和V段切除, 以及包括I段、IV(IVb)段、V段和VIII段的肝中叶切除, 虽然对于这一手术方式仍存有争议, 其 R_0 切除率及预后仍需多中心研究支持, 但是该术式对于降低术前PBD率、术后并发症率及病死率方面的作用是值得肯定的。

联合大范围肝切除术对于Bismuth III/IV型肿瘤的手术方式通常在IIIa及IV型(病变以右肝为主)中选择右半肝或扩大右半肝切除, 在IIIb及IV型(病变以左肝为主)中选择左半肝或扩大左半肝切除, 但是, 右半肝及扩大右半肝切除术后病死率比较左半肝及扩大左半肝切除增高, 同时,

有报道对于病变左肝为主的病例扩大左半肝切除也能获得高的 R_0 切除率^[40], 并且左半肝及扩大左半肝切除对于IIIb型与右肝切除对于IIIa及IV型在 R_0 切除率及生存率的比较无明显差异, 而术后病死率减低^[41], 因此, 手术方式的选择应该结合病变位置、预计残余肝脏体积、肝脏基础病变以及手术医师经验来共同决定。

4 联合门静脉、肝动脉切除与重建

如前文所述, 虽然不少研究^[15, 18]证实联合门静脉切除及重建设没有增加术后并发症率及病死率, 但是患者的生存率也未从中获益^[13-15]; 然而, 这些研究当中也有阐述行门静脉切除重建的病例往往肿瘤分期更晚, 即肿瘤生物学行为更具有浸润性^[15], 这些病例即使与没有门静脉切除重建病例的生存率相同, 但该群患者仍然是获益的, 因此, 门静脉切除重建在经验丰富的专业中心仍然被推崇, 并且也有支持患者术后生存率获益的研究报道^[16-18, 42-43]。而肝动脉切除重建术后并发症率, 包括血栓形成、狭窄等血管特异性并发症, 其他非特异性并发症率及病死率均较门静脉切除重建增高^[13, 20, 42-44], 因此, 该技术在HC的手术切除中并不做常规推荐; 但是, 与门静脉切除重建患者的肿瘤分期较晚相似, 该群患者术后生存是否也能从中获益仍需要更多论证, 同时, 该技术在专业中心开展, 随着术者手术例数增加及选择经过严格评估后的合适病例, 并发症率及病死率逐渐在可控制范围^[42, 44]。

5 淋巴结清扫数目与范围

大量研究^[4-5, 17, 45-47]证实区域淋巴结转移(N_1)是与 R_0 切除一样影响HC手术切除预后的独立危险因素, 淋巴结转移的HC术后5年生存率低于25%^[4, 17, 46]。Mao等^[46]研究发现在 N_0 的HC中淋巴结清扫数目>13个预后会优于清扫数目<3个, 而 N_1 (胆囊管、胆总管、肝动脉及门静脉周围淋巴结阳性)与 N_2 (主动脉旁、腔静脉旁、肠系膜上动脉和/或腹腔动脉淋巴结阳性)的预后没有明显差异, 但多于3个阳性淋巴结及阳性率>0.27的病例预后显著差过<3个及<0.27, 因此, 清扫13个淋巴结应该作为肿瘤准确分期的要求, 并且, 预后应由转移淋巴结的数目及阳性率而不是位置所决定。Kambakamba等^[45]认为清扫淋巴结数目应该

至少7个才能对预后准确分期,而>15个淋巴结也并不能提高阳性发现率。Giuliante等^[47]报道阳性率超过0.2可作为影响预后的独立因素,但阳性率受清扫淋巴结总数影响,应达到5个以上。大多数外科医师推崇清扫范围包括肝十二指肠韧带、肝总动脉旁及胰腺旁,不主张行腹主动脉旁淋巴结清扫,因为这不能提高预后^[4, 42, 46, 48]。

6 腹腔镜技术应用

腹腔镜技术在HC中的应用始于肿瘤探查分期,14%~45%的病例通过腹腔镜探查可发现肝脏或腹膜转移,准确率达32%~71%^[20,49]。此外,腹腔镜下门静脉结扎能获得与PVE相似的效果^[49],完全腹腔镜或机器人辅助胆肠吻合也用于晚期梗阻患者的姑息治疗,并发症率低、生活质量提高^[50-51]。至于完全或辅助下的腹腔镜根治性切除,尽管有相关病例报道^[52-54],但是否符合联合尾状叶切除及淋巴结清扫的原则,仍存有争议,期待更多病例研究证实。然而,随着腹腔镜技术在肝胆胰外科应用的发展,在严格挑选的HC病例中,遵循根治性原则的前提下应用腹腔镜切除术,也能够达到理想的效果^[55-56]。

7 肝移植在HC中应用

联合新辅助放化疗的肝移植应用于适应证严格的HC患者,5年无瘤生存率达到59%~82%,并且在合并硬化性胆管炎的患者中预后好于单纯手术切除^[57-60]。适应证包括无法切除的直径≤3 cm的病灶且没有肝内及肝外转移,有区域淋巴结转移的患者在移植前经过腹腔镜探查排除。目前,没有明确证据支持可以手术切除的患者能够从肝移植中获益,而对于可能切除的患者,选择手术切除还是肝移植仍然困难,有待更多临床研究确定^[59]。

8 展望

HC外科治疗在不断发展,更加强调临床证据来选择治疗方案,而在精准医学时代,证据来源应该更多地依据肿瘤的生物特征,凭借以无创或微创方式获得的肿瘤细胞分子标志来制定基因分型,更准确地指导外科手术方案的选择,从而

让更多HC患者获益。

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