指南与共识

DOI:10.19538/j.cjps.issn1005-2208.2024.05.01

胃癌肝转移诊断与综合治疗中国专家共识(2024版)

中国抗癌协会胃癌专业委员会
中国医师协会外科医师分会上消化道外科医师专家工作组
中国老年保健协会消化系统疾病诊疗分会
中国研究型医院学会消化道肿瘤专业委员会

Chinese expert consensus on the diagnosis and comprehensive treatment of gastric cancer liver metastasis (2024 edition)

Gastric Cancer Association, China Anti-Cancer Association; Expert Working Group of Society of Upper Gastrointestinal Surgeons, Chinese Medical Doctor Association; Digestive System Disease Branch of Chinese Geriatric Society; Digestive Tract Cancer Committee of Chinese Research Hospital Association

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Keywords gastric cancer; liver metastases; Chinese consensus classification for gastric cancer liver metastasis; multidisciplinary team; expert consensus

【关键词】 胃癌;肝转移瘤;中国专家共识分型;多学科综合治疗协作组;专家共识

中图分类号:R6 **文献标志码**:A

肝脏是胃癌血行转移最常见的靶器官[1],胃癌肝转移的发生率为9.9%~18.7%[2-3],中位发病年龄62岁,男女发病比例约为4∶1[4]。胃癌肝转移病人总体中位生存时间约12个月,5年生存率<20%[5]。行原发灶、转移灶根治性切除的胃癌肝转移病人5年生存率可提高至23.8%~24.7%[6-8]。

胃癌异质性强、病情进展快,胃癌肝转移预后差,临床诊疗具有挑战性。现代治疗技术和诊疗理念的进展为胃癌肝转移的治疗提供了新选择,并逐渐形成以多学科综合治疗协作组(multidisciplinary team,MDT)为核心的治疗模式,但具体方案尚存诸多争议。为进一步提高我国胃癌肝转移诊断和综合治疗的水平,中国研究型医院学会消化道肿瘤专业委员会、中国医师协会外科医师分会上消化道外科医师委员会、中国抗癌协会胃癌专业委员会联合中华医学会外科学分会胃肠外科学组组织国内相关领域专家进行讨论、制定了《胃癌肝转移诊断与综合治疗中国专家共识(2019版)》(以下简称2019版共识)[9]。随着近年来诊疗技术和理念的持续更新,以及新的循证医学证据的出现,中国抗癌协会胃癌专业委员会、中国医师协会外科医师分会上消化道外科医师专家工作组、中国研究型医院学会消化道肿瘤专业委员会联合中国老年保健协会消化系统疾病诊疗分会于2023年再次总结国内外先进经验和最新研究进展,经业内专家讨论、修改和审议,制定了《胃癌肝转移诊断与综合治疗中国专家共识(2024版)》。经执笔团队的初稿撰写、专家讨论、共识修改后,编审专家组成员于2023-11-25在北京召开了本共识的定稿会,并对相关推荐意见进行了匿名投票。本共识对胃癌肝转移的病理特征与诊断、胃癌肝转移中国专家共识(Chinese Consensus Classification for Gastric Cancer Liver Metastasis,C-GCLM)分型系统标准、MDT模式的应用与价值、初次诊疗流程、不同分型的胃癌肝转移诊疗要点等内容进行了修订,并基于胃癌肝转移全国多中心回顾性队列研究(RECORD研究)[10-12]和近5年其他研究的结果[7,13-17],更新了胃癌肝转移的临床流行病学特征和诊疗进展。

本共识的证据级别采用GRADE(grading of recommendations assessment,development and evaluation)系统界定,证据水平与推荐分级标准见表1[18-19];推荐程度根据专家赞同率分为:高,≥90%;中,75%~<90%;低,50%~<75%。

1 胃癌肝转移病理特征与诊断

胃癌肝转移灶病理类型常与胃原发癌灶相同,以腺癌

表1 证据水平与推荐分级标准[18]

推荐分级	证据水平	证据类型
A	1a	高质量RCT的系统评价
	1b	高质量RCT
B	2a	队列研究的系统评价
	2b	队列研究(包括质量较差的RCT)
	2c	结局研究(大样本分析、群体数据)
	3a	病例对照的系统综述
	3b	单项病例对照研究
C	4	系列病例分析或质量较差的病例对照研究
D	5	无分析评价的专家意见、实验室或动物研究

注:RCT,随机对照试验

基金项目:国家自然科学基金项目(No. 81972790, No. 82273231, No. 81773135)

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为主，其他少见类型还包括腺鳞癌、髓样癌、肝样腺癌、鳞状细胞癌及未分化癌。Lauren分型进一步将腺癌分为弥漫型、肠型和混合型[20]。影响胃癌肝转移预后的因素除胃癌原发灶特征外，肝转移灶的部位、数量和大小也同样重要[21]。根据肝转移灶出现时间的不同，可将胃癌肝转移分成两类：同时性胃癌肝转移（胃癌确诊或手术后6个月内出现肝转移灶）和异时性胃癌肝转移（胃癌确诊或手术后＞6个月出现肝转移灶）[22]，其中同时性胃癌肝转移病人约占所有病人的80%，异时性肝转移发现的中位间隔时间约14个月，多项研究结果表明同时性胃癌肝转移病人的总体生存劣于异时性病人[7-8]。

1.1　影像学检查　腹部增强磁共振（MRI）和超声造影是明确肝脏转移瘤的必要手段，肝细胞特异性造影剂在发现肝脏微小转移灶（直径<1 cm）方面具有很高的敏感度[23-27]。MRI可以明确转移灶大小、数目、位置及周围毗邻关系；而术中肝脏超声或超声造影检查还可发现术前影像检查未发现的转移灶[28]。正电子发射断层扫描（PET）-CT能够显示病人的全身状况，提示肝外转移灶，在术前分期、术后复发与转移的评估方面具有重要意义[29]。此外，肝转移灶^{18}F-氟代脱氧葡萄糖（^{18}F-FDG）代谢值的改变不仅可以在化疗早期阶段（2周）区分有应答病例，还可作为判断病人预后的指标[30]。

推荐意见：胃癌肝转移病人，建议行腹部增强MRI和（或）PET/CT检查，以明确肝脏微小转移灶及全身是否有扩散转移，使临床分期更加精准。（证据级别：2b）

专家赞同率：100%（36/36）；推荐度：高。

1.2　诊断性腹腔镜探查　在胃癌肝转移病人初始治疗前，施行诊断性腹腔镜探查联合腹腔灌洗液细胞学检查，有助于排除影像学或肉眼不可见的肝转移灶或腹膜播散种植转移[31-32]。

推荐意见：胃癌肝转移病人拟行初始治疗前应常规行诊断性腹腔镜探查、腹腔脱落细胞学检查。（证据级别：2c）

专家赞同率：86.1%（31/36）；推荐度：中。

1.3　病理学检查　对于拟诊断肝转移的胃癌病人，胃原发灶除常规诊断所需的病理形态学检查外，还应增做免疫组化、分子检测等必要项目，如：人表皮生长因子受体2（HER-2）[33]、程序性死亡受体1（PD-1）和程序性死亡受体配体-1（PD-L1）（CPS评分）[34]、微卫星不稳定性（MSI）和错配修复蛋白（MMR）[35]、Claudin-18.2[36]、肿瘤突变负荷（TMB）、EB病毒（EBV）、成纤维细胞生长因子受体2b（FGFR2b）、*MET*基因扩增等，有条件的病人可考虑二代基因测序检测，以指导基于分子标记物的精准治疗。肝转移灶的经皮穿刺活检为诊断转移的金标准，但鉴于穿刺为有创检查，肝穿刺仅应用于病情需要的病人（如胃原发灶存在特殊类型癌、影像学无法确认的转移瘤、胃原发灶与肝脏转移灶的疗效不一致等）。

推荐意见：胃癌原发灶应常规行病理、免疫组化及分子病理检测。（证据级别：1a）

专家赞同率：97.2%（35/36）；推荐度：高。

1.4　血清学检查　胃癌肝转移病人术前血清肿瘤标记物癌胚抗原（CEA）、糖类抗原（CA）19-9、CA72-4、CA125、甲胎蛋白（AFP）升高提示复发率高和预后不良[21, 37-43]。胃癌根治术后淋巴细胞与单核细胞比值降低与肝转移的发生密切相关，也提示有较高的复发可能[44]。部分复发的病人血清肿瘤标记物指标升高要先于影像学诊断2~3个月[45]。

推荐意见：胃癌肝转移病人应常规检测血清肿瘤标记物CEA、CA19-9、CA72-4、CA125、AFP等。（证据级别：2a）

专家赞同率：97.2%（35/36）；推荐度：高。

2　C-GCLM分型

在严格筛选病人群体的前提下[22, 46-49]，积极治疗原发灶和转移灶，达到R0切除或无疾病证据（no evidence of disease, NED）状态可将胃癌肝转移5年总体生存率提高至20%以上[6, 7, 13, 21, 50-52]。而现有的胃癌肝转移分型系统，如同时性和异时性分类、日本《胃癌治疗指南》H分型系统，对治疗指导价值有限。因此，综合现有研究[3, 4, 6, 21, 23, 46, 47, 50-80]、国内外胃癌诊疗指南[81-84]和专家讨论意见，以原发灶及转移灶的可切除性为基础，本共识完善了2019版共识提出的胃癌肝转移临床分型体系，即C-GCLM分型（图1），以利于临床诊疗决策的制定。本共识主要针对原发灶和转移灶分型不一致的情形，并对肝脏储备功能评估的推荐意见进行了更新和修订（表2）[9, 85-86]。

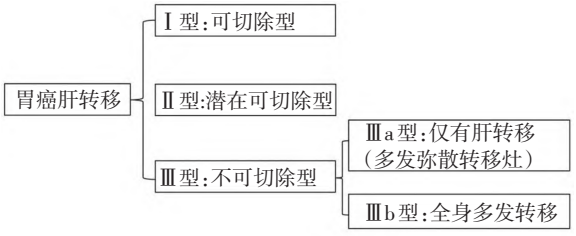


图1　胃癌肝转移中国专家共识（C-GCLM）分型系统

3　MDT模式在胃癌肝转移中的应用与价值

MDT模式需贯穿胃癌肝转移病人的诊疗全程[27, 87]。由MDT讨论其诊断、临床分型、治疗方案选择、疗效评估及随访流程，制定个体化方案[88]。MDT至少应由以下科室人员组成：普通外科（胃肠外科、肝脏外科）、肿瘤内科、消化内科、介入科、影像科等，必要时可增加营养科、重症医学科、麻醉科、手术室等。本共识对MDT模式在胃癌肝转移中的应用与价值达成以下意见。

（1）对于原发灶和转移灶均可R0切除者，可选择同期切除原发灶和转移灶，根据MDT评估结果决定围手术期系统治疗方案。

（2）对于原发灶或转移灶其一不可切除者，可行术前系统治疗并定期评估，如可转化为原发灶、转移灶均可R0切除者行手术治疗，其一不可切除的再次进入MDT治疗评估流程；如Ⅱ型病人全身条件良好，经系统治疗达到疾病部分缓解（partial remission, PR）或疾病稳定（stable disease,

表2 胃癌肝转移中国专家共识分型(C-GCLM分型)具体标准[1)]

Ⅰ型	胃原发灶:浸润深度≤T4a期;淋巴结转移D2清扫范围内(不包括Bulky N2[2)])
	肝转移灶:肝脏转移灶1~3个,最大病灶直径≤4 cm(或病灶局限于肝脏一叶内),不累及重要血管和胆管
	具体情况判断:(1)经肝胆外科专科医师评估转移灶技术上是否可切除;(2)经肝脏储备功能评估是否可耐受肝切除手术(肝脏残余容积≥30%~40%)
Ⅱ型	胃原发灶:胃原发灶浸润深度T4b期,或Bulky N2,或局限的No.16a2、No.b1淋巴结肿大
	肝转移灶:数量与大小超出Ⅰ型范围,但从外科技术上仍具切除可能性
Ⅲ型	胃原发灶:(1)肿瘤外侵严重,与周围正常组织无法分离或包裹重要血管(包括脾动脉);(2)区域淋巴结转移固定、融合成团,或转移淋巴结不在手术可清扫范围内,如肿瘤浸润肠系膜根部或累及腹主动脉旁淋巴结(影像学高度怀疑或活检证实)[82]
	转移灶:Ⅲa型,弥散型肝转移灶,不伴肝外转移;Ⅲb型,肝转移同时合并1个或多个肝外器官转移,伴或不伴腹膜转移

注:1)若原发灶与转移灶的分型不一致,则依据分型较晚的部位进行评估 2)Bulky N2,肝总动脉、腹腔干、脾动脉周围单个淋巴结直径≥3 cm(可以是融合成团的淋巴结)或≥3个连续的淋巴结直径≥1.5 cm[85-86]

SD)状态,即使仍无法达到R0切除,胃原发灶切除亦可能使病人受益,应根据MDT意见考虑积极手术治疗[89]。

(3)对于原发灶和转移灶均无法切除者,建议行全身化疗为主的综合治疗,治疗期间定期行MDT评估。

(4)对于病人一般状况差,不适合积极治疗者,采取最佳支持治疗。

(5)对于合并出血、穿孔、梗阻等情况的病人,根据病人全身情况,可行局部姑息性手术治疗。

(6)对于联合肝外转移等情况复杂的病人,根据MDT讨论结果制定具体计划。

4 胃癌肝转移诊疗流程图

基于C-GCLM分型系统制定的诊疗流程图见图2。

5 不同C-GCLM分型胃癌肝转移综合治疗

胃癌肝转移的多学科综合治疗主要包括系统治疗(全身化疗、靶向治疗和免疫治疗等)、手术切除、局部物理治疗和放射治疗等疗法,诊疗团队可根据MDT讨论意见基于C-GCLM分型选择其中1种或多种疗法。

5.1 Ⅰ型:可切除型 Ⅰ型病人占胃癌肝转移总体病人的20%左右[8]。根据MDT的综合评估,胃原发灶和肝转移灶均可手术切除,可选择直接手术切除或行术前系统治疗。术前系统治疗建议联合化疗,HER-2阳性者联合靶向治疗[90],无免疫治疗禁忌证的病人应考虑联合PD-1/PD-L1免疫治疗,具体方案选择参照相关指南。术前治疗时限原则上≤6~8周期。

胃原发灶手术切除标准:胃癌根治术+D2淋巴结清扫。肝转移灶手术切除标准:R0切除。肝转移灶切除范围:(1)局部肝切除术。(2)肝区、段切除术。(3)半肝切除术。(4)联合肝区、段切除术。手术技术方法:开放、腹腔镜或机器人手术。射频消融(RFA)是继手术切除后对肝脏转移灶又一有效毁损方法,可辅助手术治疗[55,67],也可单独使用。术后推荐每2~3个月进行1次评估[56,91-92]。

推荐意见:C-GCLM Ⅰ型病人建议行术前系统治疗,在评估原发灶和(或)转移灶能达到R0切除时应积极考虑外科手术和(或)肝脏局部损毁治疗。(证据级别:2b)

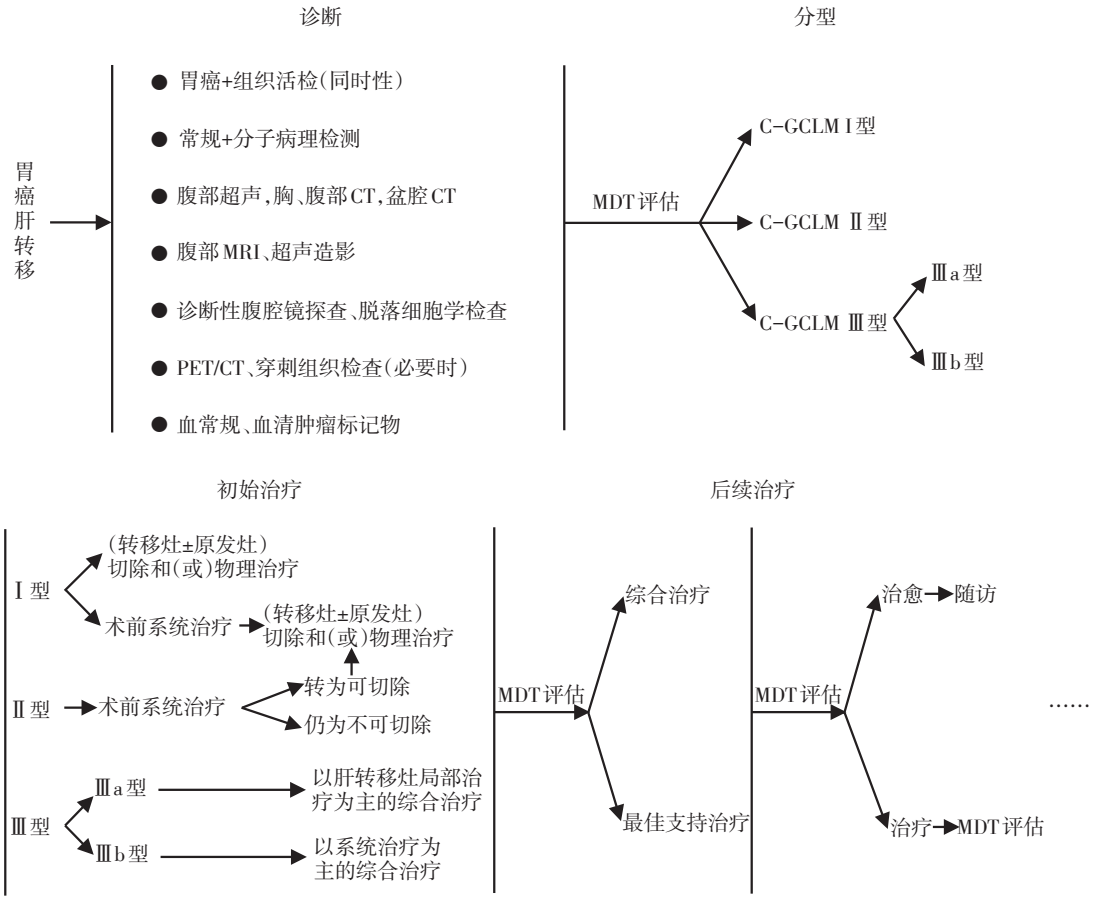
专家赞同率:88.9%(32/36);推荐度:中。

5.2 Ⅱ型:潜在可切除型 Ⅱ型病人占胃癌肝转移总体病人的25%左右[8]。术前系统治疗也应争取使用联合化疗方案结合免疫或靶向治疗,以争取手术机会。另外,肝脏局部化疗方式[经肝动脉化疗栓塞术(TACE)[5,56,93-95]和肝动脉灌注化疗(HAIC)[96-98]]在提高肝脏局部药物浓度的同时不增加全身毒副反应,可用于术前系统治疗也可用于术后防止肝内复发。三维适形放射(3D-CRT)治疗可联合化疗应用于胃癌肝转移病人的术前辅助治疗[31]。立体定向放射治疗(SBRT)和调强放射治疗(IMRT)技术,可处理一些位置特殊(如肝门区、包绕大血管)的转移灶,尤其适用于最大直径<5 cm的寡转移灶。对于一般情况不适宜或拒绝手术的异时性肝转移和(或)肝内复发者,RFA可多次反复使用[99-101]。微波消融[102]、经皮冷冻消融术[103]、质子射线治疗[104]等局部物理疗法也逐步应用到胃癌肝转移的治疗中,并取得了初步成果。局部物理疗法适用于最大直径<3 cm的转移灶,建议单次最多消融5枚。

推荐意见:C-GCLM Ⅱ型胃癌肝转移病人应先行系统治疗,并只有在具备R0切除可能时才推荐手术治疗。但部分Ⅱ型病人如全身条件良好,经系统治疗达到疾病PR或SD状态,即使仍无法施行R0切除,胃原发灶切除亦可能使病人受益,应根据MDT意见考虑积极手术治疗。(证据级别:2b)

专家赞同率:66.7%(24/36);推荐度:低。

5.3 Ⅲ型:不可切除型 Ⅲ型病人占胃癌肝转移总体病人的55%左右[8]。对于一般情况较好能够耐受化疗的病人,可根据分子标记物(MMR表达/MSI状态,PD-L1表达,HER-2表达,Claudin 18.2表达,FGFR2b表达和*FGFR2*扩增,*MET*扩增,*NRTK*融合等)选择一线治疗方案或加入相应的临床试验:包括免疫检查点抑制剂PD-1/PD-L1抗体治疗或联合化疗[105-107]、免疫检查点抑制剂联合抗HER-2药物(曲妥珠单抗)联合化疗[108]、基于Claudin 18.2的靶向



MDT:多学科综合治疗协作组

图2　基于胃癌肝转移中国专家共识分型(C-GCLM)系统的诊疗流程图

药物[单克隆抗体(佐妥昔单抗)[109]、双特异性抗体、ADC类药物]联合化疗或者FGFR2b单克隆抗体联合化疗等。既往治疗失败的病人还可尝试使用新型免疫疗法如嵌合抗原受体T细胞[110]、细胞免疫、热休克蛋白gp96[111]等具体疗法。其他综合用药如胸腺法新可诱导T细胞的成熟分化,可用于增强机体免疫及抗肿瘤疗效[112]。另外,TACE或HAIC还可作为一线、二线化疗方案失败病人的补充治疗。部分Ⅲ型病人还可从放射治疗中获益。当出现穿孔、梗阻、出血等并发症时,可行姑息手术以缓解症状。对于肿瘤所致的狭窄、持续性出血,能够安全地进行胃切除时行姑息性胃切除;但存在困难或危险时应行胃空肠吻合等短路手术。

推荐意见:C-GCLM Ⅲ型病人出现并发症时应即时行手术治疗,除此之外,不建议行减瘤手术;鼓励病人在MDT指导下根据分子标记物参加免疫治疗或靶向治疗临床试验。(证据级别:2b)

专家赞同率:100%(36/36);推荐度:高。

6　胃癌肝转移随访

随访检查项目及间隔时间见表3。

表3　胃癌肝转移随访检查项目及间隔时间

检查项目	随访间隔时间
病史、体格检查、营养状况评估、血常规、血生化、肿瘤标记物、腹部超声	1、3、6、9、12、15、18、21、24、30、36、42、48、54、60个月;5年后,每年1次
胸部CT平扫或增强(必要时);腹部、盆腔增强CT	6、12、18、24、36、48、60个月;5年后,必要时
腹部增强MRI、PET-CT、胃镜	重大临床决策时;必要时

《胃癌肝转移诊断与综合治疗中国专家共识(2024版)》编审委员会成员名单

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(2024-03-21收稿)

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