· 指南与共识 ·

中国结直肠癌肝转移诊断和综合治疗指南(2018 版)

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Guideline for the diagnosis and comprehensive treatment of colorectal cancer liver metastasis (2018 edition)　*Section of Gastrointestinal Surgery, Branch of Surgery, Chinese Medical Association; Section of Colorectal Surgery, Branch of Surgery, Chinese Medical Association; Chinese Society of Colon Cancer, China Anti-cancer Association; Chinese Society of Colon and Rectal Surgeons, Branch of Surgeons, Chinese Medical Doctor Assocication; Chinese Society of Tumor Metastasis, Branch of Anal Surgeons, Chinese Medical Doctor Assocication; Chinese Society of Colon and Rectal Tumors, Chinese Medical Doctor Assocication; Committee of Colorectal Experts, Chinese Society of Clinical Oncology; Professional Committee of Treatment for Colorectal Cancer Liver Metastasis, China International Exchange and Promotive Association for Medical and Healthcare*

【Key words】 Colorectal neoplasms; Liver metastases; Diagnosis; Comprehensive treatment; Guideline

【关键词】 结直肠肿瘤; 肝转移; 诊断; 综合治疗; 指南

肝脏是结直肠癌血行转移最主要的靶器官,结直肠癌肝转移(colorectal cancer liver metastases)是结直肠癌治疗的重点和难点之一[1-2]。有 15%~25%结直肠癌患者在确诊时即合并有肝转移,而另 15%~25%的患者将在结直肠癌原发灶根治术后发生肝转移,其中绝大多数(80%~90%)的肝转移灶初始无法获得根治性切除[3-7]。结直肠癌肝转移也是结直肠癌患者最主要的死亡原因[1]。未经治疗的肝转移患者中位生存时间仅 6.9 个月,无法切除患者的 5 年生存率低于 5%[8-9],而肝转移灶能完全切除[或可以达到无疾病证据(no evidence of disease, NED)状态]患者的中位生存时间为 35.0 个月,5 年生存率可达 30%~57%[10-14]。有研究结果表明:有一部分最初肝转移灶无法根除的患者经治疗后可以转化为可切除或达到 NED 状态[8]。因此,通过多学科团队(multidisciplinary team, MDT)对结直肠癌肝转移患者进行全面评估,个性化地制订治疗目标,开展相应的综合治疗,以预防结直肠癌肝转移的发生、提高肝转移灶手术切除率和 5 年生存率[15-16]。

为了提高我国结直肠癌肝转移的诊断和综合治疗水平,受卫生部临床重点学科项目资助(2008—2010 年),中华医学会外科学分会胃肠外科学组和结直肠外科学组、中国抗癌协会大肠癌专业委员会自 2008 年起联合编写了《结直肠癌肝转移诊断和综合治疗指南》(草案),以指导我国结直肠癌肝转移的诊断和治疗,并于 2010、2013 年先后进行了两次修订。2016 年再联手中国医师协会外科医师分会结直肠外科医师委员会、中国医疗保健国际交流促进会结直肠癌肝转移治疗专业委员会修订了该指南。2018 年,编写组进一步与中国临床肿瘤学会(CSCO)结直肠癌专家委员会、中国医师协会结直肠肿瘤专业委员会、中国医师协会肛肠医师分会肿瘤转移委员会联合,总结国内外先进经验和最新进展修订《中国结直肠癌肝转移诊断和综合治疗指南(2018 版)》(以下简称指南)。

注 1:本《指南》对结直肠癌肝转移的诊断、预防、外科手术和其他综合治疗提出的建议,请各地医院根据实际情况予以应用。本文中出现的推荐级别、循证医学证据分类的界定,详见附录 1。

注 2:本《指南》内容暂不涉及未在中国大陆范围内批准应用的技术和药物。

1　结直肠癌肝转移的诊断与随访

1.1　结直肠癌肝转移的定义

按照国际共识:同时性肝转移(synchronous liver metastases)是指结直肠癌确诊前或确诊时发现的肝

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转移;而结直肠癌根治术后发生的肝转移称为异时性肝转移(metachronous liver metastases)[17]。本指南为便于诊疗策略的制定,将按照"结直肠癌确诊时合并肝转移"和"结直肠癌根治术后发生肝转移"两方面阐述。

1.2 结直肠癌确诊时肝转移的诊断常规

对已确诊结直肠癌的患者,除血清 CEA、CA19-9 检查、病理学分期评估外,应常规进行肝脏超声和增强腹部 CT 等影像学检查筛选及诊断肝脏转移瘤。对于超声或 CT 影像学检查高度怀疑但不能确诊的患者可加行血清 AFP、肝脏超声造影和肝脏 MRI 平扫及增强检查[18-19](**1a 类证据,A 级推荐**),临床有需要时可行肝脏细胞特异性造影剂增强 MRI 检查。PET/CT 检查不作为常规推荐,可在病情需要时酌情应用[20-21](**2a 类证据,B 级推荐**)。

肝转移灶的经皮针穿刺活组织检查仅限于病情需要时应用[22]。

结直肠癌手术中必须常规探查肝脏以进一步排除肝转移的可能,对可疑的肝脏结节可考虑术中活组织检查[23](**3a 类证据,B 级推荐**)。

1.3 结直肠癌根治术后肝转移的监测

结直肠癌根治术后应对患者定期随访,了解有无肝转移的发生[24-27]。

(1)每 3~6 个月进行 1 次病史询问、体格检查和肝脏超声检查,持续 2 年,以后每 6 个月 1 次直至满 5 年,5 年后每年 1 次。

(2)每 3~6 个月检测 1 次血清 CEA、CA19-9 等适当的肿瘤标志物,持续 2 年,以后每 6 个月 1 次直至满 5 年[28](1a 类证据,A 级推荐),5 年后每年 1 次。

(3)Ⅱ期和Ⅲ期的结直肠癌患者,建议每年进行 1 次胸、腹、盆腔增强 CT 扫描,共 3~5 年[29](**1b 类证据,A 级推荐**),以后每 1~2 年 1 次。对于超声或 CT 影像学检查高度怀疑肝转移瘤但不能确诊的患者应加行肝脏 MRI 等检查,并建议在随访过程保持影像学检查方法的一致性。PET/CT 扫描检查不作常规推荐。

(4)术后 1 年内应进行电子结肠镜检查,若发现异常,需在 1 年内复查[30];否则术后第 3 年复查,以后每 5 年 1 次。如果患者发病年龄<50 岁则应适当增加电子结肠镜的检查频度。对于结直肠癌根治术前因梗阻等原因无法行全结肠镜检查的患者,应在术后 3~6 个月内完成首次电子结肠镜检查[30](**1a 类证据,A 级推荐**)。

1.4 结直肠癌肝转移灶达到 NED 后的随访

结直肠癌肝转移灶达到 NED 后,对患者也应进行密切随访,了解有无肝转移复发。

(1)根据术前肿瘤标志物的升高情况,建议术后 2 年内每 3 个月随访血清 CEA、CA19-9 等适当的肿瘤标志物,以后第 3~5 年内每 6 个月随访 1 次(**1a 类证据,A 级推荐**),5 年后每年 1 次。

(2)术后 2 年内每 3~6 个月进行 1 次胸、腹、盆腔增强 CT 扫描检查。临床重大决策时建议行 MRI 平扫及增强扫描,必要时行肝脏细胞特异性造影剂增强 MRI 检查。以后每 6~12 个月进行 1 次,共 5 年[29](**1a 类证据,A 级推荐**),5 年后每年 1 次。不推荐常规 PET/CT 扫描检查。

(3)其他随访内容和频次参照结直肠癌原发灶根治术后的随访进行。

1.5 结直肠癌及其肝转移的相关基因检测

1.5.1 RAS 检测:推荐结直肠癌肝转移患者均进行 KRAS 第 2、3、4 外显子以及 NRAS 第 2、3、4 外显子的检测[31-34]。RAS 基因是否突变不仅有一定的预后意义,更是抗 EGFR 治疗有效性的重要生物学标记物[35-38](**1a 类证据,A 级推荐**)。

1.5.2 BRAF 检测:推荐结直肠癌肝转移患者行 V600E 突变检测,作为预后的评估指标[39-43](**1b 类证据,A 级推荐**)以及疗效预测,以指导治疗方案选择。

1.5.3 错配修复基因(mismatch repair gene, MMR)/微卫星不稳定性(microsatellite instability, MSI)检测:推荐结直肠癌患者进行 MMR 和 MSI 检测,以便更精准地制定治疗策略[44-45]。免疫组织化学染色检测 MMR 的蛋白表达(包括 MLH1、MSH2、MSH6、PMS2)。

1.5.4 UGT1A1 检测:UGT1A1 是伊立替康的药物代谢酶,其基因的多样性会显著影响该酶的活性。非野生型的 UGT1A1 患者接受伊立替康化疗,可能会增加Ⅲ度以上骨髓抑制以及腹泻的风险[46-48]。

结直肠癌原发灶和肝转移灶的基因状态大多无差别[49-51],对于无法获取肿瘤组织进行检测时可考虑液态活组织检查技术。

2 结直肠癌肝转移的预防

2.1 结直肠癌原发灶根治性切除术

根治性手术是迄今为止结直肠癌最有效的治愈方法,也是预防肝转移发生的重要环节[52]。

(1)结肠癌根治性手术范围包括肿瘤全部及其

两端足够肠段和周围可能被浸润的组织和器官以及相关系膜、主要供应血管和淋巴引流区，具体手术方式依照肿瘤部位不同而异，但均应遵循完整结肠系膜切除（complete mesocolic excision，CME）原则。

（2）直肠癌根治性手术范围应包括肿瘤全部及其两端足够肠段、周围可能被浸润的组织和器官以及相关的肠系膜和淋巴结。直肠中下段的肿瘤应遵循全直肠系膜切除（total mesorectal excision，TME）原则。

（3）术中发现存在切除范围外的可疑淋巴结，应进行术中活组织检查或切除。

2.2　结直肠癌确诊时无肝转移（及其他远处转移）的新辅助治疗

术前通过新辅助治疗杀灭未被影像学检测到的微小转移灶，可以最大程度地减少根治性手术后的远处转移[53-54]。

2.2.1　中低位直肠癌的新辅助治疗（注：高位直肠癌即肿瘤下缘距肛缘>12 cm，其新辅助治疗参照结肠癌。）

（1）联合放化疗或放疗：建议术前诊断为 T3 期及以上或任何 T 分期但淋巴结阳性的直肠癌，在不伴有明显出血、梗阻症状、无穿孔以及其他远处转移等情况时应用[55-58]。

①联合放化疗：总剂量 45.0～50.4 Gy 的放疗，采用常规分割剂量（通常每周 5 d，共 5 周），并应用以 5-氟尿嘧啶（5-fluorouracil，5-FU）或卡培他滨为主的化疗。放化疗治疗结束后 6～8 周行直肠癌根治性手术[57,59]（**1a 类证据，A 级推荐**）。放疗作用于局部使肿瘤降期甚至缓解，化疗可在术前杀灭“微转移灶”预防肿瘤远处转移，还能提高放疗的敏感性[60]。

②单纯短程放疗：也可考虑直肠癌肿瘤部位及淋巴引流区短程（5 d）总剂量 25.0 Gy 的放疗[58,61-63]，并于放疗后 1 周内行根治性手术。短程放疗较联合放化疗更少出现急性的不良反应[64-65]。但短程放疗不能使肿瘤降期，更适合于可手术切除的Ⅱ期或Ⅲ期直肠癌。短程放疗后再手术的晚期并发症发生率较高，应予以重视[66]（**2b 类证据，B 级推荐**）。

（2）肝动脉和肿瘤区域动脉联合灌注化疗：对于术前分期为Ⅲ期，且不伴有出血、梗阻症状或无穿孔的患者，在有条件的单位可考虑应用。5-FU（或其前体药物）并可联合奥沙利铂，经肝动脉、肿瘤区域动脉分别灌注，化疗后 7～10 d 施行根治性切除术。目前的临床研究结果表明：该方案虽不能使肿瘤明显降期，但对Ⅲ期结直肠癌患者有预防肝转移的作用[67-68]。建议在有条件的单位开展，不作为常规推荐。

2.2.2　结肠癌的新辅助治疗：结肠癌的新辅助治疗尚无明确的循证医学证据，对于术前判断为Ⅲ期的患者可考虑肝动脉和肿瘤区域动脉联合灌注化疗，以减少肝转移的发生[67-68]，不作常规推荐。

2.3　无转移结直肠癌患者术中门静脉化疗、腹腔化疗

对于无转移结直肠癌患者，术中行门静脉化疗、腹腔化疗目前有了一些令人鼓舞的数据，如能联合术后辅助化疗，将可以减少肝转移的发生[69]。但这一结果仍需进一步临床研究结果证实，故不作为常规手段推荐，临床研究可关注。

2.4　非转移性结直肠癌患者根治术后的辅助治疗

（1）术后辅助化疗对于Ⅲ期结肠癌，能延长 5 年无病生存率及总体生存率[70-71]。因此，上述结肠癌患者在手术治疗后应进行 3～6 个月的辅助化疗，可选择的治疗方案有：FOLFOX，CapeOX，5-FU/LV 或卡培他滨单药[71-74]（**1a 类证据，A 级推荐**）。

Ⅱ期不存在转移高危因素的结直肠癌患者，术后两药联合的辅助化疗在许多临床研究中未见到明显的效果，故建议接受临床观察和随访[75]（**1b 类证据，A 级推荐**），或建议氟尿嘧啶单药治疗（MSI-H 患者除外）。但对于高危Ⅱ期患者［T4 期、组织分化差（MSI-H 患者除外）、肿瘤周围淋巴管神经侵犯、肠梗阻、或 T3 期伴有局部穿孔、切缘不确定或阳性、淋巴结活组织检查数目<12 枚］应予以辅助化疗，方案参照Ⅲ期患者[71,76]（**2a 类证据，B 级推荐**）。

（2）T3 期及以上和任何 T 分期但淋巴结阳性的中低位直肠癌患者如术前没有进行放化疗，术后辅助化疗和放化疗能提高 3 年无病生存率及降低局部复发率[77-78]。但对于能否减少直肠癌肝转移方面的研究有限，和辅助化疗的结合方式也需更多临床试验验证。术前接受过放疗或联合放化疗的患者，术后也应接受辅助治疗，但尚无充分的循证医学证据。

3　MDT 在结直肠癌肝转移诊断与治疗中的作用

对于肿瘤性疾病，MDT 治疗模式是有效的手段[79-80]。因此，建议结直肠癌肝转移患者进入 MDT 治疗模式[81]（**1a 类证据，A 级推荐**）。结直肠癌的 MDT 以患者为中心，成员应包括胃肠外科、肝外科、肿瘤内科、放疗科、放射和超声影像科及其他相关专

业有一定资质的医师[82-83]。MDT 可以减少个体医师做出的不完善决策[84],其重要作用还包括:(1)更精确的疾病分期[85]。(2)较少的治疗混乱和延误[86-87]。(3)更个性化的评估体系和治疗[88]。(4)更好的治疗衔接[89]。(5)更高的生命质量[90]。(6)最佳的临床和生存获益[91-95]。

MDT 根据患者的体力状况、年龄、器官功能、合并症等进行评估,针对不同的治疗目标,给予患者最合理的检查和最恰当的综合治疗方案[83,96](**1a 类证据,A 级推荐**)。

(1)患者全身状况较差,不适合进行高强度治疗时,建议单药(或联合靶向药物)、减量的两药方案或最佳支持治疗,以提高生命质量并尽量延长生存。如全身情况好转,可以再进行强烈治疗。

(2)适合高强度治疗的患者,还应依据肝转移的具体情况和是否伴有其他转移等,制订不同的治疗目标,给予个体化的治疗方案。

①肝转移灶初始即可以 R_0 切除,且手术难度不大、肿瘤生物学行为良好的患者,其治疗目的是获得治愈。应该围绕手术治疗进行相应的新辅助和(或)辅助治疗,以降低手术后复发的风险。肝转移灶是否可 R_0 切除的判断应由肝外科、肿瘤外科、影像科专家联合进行。

肝转移灶可以 R_0 切除,但手术难度较大时也应积极联合其他肿瘤局部毁损手段[如射频消融或(和)立体定向放疗等],以达到 NED 状态。

②肝转移初始无法切除,但经过一定的治疗有望转为可以 NED 状态,且全身情况能够接受包括转移灶切除手术在内的局部治疗手段和高强度治疗的患者。这类患者的治疗目的主要是最大程度地缩小瘤体或增加剩余肝脏体积,应采用最积极的综合治疗。

③还有一部分患者,其肝转移灶可能始终无法切除或达到 NED 状态,但全身情况允许接受较高强度的治疗。对于这类患者是以控制疾病进展为目的进行治疗,应该采用较为积极的联合治疗。

4　结直肠癌肝转移灶的手术及其他毁损治疗

4.1　手术治疗

手术完全切除肝转移灶仍是目前能治愈结直肠癌肝转移的最佳方法[97-101]。故符合条件的患者均应在适当时候接受手术治疗。部分最初肝转移灶无法切除的患者经治疗后转化为可切除病灶时也应适时接受手术治疗。

4.1.1　手术适应证和禁忌证。(1)适应证:是否适合手术切除的标准一直在演变,但主要应从以下 3 方面来判断[8,16,57,102-103](**2a 类证据,B 级推荐**):

①结直肠癌原发灶能够或已经根治性切除。

②根据肝脏解剖学基础和病灶范围,肝转移灶可完全(R_0)切除,且要求保留足够的功能性肝组织(剩余肝脏容积≥30%~40%,采用三维 CT、3D 数字成像技术等有助于评估剩余肝脏体积[104-105])。

③患者全身状况允许,没有不可切除或毁损的肝外转移病变,或仅为肺部结节性病灶,但不影响肝转移灶切除决策的患者。

随着技术的进步,肝转移灶的大小、数目、部位、分布等已不再是影响判断结直肠癌肝转移患者是否适宜手术的单一决定因素。

另外,当前的文献资料已将切缘不足 1 cm[106-109]、可切除的肝门淋巴结转移[110-111]、可切除的肝外转移病灶(包括肺、腹腔)[112-116]等也纳入了适宜手术切除的范畴(**4 类证据,C 级推荐**)。

(2)禁忌证[8,57,102,117](**3a 类证据,B 级推荐**):

①结直肠癌原发灶不能获得根治性切除。

②出现不能切除的肝外转移。

③预计术后剩余肝脏容积不够。

④患者全身状况不能耐受手术。

4.1.2　结直肠癌确诊时合并肝转移的手术治疗。(1)结直肠癌原发灶和肝转移灶一期同步切除:在肝转移灶小且多位于周边或局限于半肝,肝切除量<50%,肝门部淋巴结、腹腔或其他远处转移均可手术切除的患者可建议一期同步切除[118-120]。有研究者认为:一期同步切除肝转移灶和原发结直肠癌病灶手术的并发症和死亡率可能高于二期分阶段手术[121-125]。故患者的选择应较为慎重,尤其是需要在两切口下完成的同步手术。

急诊手术由于缺少完备的术前检查资料和较高的感染发生机会,因此不推荐原发结直肠癌和肝脏转移病灶一期同步切除[126](**2c 类证据,B 级推荐**)。

(2)结直肠癌原发灶和肝转移灶二期分阶段切除:术前评估不能满足一期同步切除条件的患者,可以先行手术切除结直肠癌原发病灶,二期分阶段切除肝转移灶,时机选择在结直肠癌根治术后 4~6 周;若在肝转移灶手术前进行系统性治疗,肝转移灶的切除可延至原发灶切除后 3 个月内进行。可根治的复发性结直肠癌伴有可切除肝转移灶的治疗按结直肠癌确诊时合并肝转移处理,但倾向于进行二期分阶段切除肝转移灶。

先切除肝转移灶、再切除结直肠原发灶的“肝优先模式”(liver first approach)也已开展应用[127-131],其手术的并发症、死亡率和 5 年生存率均与传统模式的二期分阶段切除相同[132-133](**3b 类证据,B 级推荐**)。

4.1.3 结直肠癌根治术后发生肝转移的手术治疗:既往结直肠原发灶为根治性切除且不伴有原发灶复发,肝转移灶能完全切除且肝切除量<70%(无肝硬化者),应予以手术切除肝转移灶,也可考虑先行新辅助治疗[134](**3b 类证据,B 级推荐**)。

诊断结直肠癌根治术后发生肝转移应当有两项以上的影像学检查依据,包括肝脏超声、增强 CT 及 MRI 等,必要时可结合 PET/CT 扫描检查以确定病变的范围和有无肝外转移,从而避免不必要的手术治疗[135]。

4.1.4 肝转移灶手术方式的选择[134,136-138](**3b 类证据,B 级推荐**):(1)肝转移灶切除后至少保留 3 根肝静脉中的 1 根且剩余肝脏容积≥40%(同时性肝切除)或≥30%(异时性肝切除)。转移灶的手术切除应符合 R_0 原则,切缘至少>1 mm[106,139-141]。

(2)如是局限于左半肝或右半肝的较大肝转移灶且无肝硬化患者,可行规则的半肝切除术。

(3)建议肝转移手术时采用术中超声检查,有助于发现术前影像学检查未能诊断的肝转移病灶。

(4)应用门静脉选择性的栓塞(PVE)或结扎(PVL)治疗,可使肝转移灶切除术后预期剩余肝脏代偿性增大,增加手术切除的可能。此方法被用于预计手术切除后剩余肝脏体积<30%的肝转移患者。对于剩余肝脏体积在 30%~40%,并且接受了强烈化疗而有肝实质损伤的患者,同样也可从中获益[142-146](**4 类证据,C 级推荐**)。

(5)联合肝脏分隔和门静脉结扎的二步肝切除术(associating liver partition and portal vein ligation for staged hepatectomy, ALPPS)可使剩余肝脏的体积在较短时间内明显增大而获得更多二期肝切除的机会[147-148]。但此手术复杂,并发症及死亡率均高于传统肝切除术[149-152]。故建议在严格选择的患者中由经验丰富的肝脏外科医师施行手术[153-154]。

4.1.5 肝转移灶切除术后复发和肝外转移灶的切除:在全身状况和肝脏条件允许的情况下,对于可切除的肝转移灶术后复发病灶,可进行二次、三次甚至多次的肝转移灶切除,文献报道显示其手术并发症和死亡率并不高于第一次肝转移灶的切除,而且可获得相同的术后生存率[8,155-157](**3b 类证据,B 级推荐**)。

同样,在患者全身状况允许时,如果肺[158]和腹腔[159-160]等的肝外转移病灶可完全切除,也应进行同步或分阶段切除(**3b 类证据,B 级推荐**)。

4.2 可以达到 NED 状态的肿瘤局部毁损治疗

除了手术切除肝转移灶外,有些治疗手段(如射频消融和放射治疗)也能使病灶发生彻底毁损,所以对于手术切除难度较大的个别肝转移灶应积极联合此类手段,以使更多的患者有机会达到 NED 状态,提高 5 年生存率。

5 可达到 NED 状态结直肠癌肝转移的新辅助及辅助治疗

5.1 新辅助治疗

对可达到 NED 的结直肠癌肝转移患者可考虑进行新辅助治疗,主要基于以下几方面原因[161-162]:

(1)新辅助化疗提供了“窗口期”,观察有无新的无法切除的转移灶出现,减少没有必要的手术[163]。

(2)新辅助治疗可增加 R_0 手术的机会,增加术后剩余肝脏体积[164-165]。

(3)新辅助化疗可作为评价化疗方案敏感性的依据,指导术后化疗方案的选择[166]。

(4)新辅助化疗的疗效,可作为患者预后评估的一个指标[167-171]。

(5)新辅助化疗结合辅助化疗,可能改善接受治愈性手术患者的预后[172-176]。

新辅助治疗在应用时也应关注如下情况可能:

(1)化疗可能会造成肝脏损伤:如与奥沙利铂治疗相关的肝脏血管性病变[176-181];与伊立替康治疗相关的非酒精性脂肪肝等[182-184],这些损害均可能增加肝切除术后并发症的发生率[184-188]。

(2)影像学检查显示消失的转移灶仍应切除[118,189-192],但术者无法在术中给予肝脏转移灶精确定位[166,193]。

(3)转移灶进展致使无法达到 NED。

5.1.1 结直肠癌确诊时合并肝转移的新辅助治疗:在原发灶无出血、梗阻症状或无穿孔时,除肝转移灶在技术上切除容易且不存在不良预后因素的患者[如临床危险评分(clinical risk score, CRS)<3 分]外,可考虑应用新辅助治疗[16,194-196](**2a 类证据,B 级推荐**),尤其是肝转移灶体积较大、转移灶数量较多或原发灶淋巴结可疑存在转移的患者。

系统性化疗的方案包括 FOLFOX、FOLFIRI、CapeOX 或 FOLFOXIRI[197-200],可否联合分子靶向治疗目前仍有争议[201-205],同时也可以考虑联合肝动

脉灌注化疗(hepatic arterial infusion, HAI)[206-208]。

为减少化疗对肝脏手术的不利影响,新辅助化疗原则上不超过 6 个周期[74,177,180,186,209](**1a 证据,A 级推荐**),一般建议 2~3 个月内完成并进行手术[210]。

5.1.2 结直肠癌根治术后发生肝转移的新辅助治疗:原发灶切除术后未接受过化疗的患者,或发现肝转移 12 个月前已完成化疗的患者,可采用新辅助治疗(方法同上),时间 2~3 个月[72,211](**2a 类证据,B 级推荐**)。而肝转移发现前 12 个月内接受过化疗的患者,一般认为新辅助化疗作用可能较为有限,宜考虑直接切除肝转移灶,继而行术后辅助治疗[194](**2a 类证据,B 级推荐**)。也可考虑术前联合 HAI[206-208]。

5.2 肝转移灶切除术后的辅助治疗

建议肝转移灶完全切除的患者接受术后辅助化疗[212-216],特别是没有进行过术前化疗及辅助化疗的患者,推荐手术前后的化疗时间总长≤6 个月(**1a 类证据,A 级推荐**),也可考虑同时联合 HAI[4,217-219]。经过术前化疗(包括联合分子靶向药物)证实有效的方案,术后如无禁忌应该作为首选的辅助治疗方案。

6 无法达到 NED 状态结直肠癌肝转移的综合治疗

对于无法达到 NED 的结直肠癌肝转移的综合治疗包括系统性化疗和介入化疗、分子靶向治疗以及针对肝脏病灶的局部治疗如射频消融、无水酒精注射、放射治疗等,治疗方案的选择应基于对患者治疗前的精确评估。

部分初诊无法达到 NED 的肝转移患者,经过系统的综合治疗后可转为适宜手术切除或达到 NED[98,203]。该类患者术后 5 年生存率与初始肝转移灶手术切除患者相似[220-221]。此类患者应当采取较为积极的诱导方案,应用有效的强烈化疗,并考虑联合 HAI 及分子靶向药物治疗。

对于肝转移灶始终无法达到 NED 的患者,综合治疗也可明显延长中位生存时间,控制疾病快速进展,明显改善生命质量[222-225]。因此,积极的综合治疗对于适合强烈治疗的晚期结直肠癌肝转移患者同样意义重大。

6.1 治疗策略

6.1.1 结直肠癌确诊时合并无法达到 NED 的肝转移:(1)结直肠癌原发灶存在出血、梗阻症状或穿孔时,应先行切除结直肠癌原发病灶,继而进行系统性化疗(或加用 HAI[218,226-228]),可联合应用分子靶向治疗[229-231](**1b 类证据,A 级推荐**)。治疗后每 6~8 周进行肝脏超声和 CT 增强扫描检查并依据 RECIST 标准予以评估[184]。临床重大决策时建议 MRI 平扫及增强扫描。如果肝转移灶转变成可切除或有望 NED 时,即予以手术治疗或手术联合其他肿瘤局部毁损手段;如果肝转移灶仍不能达到 NED,则继续进行综合治疗[209,232]。

(2)结直肠癌原发灶无出血、梗阻症状或无穿孔时可以行系统性化疗(或加用 HAI),并可联用分子靶向治疗[230](**1c 类证据,B 级推荐**)。每 6~8 周评估 1 次,如果转移灶转化成可切除或有望 NED 时,即手术治疗(一期同步切除或分阶段切除原发病灶和肝转移灶)或手术联合其他肿瘤局部毁损手段;如果肝转移灶仍不能达到 NED,则视具体情况手术切除结直肠癌原发病灶,术后继续对肝转移灶进行综合治疗。

此类患者也可选择先行切除结直肠癌的原发病灶,继而进一步治疗,具体方案同上。但是,对于结直肠癌原发灶无出血、梗阻症状或无穿孔时合并始终无法达到 NED 肝转移灶患者是否应该切除原发灶目前仍有争议[233-234]。

6.1.2 结直肠癌术后发生的无法达到 NED 的肝转移:(1)采用 5-FU/LV(或卡培他滨)联合奥沙利铂或伊立替康作为一线化疗[9,235-236]。并可加用分子靶向治疗,或联用 HAI[237](**1b 类证据,A 级推荐**)。

(2)在肝转移发生前 12 个月内使用过奥沙利铂为基础的化疗作为辅助治疗的患者,应采用 FOLFIRI 方案;化疗结束后>12 个月发生肝转移,仍可采用 FOLFOX 或 CapeOX 化疗方案,并可加用分子靶向药物治疗,或联用 HAI[230,238](**3a 类证据,B 级推荐**)。

治疗后每 6~8 周检查肝脏超声、CT 增强扫描检查予以评估[183-184,239],临床重大决策时建议 MRI 平扫及增强扫描检查。肝转移灶转为可切除或可以达到 NED 的患者,即应接受肝转移灶切除手术或手术联合其他肿瘤局部毁损手段,术后再予以辅助化疗;如果肝转移灶仍不能达到 NED,则应继续进行综合治疗[184,209,232]。

6.2 治疗方法

6.2.1 系统性化疗和 HAI:化疗开始前应充分评估患者的身体状况和肿瘤分期,事先规划好患者的后续治疗和预计有严重化疗毒性反应时剂量和方案的调整。开始治疗时必须考虑患者的分类(详见“3　MDT 在结直肠癌肝转移诊断与治疗中的作用”

节)、化疗的安全性以及将来手术或(和)局部病灶毁损治疗的可能性[15]。

(1)初始化疗

①对于肝转移灶有潜在 NED 可能的患者进行转化治疗至关重要。转移灶出现的早期退缩(early tumor shrinkage, ETS)更是预后的重要指标之一[240-242]。

5-FU/LV(或卡培他滨)联合奥沙利铂或伊立替康的化疗方案具有较高转化切除率[243-245](**1b 类证据, A 级推荐**),应该作为首选的化疗方案。

化疗联合分子靶向药物可以进一步提高转化率[246-250](**1b 类证据, A 级推荐**)。现有的研究数据显示:化疗联合贝伐珠单克隆抗体有良好的疾病控制率和转化切除率,而 RAS 野生型患者还可以采用化疗联合西妥昔单克隆抗体治疗[203,229,251-254]。(**1b 类证据, A 级推荐**)

BRAF 的状态是重要的预后指标,BRAF 突变的结直肠癌肝转移患者大多预后较差,有数据提示对该类患者化疗联合抗 EGFR 治疗的获益比较有限[255]。因此对 BRAF 突变的结直肠癌肝转移患者,初始治疗采用化疗联合贝伐珠单克隆抗体也是值得考虑的选择。

FOLFOXIRI 也有较高的切除转化率[224-257],在分子靶向药物无法使用且患者体质较好的情况下应该作为首选(**1b 类证据, A 级推荐**)。但该方案的不良反应较多,应予以关注。目前该方案联合贝伐珠单克隆抗体的研究有了较好的临床数据,可在选择性的患者中谨慎应用[225-227,258-260]。

②对于肝转移灶始终无法达到 NED 的患者,5-FU/LV(或卡培他滨)联合奥沙利铂或伊立替康的化疗方案是首选,也可以联合分子靶向药物治疗(**2b 类证据, B 级推荐**)。FOLFOXIRI 尽管有较高的反应率,但毒性也较大,是否应在此类患者中应用尚不明确。

(2)诱导化疗后病情缓解或稳定,但肝转移灶仍无法 R_0 切除时可考虑进入维持治疗(如采用毒性较低的 5-FU/LV 或卡培他滨单药,均可联合贝伐珠单克隆抗体)或暂停化疗,以降低持续高强度联合化疗的不良反应[261-265]。

(3)病情进展后的化疗选择

①FOLFOX(或 CapeOX)方案±分子靶向治疗,如果病情进展后可以考虑改用 FOLFIRI(或 mXELIRI[266])方案;FOLFIRI 方案±分子靶向治疗,如果病情进展可考虑改用 FOLFOX(或 CapeOX)方案,仍可考虑与分子靶向药物联合使用[267-269]。如果病情第 2 次进展,可以使用瑞戈非尼[270-271]或西妥昔单克隆抗体[272-273](仅限于未用过此类药的 RAS 野生型患者,可联合伊立替康)或最佳支持治疗[54](**2a 类证据, B 级推荐**)。

②5-FU/LV 联合分子靶向治疗后如果病情进展,应改用 FOLFOX、FOLFIRI 或 CapeOX(均可联合分子靶向治疗),病情再次进展时推荐瑞戈非尼或进行最佳支持治疗[274](**3b 类证据, B 级推荐**)。

(4)上述治疗期间可在适当时机联合应用 HAI 或肝动脉化疗栓塞(transarterial chemoembolization, TACE),有助于延长疾病无进展时间和总体生存时间[275-278],尤其是 HAI 灌注药物洗脱微球(drug-eluting beads, DEB),可以进一步提高疗效[279]。但是单独应用这些治疗并不比全身化疗更具优势[280-281]。

6.2.2　局部毁损治疗:对于无法手术切除的肝转移灶,应根据其位置、治疗目标、治疗相关并发症及患者自身情况,在系统性化疗基础上选择适当的局部毁损工具(如射频消融、放射治疗等)以加强局部病灶的控制,具体应由 MDT 进行决策并结合患者意愿。

(1)消融治疗

①射频消融

射频消融术使用方便,安全性好,且能高效破坏肝转移灶的肿瘤细胞[282-284]。对于始终无法达到 NED 状态的晚期结直肠肝转移患者,现有资料表明单独使用射频消融治疗肝转移病灶的生存率仅略微高于其他非手术治疗,目前仅作为化疗无效后的治疗选择或肝转移灶术后复发的治疗[285-289]。建议应用时选择肝转移灶最大直径<3 cm 且一次最多消融 5 枚[8,16,290]。

对于预期术后剩余肝脏体积过小时,可先切除部分较大的肝转移灶,对剩余直径<3 cm 的转移病灶进行射频消融。或对于一般情况不适宜或不愿意接受手术治疗的可切除结直肠癌肝转移患者也可以考虑射频消融治疗。但应注意避免肝外热损伤和针道转移[291-293]。

②微波消融

微波的传导不受组织干燥碳化的限制,使肿瘤内部在较短的时间内就可产生较高的温度和更大的消融带,而使肿瘤细胞的坏死更彻底[294]。与单纯化疗相比,结合微波消融治疗经过选择的不可切除的结直肠癌肝转移患者可以更有效地提高生存率[295-296]。

③冷冻治疗

尽管冷冻治疗严格挑选不可切除的结直肠癌肝

转移患者在一定程度上提高了生存率[297-299]。但是较高的局部复发率和并发症发生率(可达 35%,包括 ARDS 和 DIC 等)限制了该技术的广泛应用[300]。

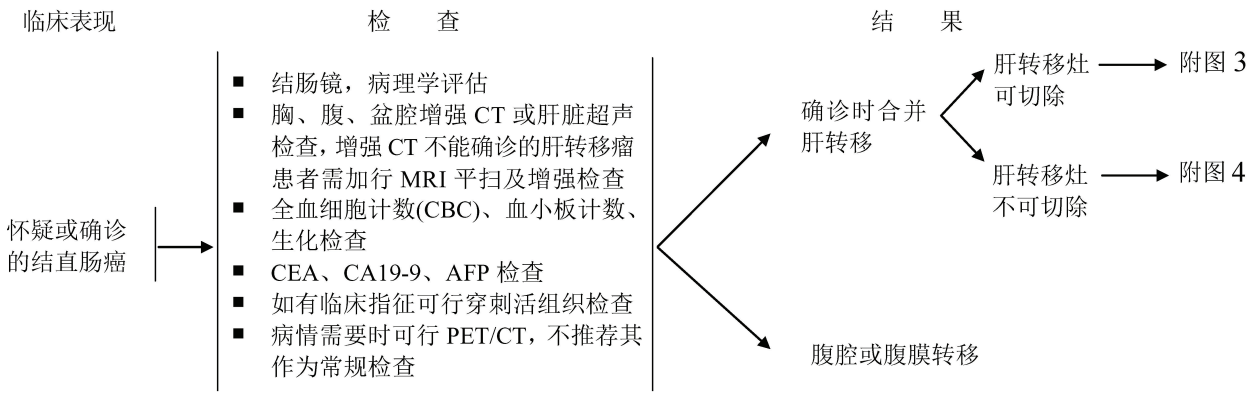
(2)放射治疗

由于全肝放射耐受剂量远低于肿瘤细胞所需的致死剂量,常规放射治疗在肿瘤直径较大或多发肝转移灶的治疗中仅能起到姑息作用。无肝硬化时的全肝平均安全照射剂量为 30 Gy[301],虽然该剂量可以显著减轻由于肝转移灶侵犯而引起的疼痛或黄疸[302-304],但尚没有依据表明能延长患者生存时间,因此不推荐采用常规放疗技术进行肝转移治疗。

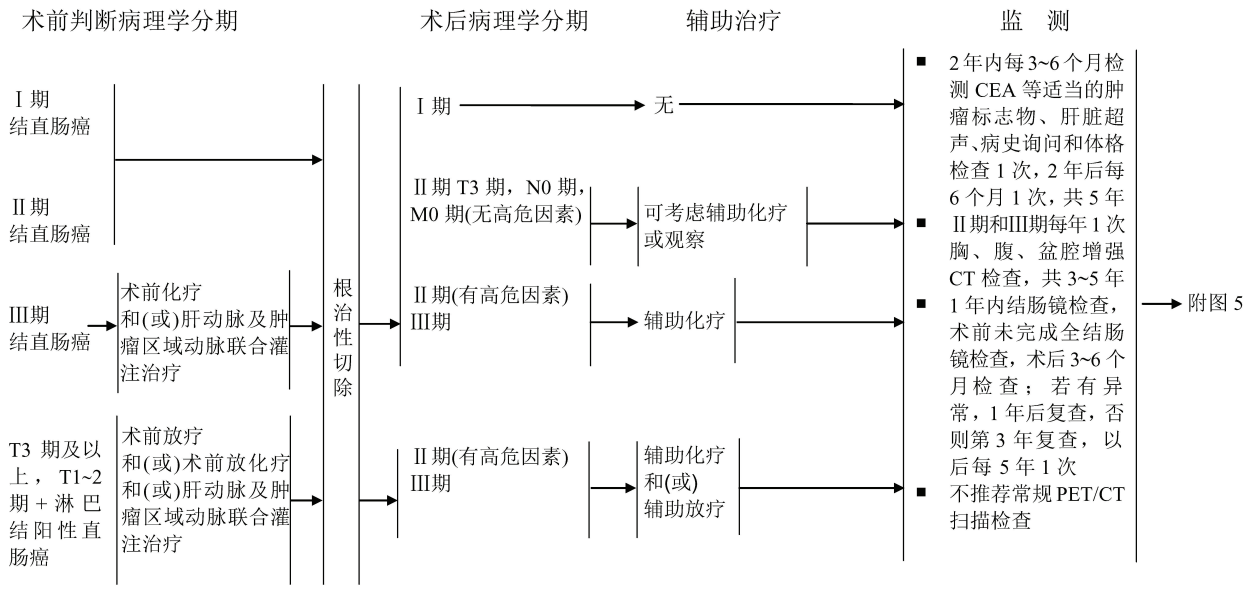
采用超分割或限制肝脏受照射体积,针对转移灶的局部剂量可提高到 60~70 Gy,并可获得较高的局部控制率(12 个月>80%)[16,305-311]。可运用的技术包括:三维适形放射治疗(3D CRT)、立体定向放射治疗(SBRT)和调强放射治疗(IMRT)[312-315]。图像引导技术的运用可以使放射治疗更加精准从而降低正常组织的不良反应[316-318]。放疗前肝功能必须正常,肝脏受到射线的剂量必须在安全范围,以防止严重放射性肝损伤出现[319-321]。

6.2.3　其他治疗方法:其他治疗方法包括无水酒精瘤内注射、选择性内放射和中医中药治疗等,但其疗效并不优于上述各项治疗,仅能作为综合治疗的一部分,单独使用可能会失去其治疗意义。

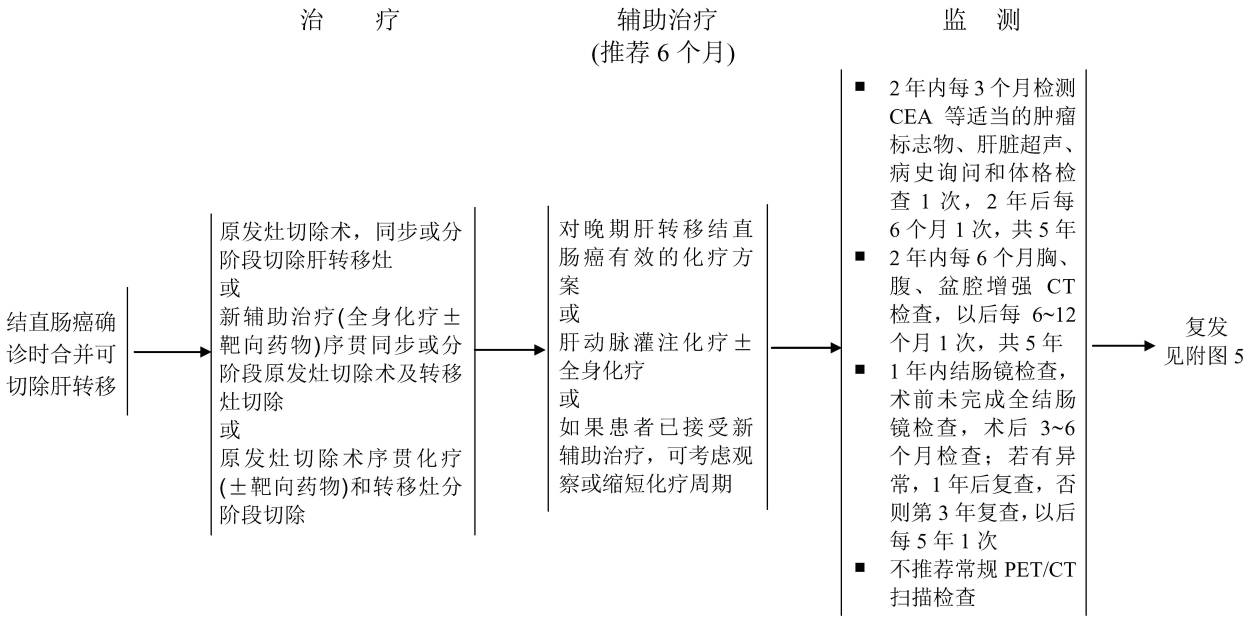
附录 1　诊断与治疗流程图



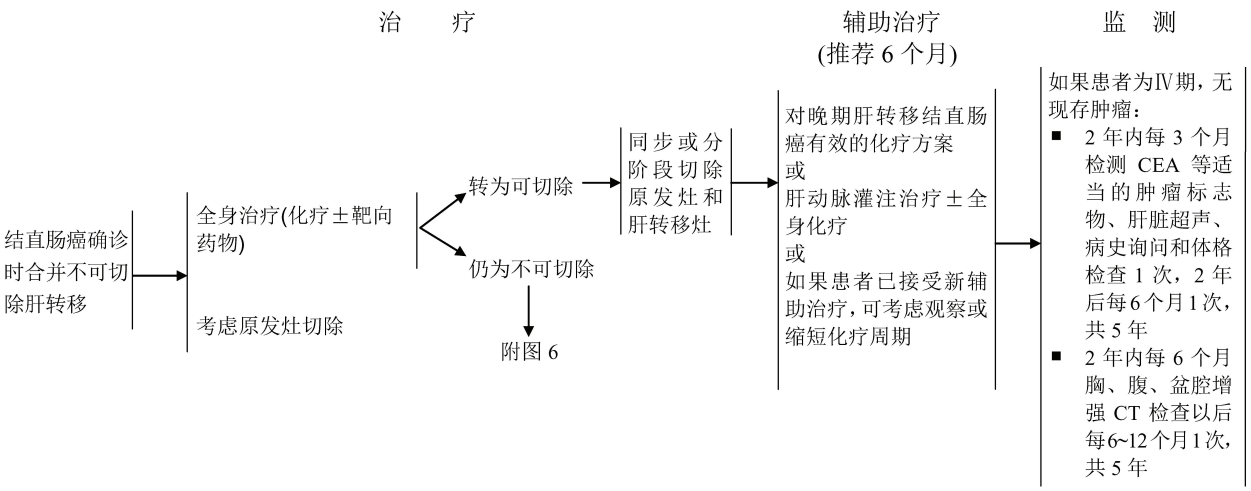
附图 1　结直肠癌确诊时肝转移的诊断



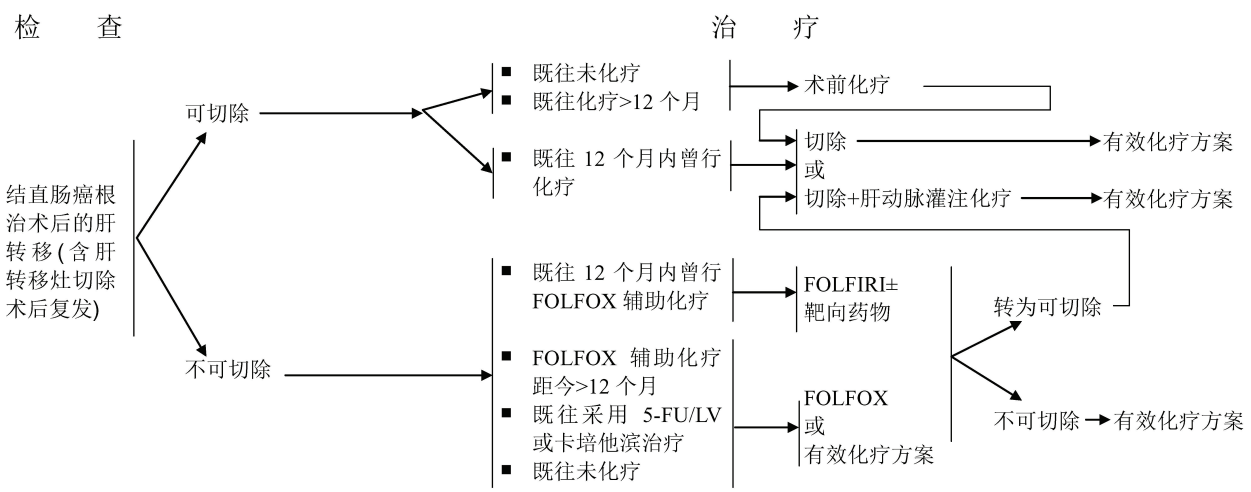
附图 2　结直肠癌肝转移的预防



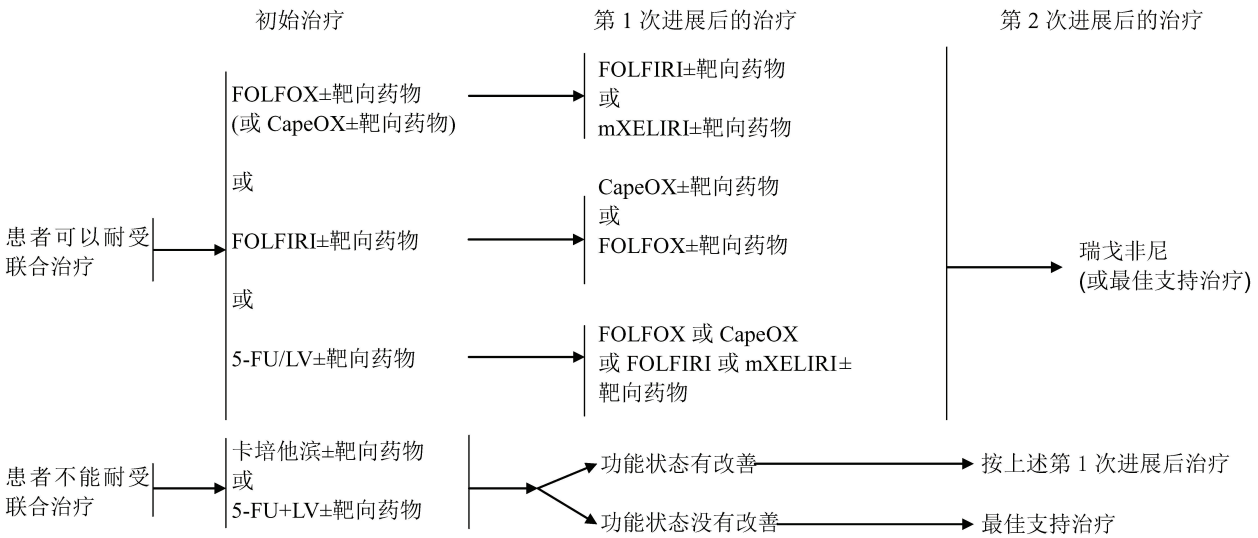
附图 3　结直肠癌确诊时合并肝转移的治疗(转移灶可切除)



附图 4　结直肠癌确诊时合并肝转移的治疗(转移灶不可切除)



附图 5　结直肠癌根治术后发现肝转移灶的治疗



附图 6　不可切除结直肠癌肝转移的化疗

附录 2　推荐级别的分类

推荐分级	证据水平	证　　据
A	1a	随机对照试验的系统综述
	1b	单项随机对照试验(95%可信区间较窄)
	1c	全或无,必须满足以下要求: (1)传统方法治疗全部致残或治疗失败,新方法治疗后,有部分患者存活或治愈。 (2)传统方法治疗许多患者死亡或治疗失败,新方法治疗后,无一死亡或治疗失败。
B	2a	队列研究的系统综述
	2b	单项队列研究(包括质量较差的随机对照试验,如随访率<80%)
	2c	结局研究
	3a	病例对照研究的系统综述
	3b	单项病例对照研究
C	4	系列病例分析及质量较差的病例对照研究
D	5	没有分析评价的专家意见

附录 3　结直肠癌分期

美国癌症联合委员会(AJCC)结直肠癌 TNM 分期系统(第 8 版,2017 年)

原发肿瘤(T)

Tx　原发肿瘤无法评估
T0　无原发肿瘤
Tis　原位癌:黏膜内癌(侵犯黏膜固有层)
T1　肿瘤侵犯黏膜下层
T2　肿瘤侵犯固有肌层
T3　肿瘤穿透固有肌层抵达浆膜下,或侵犯无腹膜覆盖的结直肠旁组织
T4a　肿瘤穿透至脏层腹膜(包括肿瘤所致肠道严重穿孔或肿瘤经炎症区域持续浸润到达脏层腹膜表面)
T4b　肿瘤与邻近器官或组织结构粘连,或直接侵犯其他器官或组织

区域淋巴结(N)

Nx　区域淋巴结无法评估
N0　区域淋巴结无转移
N1　1~3 枚区域淋巴结转移(淋巴结中的肿瘤≥0.2 mm),或存在癌结节而淋巴结阴性
N1a　1 枚区域淋巴结转移
N1b　2~3 枚区域淋巴结转移
N1c　无区域淋巴结转移,但肿瘤在浆膜下、肠系膜或无腹膜覆盖的结直肠旁或直肠系膜组织中种植
N2　4 枚或 4 枚以上区域淋巴结转移
N2a　4~6 枚区域淋巴结转移
N2b　7 枚或更多的区域淋巴结转移

远处转移(M)

M0　无远处转移
M1　有远处转移
M1a　转移局限在单个器官或部位(如肝脏、肺、卵巢,非区域淋巴结转移),无腹膜转移
M1b　转移超过 1 个器官或部位,无腹膜转移
M1c　转移至腹膜表面,伴或不伴其他器官或部位转移

分期分组

分期	T	N	M	Dukes 分期	MAC
0	Tis	N0	M0	-	-
Ⅰ	T1	N0	M0	A	A
	T2	N0	M0	A	B1
ⅡA	T3	N0	M0	B	B2
ⅡB	T4a	N0	M0	B	B2
ⅡC	T4b	N0	M0	B	B3
ⅢA	T1~T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
ⅢB	T3~T4a	N1/N1c	M0	C	C2
	T2~T3	N2a	M0	C	C1/C2
	T1~T2	N2b	M0	C	C1

ⅢC	T4a	N2a	M0	C	C2
	T3~T4a	N2b	M0	C	C2
	T4b	N1~N2	M0	C	C3
ⅣA	任何 T	任何 N	M1a	-	-
ⅣB	任何 T	任何 N	M1b	-	-
ⅣC	任何 T	任何 N	M1C	-	-

注：-未著录

组织学分级(G)

Gx　分化程度不能被评估

G1　高度分化

G2　中度分化

G3　低度分化

G4　未分化

附录 4　临床危险评分(CRS)

包括以下 5 项参数，每符合一项计 1 分(0~2 分为 CRS 低评分，3~5 分为 CRS 高评分)：

(1)原发肿瘤淋巴结阳性

(2)同时性肝转移或原发灶切除后无病生存时间<12 个月

(3)肝转移肿瘤数目>1 个

(4)术前 CEA>200 μg/L

(5)转移肿瘤最大直径>5 cm

附录 5　分子靶向药物简介

在无法达到 NED 状态的结直肠癌肝转移治疗中应用分子靶向药物已被证实安全有效[71,322-324]。但目前的研究资料不建议多种靶向药物联合应用[325-328]。目前中国大陆范围内批准使用的分子靶向药物如下：

(1)西妥昔单克隆抗体

西妥昔单克隆抗体为人鼠嵌合型的 EGFR 单克隆抗体，单用或联合化疗治疗结直肠癌肝转移均有良好的临床效果[252,247,329-331]。但是西妥昔单克隆抗体只对 RAS 基因野生型患者治疗有较好的效果，而在 RAS 基因突变型患者中应用并不提高疗效[332-334]。BRAF 突变的患者获益有限，这可能与疾病的不良预后有关[39,330,335-337]。

目前认为可以同西妥昔单克隆抗体联合的化疗方案包括 FOLFOX 和 FOLFIRI[229,252-253]。不建议其与 CapeOX 或 5-FU 推注方案联用[39,338]。且对于西妥昔单克隆抗体的跨线治疗是否有效仍存在争议[187]。约有 3%的患者会在西妥昔单克隆抗体给药过程中出现严重的输液反应，包括过敏性反应，应引起足够的重视[339]。

◆含西妥昔单克隆抗体的方案

西妥昔单克隆抗体首次剂量 400 mg/m^2 输注，输注时间为 120 min，然后每周 250 mg/m^2 输注时间为 60 min，联合 FOLFIRI 或 FOLFOX。

西妥昔单克隆抗体首次剂量 400 mg/m^2 输注，输注时间为 120 min，然后每两周 500 mg/m^2 输注时间为 120 min，联合 FOLFIRI 或 FOLFOX。

(2)贝伐珠单克隆抗体

贝伐珠单克隆抗体为人源化的 VEGF 单克隆抗体，联合化疗作为不可切除的结直肠癌肝转移一线治疗药物有良好的效果[340-344]。同样贝伐珠单克隆抗体在肿瘤进展后的二线治疗上疗效也得到了证实[345-349](**3b 类证据，B 级推荐**)。但贝伐珠单克隆抗体易引起出血和伤口延迟愈合，如在其治疗后需进行手术，建议手术时机选择在最后一次贝伐珠单克隆抗体使用后的 6~8 周[198,350-352]。

◆含贝伐珠单克隆抗体的方案

贝伐珠单克隆抗体 5.0 mg/kg 静脉滴注，每 2 周重复，联合 5-FU 或 FOLFOX 或 FOLFIRI

贝伐珠单克隆抗体 7.5 mg/kg 静脉滴注，每 3 周重复，联合 CapeOX

(3)瑞戈非尼

瑞戈非尼(Regorafenib)是一种口服多靶点酪氨酸激酶抑制剂(TKI)，可以阻断数个促血管生成的血管内皮生长因子受体、抑制与肿瘤生成和肿瘤微环境相关的多种激酶的活性。目前，瑞戈非尼已获批用于治疗之前接受过氟尿嘧啶、奥沙利铂和伊立替康为基础的化疗，以及既往接受过抗 VEGF 治疗，抗 EGFR 治疗(RAS 野生型)的转移性结直肠癌患者[270-271]。

新近的临床研究表明：对于 RAS 野生型的转移性结直肠癌患者在初始化疗进展后应用瑞戈非尼序贯二线化疗联合分子靶向药物治疗有更好的生存获益[353]。但仍需更多的临床研究结果证实。

瑞戈非尼大部分的不良反应发生在治疗的早期阶段，主要包括手足皮肤反应、疲乏、腹泻、高血压、皮疹等，均可预测且可通过暂停给药、剂量下调及对症处理后缓解。

◆瑞戈非尼用法

瑞戈非尼 160 mg 口服，每日 1 次，第 1~21 天，每 28 d 重复

附录 6　化疗方案

◆5-FU/LV

①LV 500 mg/m^2 静脉滴注 2 h，每周 1 次×6

5-FU 500 mg/m^2 在 LV 滴注开始 1 h 后静脉推注，每周 1 次×6

②5-FU 370~400 mg/m^2+LV 400 mg/m^2 每日 1 次×5，每 28 d 重复

◆卡培他滨

卡培他滨 1 250 mg/m^2 每日 2 次口服，第 1~14 天，每 3 周重复

◆FOLFOX

▲mFOLFOX6

奥沙利铂 85 mg/m^{2}静脉滴注 2 h，第 1 天

LV 400 mg/m^{2}静脉滴注 2 h，第 1 天

5-FU 400 mg/m^2 静脉推注，第 1 天，然后 1 200 mg/(m^2·d)×2 持续静脉输注(总量 2 400 mg/m^2，输注 46~48 h)

每 2 周重复

◆CapeOX

奥沙利铂 130 mg/m^2,第 1 天

卡培他滨 850~1 000 mg/m^2,每日 2 次,持续 14 d

每 3 周重复

◆FOLFIRI

①伊立替康 180 mg/m^{2}静脉滴注 30~120min,第 1 天

LV 400 mg/m^2 与伊立替康同时输注,持续时间相同,在 5-FU 之前,第 1 天和第 2 天

5-FU 400 mg/m^{2}静脉推注,然后 600 mg/m^{2}持续静脉输注 22 h,第 1 天和第 2 天

每 2 周重复

②伊立替康 180 mg/m^2 静脉滴注 30~120 min,第 1 天

LV 400 mg/m^2 与伊立替康同时输注,持续时间相同,第 1 天

5-FU 400 mg/m^2 静脉推注,第 1 天,然后 1200 mg/(m^2·d)×2 持续静脉输注(总量 2 400 mg/m^2,输注 46~48 h)

每 2 周重复

◆mXELIRI

伊立替康 200 mg/m^2,第 1 天

卡培他滨 800 mg/m^2,每日 2 次,持续 14 d

每 3 周重复

◆FOLFOXIRI

伊立替康 150 mg/m^2,奥沙利铂 85 mg/m^2,LV 400 mg/m^2 静脉滴注,第 1 天

5-FU 2 400 mg/m^2 持续滴注 48 h,第 1 天开始

每 2 周重复

附录 7　直肠癌的联合放化疗

放疗剂量总量 45~54 Gy,采用常规分割剂量(通常为 35 d),同时接受如下方案化疗:

◆不伴有肝转移:卡培他滨 850~1000 mg/m^2,每日 2 次,每周 5 d

◆伴有肝转移:

①奥沙利铂 每周 60mg/m^2,共 6 周;5-FU 200mg/m^2,第 1~40 天

②伊立替康 50mg/m^2,第 1、8、15、22 天;5-FU 200 mg/m^2,第 1~33 天

③奥沙利铂每周第 1 天 60mg/m^2,卡培他滨 650mg/m^2 每日 2 次,第 1~5 天,共 6 周

附录 8　肝动脉和结直肠肿瘤区域联合灌注化疗

奥沙利铂 75 mg/m^2,FUDR 650 mg/m^2,丝裂霉素 8 mg/m^2

采用股动脉穿刺法(Seldinger 法),经动脉导管超选择插管至结直肠肿瘤主要的滋养动脉内注入化疗药物 1/2 剂量;再超选择插管至肝固有动脉或肝肿瘤的滋养动脉内注入化疗药物 1/2 剂量。

《中国结直肠癌肝转移诊断和综合治疗指南(2018 版)》修订专家名单(按姓氏汉语拼音排序)

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参考文献

[1] Foster JH. Treatment of metastatic disease of the liver: a skeptic's vie w[J]. Semin Liver Dis, 1984, 4(2): 170-179. DOI: 10.1055/s-2008-1040656.

[2] Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metas tases[J]. J Clin Oncol, 1997, 15(3): 938-946. DOI: 10.1200/JCO.1997.15.3.938.

[3] Vibert E, Canedo L, Adam R. Strategies to treat primary unresectable colo rectal liver metastases[J]. Semin Oncol, 2005, 32(6 Suppl 8): 33-39. DOI: 10.1053 /j.seminoncol.2005.07.015.

[4] Kemeny N. Management of liver metastases from colorectal cancer [J]. Onc ology (Williston Park, NY), 2006, 20(10): 1161-1176.

[5] Lau WY, Lai EC. Hepatic resection for colorectal liver metastases [J]. S ingapore Med J, 2007, 48(7): 635-639. DOI: 10.1007/978-1-4612-1666-7_8.

[6] Taniai N, Akimaru K, Yoshida H, et al. Surgical treatment for better prog nosis of patients with liver metastases from colorectal cancer[J]. Hepatogastr oenterology, 2007, 54(78): 1805-1809.

[7] Arru M, Aldrighetti L, Castoldi R, et al. Analysis of prognostic factors in uencing long-term survival after hepatic resection for metastatic colorectal cancer[J]. World J Surg, 2008, 32: 93-103.

[8] Sharma S, Camci C, Jabbour N. Management of hepatic metastasis from color ectal cancers: an update[J]. J Hepatobiliary Pancreat Surg, 2008, 15(6): 570-580 . DOI: 10.1007/s00534-008-1350-x.

[9] Norén A, Eriksson HG, Olsson LI. Selection for surgery and survival of s ynchronous colorectal liver metastases, a nationwide study[J]. Eur J Cancer, 20 16, 53: 105-114. DOI: 10.1016/j.ejca.2015.10.055.

[10] de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of rec urrence following curative intent surgery for colorectal liver metastasis: an in ternational multi-institutional analysis of 1669 patients[J]. Ann Surg, 2009, 2 50(3): 440-448. DOI: 10.1097/SLA.0b013e3181b4539b.

[11] Giuliante F, Ardito F, Vellone M, et al. Role of the surgeon as a variable in long-term survival after liver resection for colorectal metastases [J]. J Surg Oncol, 2009, 100(7): 538-545. DOI: 10.1002/jso.21393.

[12] Norén A, Sandstrom P, Gunnarsdottir K, et al. Identification Of I nequalities In The Selection Of Liver Surgery For Colorectal Liver Metastases In Sweden [J]. Scand J Surg, 2018: 1457496918766706. DOI: 10.1177/1457496918766706. [Epub

ahead of print].

[13] Taylor A, Kanas G, Langeberg W, et al. Survival after surgical r esection of hepatic metastases from colorectal cancer: A systematic review and m eta-analysis[J]. Ann Oncol, 2010, 21 Suppl 8: 632.

[14] Yang AD, Brouquet A, Vauthey JN. Extending limits of resection for metastatic colorectal cancer: risk benefit ratio[J]. J Surg Oncol, 2010, 102(8): 996-1001. DOI: 10.1002/jso.21701.

[15] Fahy BN, D'Angelica M, DeMatteo RP, et al. Synchronous hepatic me tastases from colon cancer: changing treatment strategies and results of surgica l intervention[J]. Ann Surg Oncol, 2009, 16(2): 361-370. DOI: 10.1245/s10434-008 -0217-3.

[16] Timmerman RD, Bizekis CS, Pass HI, et al. Local surgical, ablative , and radiation treatment of metastases[J]. CA Cancer J Clin, 2009, 59(3): 145-1 70. DOI: 10.3322/caac.20013.

[17] Adam R, de Gramont A, Figueras J, et al. Managing synchronous live r metastases from colorectal cancer: amultidisciplinary international consensus[J]. Cancer Treat Rev, 2015, 41(9): 729-741. DOI: 10.1016/j.ctrv.2015.06.006.

[18] Bipat S, van Leeuwen MS, Ijzermans JN, et al. Evidence-base guide line on management of colorectal liver metastases in the Netherlands[J]. Neth J Med, 2007, 65(1): 5-14.

[19] Coenegrachts K, De Geeter F, ter Beek L, et al. Comparison of MRI (including SS SE-EPI and SPIO-enhanced MRI) and FDG-PET/CT for the detection of colorectal liver metastases[J]. Eur Radiol, 2009, 19(2): 370-379. DOI: 10.1007 /s00330-008-1163-y.

[20] Delbeke D, Martin WH. PET and PET-CT for evaluation of colorectal carcinoma[J]. Semin Nucl Med, 2004, 34(3): 209-223. DOI: 10.1053/j.semnuclmed.20 04.03.006.

[21] Kuehl H, Antoch G, Stergar H, et al. Comparison of FDG-PET, PET/C T and MRI for follow-up of colorectal liver metastases treated with radiofreque ncy ablation: initial results[J]. Eur J Radiol, 2008, 67(2): 362-371. DOI: 10.101 6/j.ejrad.2007.11.017.

[22] Jones OM, Rees M, John TG, et al. Biopsy of resectable colorectal liver metastases causes tumour dissemination and adversely affects survival afte r liver resection[J]. Br J Surg, 2005, 92(9): 1165-1168. DOI: 10.1002/bjs.4888.

[23] Koshariya M, Jagad RB, Kawamoto J, et al. An update and our experi ence with metastatic liver disease[J]. Hepatogastroenterology, 2007, 54(80): 2232 -2239.

[24] Tsikitis VL, Malireddy K, Green EA, et al. Postoperative surveilla nce recommendations for early stage colon cancer based on results from the clini cal outcomes of surgical therapy trial[J]. J Clin Oncol, 2009, 27(22): 3671-3676 . DOI: 10. 1200/JCO. 2008. 20. 7050.

[25] Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer[J]. Ann Oncol, 2005, 16(5): 7 56-761. DOI: 10.1093/annonc/mdi151.

[26] Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless[J]. Surg Oncol, 2006, 15(1): 1-12. DOI: 10. 1016/j.suronc.2006.0 6.001.

[27] Pfister DG, Benson AB 3rd, Somerfield MR. Clinical practice. Surve illance strategies after curative treatment of colorectal cancer [J]. N Engl J Med, 2004, 350(23): 2375-2382. DOI: 10.1056/NEJMcp010529.

[28] Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recomm endations for the use of tumor markers in gastrointestinal cancer[J]. J Clin O ncol, 2006, 24(33): 5313-5327. DOI: 10. 1200/JCO.2006.08.2644.

[29] Desch CE, Benson AB 3rd, Somerfield MR, et al. Colorectal cancer s urveillance: 2005 update of an American Society of Clinical Oncology practice gu ideline[J]. J Clin Oncol, 2005, 23(33): 8512-8519. DOI: 10.1200/JCO.2005.04.0063.

[30] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy survei llance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer[J]. CA Cancer J Clin, 20 06, 56(3): 160-167. DOI: 10. 3322/canjclin.56.3.160.

[31] Ma Y, Yang Y, Wang F, et al. Obesity and risk of colorectal cancer : a systematic review of prospective studies[J]. PLoS One, 2013, 8(1): e53916. DOI : 10.1371/journal.pone.0053916.

[32] Magalh es B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis[J]. Eur J Cancer Prev, 2012, 21 (1) : 15-23. DOI: 10. 1097/CEJ. 0b013e3283472241.

[33] Parajuli R, Bjerkaas E, Tverdal A, et al. The increased risk of co lon cancer due to cigarette smoking may be greater in women than men[J]. Cance r Epidemiol Biomarkers Prev, 2013, 22(5): 862-871. DOI: 10.1158/1055-9965.EPI-12 -1351.

[34] Modest DP, Ricard I, Heinemann V, et al. Outcome according to KRAS -, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group[J]. Ann Oncol, 2016, 27(9): 1746-1753. DOI: 10.1093/annonc/mdw261.

[35] Brudvik KW, Mise Y, Chung MH, et al. RAS Mutation Predicts Positiv e Resection Margins and NarrowerResection Margins in Patients Undergoing Resecti on of Colorectal Liver Metastases[J]. Ann Surg Oncol, 2016, 23(8): 2635-2643. DO I: 10. 1245/s10434-016-5187-2.

[36] Margonis GA, Buettner S, Andreatos N, et al. Anatomical Resection s Improve Disease-free Survival in PatientsWith KRAS-mutated Colorectal Liver Metastases[J]. Ann Surg, 2017, 266(4): 641-649. DOI: 10.1097/sla.0000000000002367 .

[37] Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials[J]. Ann Oncol, 2015, 26(1): 13 -21. DOI: 10. 1093/annonc/mdu378.

[38] Hendifar A, Tan CR, Annamalai A, et al. Biomarker-driven EGFR the rapy improves outcomes in patients with metastatic colorectal cancer[J]. Exper t Rev Anticancer Ther, 2014, 14(9): 1051-1061. DOI: 10.1586/14737140.2014.922881.

[39] Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to ox aliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial[J]. Lancet , 2011, 377(9783): 2103-2114. DOI: 10.1016/S0140-6736(11)60613-2.

[40] Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorect al cancer[J]. N Engl J Med, 2009, 361(1): 98-99. DOI: 10. 1056/NEJMc0904160.

[41] Guren TK, Thomsen M, Kure EH, et al. Cetuximab in treatment of met astatic colorectal cancer: final survival analyses and extended RAS data from th e NORDIC-Ⅶ study[J]. Br J Cancer, 2017, 116(10): 1271-1278. DOI: 10.1038/bjc.20 17.93.

[42] Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA Mismatc h Repair and Mutations in BRAF and KRAS With Survival After Recurrence in Stage Ⅲ Colon Cancers: A Secondary Analysis of 2 Randomized Clinical Trials[J]. JAM A Oncol, 2017, 3(4): 472-480. DOI: 10.1001/jamaoncol.2016.5469.

[43] Pikoulis E, Margonis GA, Andreatos N, et al. Prognostic Role of BR AF Mutations in Colorectal Cancer Liver Metastases[J]. Anti-

cancer Res, 2016, 36(9) : 4805-4811. DOI: 10.21873/anticanres.11040.

[44] Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer[J]. JAMA, 2012, 308(15): 1555-1565. DOI: 10.1001/jama.2012.13088.

[45] Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatelli te instability[J]. J Natl Cancer Inst, 2004, 96(4): 261-268. DOI: 10.1093/jnci/dj i158.

[46] Marsh S, Hoskins JM. Irinotecan pharmacogenomics[J]. Pharmacogen omics, 2010, 11(7): 1003-1010. DOI: 10.2217/pgs.10.95.

[47] Barbarino JM, Haidar CE, Klein TE, et al. PharmGKB summary: very i mportant pharmacogene information for UGT1A1[J]. Pharmacogenet Genomics, 2014, 2 4(3): 177-183. DOI: 10.1097/FPC.0000000000000024.

[48] Hoskins JM, Goldberg RM, Qu P, et al. UGT1A1 * 28 genotype and irino tecan-induced neutropenia: dose matters[J]. J Natl Cancer Inst, 2007, 99 (17): 12 90-1295. DOI: 10. 1093/jnci/djm115.

[49] Artale S, Sartore-Bianchi A, Veronese SM, et al. Mutations of KRA S and BRAF in primary and matched metastatic sites of colorectal cancer[J]. J Clin Oncol, 2008, 26(25): 4217-4219. DOI: 10.1200/JCO.2008.18.7286.

[50] Etienne-Grimaldi M C, Formento J L, Francoual M, et al. K-Ras Mu tations and Treatment Outcome in Colorectal Cancer Patients Receiving Exclusive Fluoropyrimidine Therapy[J]. Clin Cancer Res, 2008, 14(15): 4830-4835. DOI: 10.11 58/1078-0432.ccr-07-4906.

[51] Knijn N, Mekenkamp LJ, Klomp M, et al. KRAS mutation analysis: a c omparison between primary tumours and matched liver metastases in 305 colorectal cancer patients[J]. Br J Cancer, 2011, 104(6): 1020-1026. DOI: 10.1038/bjc.2011. 26.

[52] Okuno K. Surgical treatment for digestive cancer. Current issues-colon cancer[J]. Dig Surg, 2007, 24(2): 108-114. DOI: 10.1159/000101897.

[53] Borschitz T, Wachtlin D, M hler M, et al. Neoadjuvant chemoradiati on and local excision for T2-3 rectal cancer[J]. Ann Surg Oncol, 2008, 15(3): 71 2-720. DOI: 10.1245/s10434-007-9732-x.

[54] Chau I, Chan S, Cunningham D. Overview of preoperative and postope rative therapy for colorectal cancer: the European and United States perspective s[J]. Clin Colorectal Cancer, 2003, 3(1): 19-33. DOI: 10.3816/CCC.2003.n.009.

[55] Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma[J]. Ann Surg, 2007, 246(5): 693-701. DOI: 10.1097/01.sla.0000257358.56863.ce.

[56] Johal BS, Phang P, McGahan C, et al. Treatment patterns and outc omes of patients with pT3N0 rectal cancer in a population-based setting[J]. J Clin Oncol, 2007, 25(18S: Abstract 4039.

[57] van der Voort van Zijp J, Hoekstra HJ, Basson MD. Evolving managem ent of colorectal cancer[J]. World J Gastroenterol, 2008, 14(25): 3956-3967. DOI: 10.3748/wjg.14.3956.

[58] Cervantes A, Roselló S, Rodríguez-Braun E, et al. Progress in t he multidisciplinary treatment of gastrointestinal cancer and the impact on clin ical practice: perioperative management of rectal cancer[J]. Ann Oncol, 2008, 19 (Suppl 7): vii266-72. DOI: 10.1093/annonc/mdn438.

[59] Klautke G, Fietkau R. Intensified neoadjuvant radiochemotherapy fo r locally advanced rectal cancer: a review[J]. Int J Colorectal Dis, 2007, 22(5): 457-465. DOI: 10.1007/s00384-006-0204-8.

[60] Martijnse IS, Dudink RL, Kusters M, et al. T3+ and T4 rectal cance r patients seem to benefit from the addition of oxaliplatin to the neoadjuvant c hemoradiation regimen[J]. Ann Surg Oncol, 2012, 19(2): 392-401. DOI: 10.1245/s104 34-011-1955-1.

[61] Roohipour R, Patil S, Goodman KA, et al. Squamous-cell carcinoma of the anal canal: predictors of treatmentoutcome[J]. Dis Colon Rectum, 2008, 51 (2): 147-153. DOI: 10. 1007/s10350-007-9125-z.

[62] Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative ra diotherapy versus selective postoperative chemoradiotherapy in patients with rec tal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial[J]. Lancet, 2009, 373(9666): 811-820. DOI: 10.1016/s0140-6736(09)60484-0.

[63] Siegel R, Burock S, Wernecke KD, et al. Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cance r: a multi-centre prospectively randomised study of the Berlin Cancer Society[J]. BMC Cancer, 2009, 9: 50. DOI: 10.1186/1471-2407-9-50.

[64] BuJko K, Wyrwicz L, Rutkowski A, et al. Long-course oxaliplatin-based preoperative chemoradiation versus 5 * 5 Gy and consolidation chemotherap y for cT4 or fixed cT3 rectal cancer: results of a randomized phase Ⅲ study[J]. Ann Oncol, 2016, 27: 834-842.

[65] Kim KH, Shin SJ, Cho MS, et al. A phase Ⅱ study of preoperative m FOLFOX6 with short-course radiotherapy in patients with locally advanced rectal cancer and liver-only metastasis[J]. Radiother Oncol, 2016, 118(2): 369-374. D OI: 10.1016/j.radonc.2015.11.029.

[66] Vermaas M, Gosselink MP, Ferenschild FT, et al. Introduction of pr eoperative radiotherapy in the treatment of operable rectal cancer in the Southw est region of the Netherlands[J]. Eur J Surg Oncol, 2007, 33(7): 862-867. DOI: 10 .1016/j.ejso.2006.12.005.

[67] Xu J, Zhong Y, Weixin N, et al. Preoperative hepatic and regional arterial chemotherapy in the prevention of liver metastasis after colorectal can cer surgery [J]. Ann Surg, 2007, 245(4): 583-590.

[68] Xu J, Xia J, Gu Y, et al. Effect of preoperative hepatic and regio nal arterial chemotherapy on metachronous liver metastasis after curative colore ctal cancer resection: A prospective, multicenter, randomized controlled trial. [J]. J Clin Oncol, 2015, 33(3): 511-511. DOI: 10.1200/jco.2015.33.3_suppl.511.

[69] Chang W, Wei Y, Ren L, et al. Randomized Controlled Trial of Intra portal Chemotherapy Combined With Adjuvant Chemotherapy (mFOLFOX6) for Stage Ⅱ and Ⅲ Colon Cancer[J]. Ann Surg, 2016, 263(3): 434-439. DOI: 10.1097/SLA.0000000 000001374.

[70] de Gramont A, Boni C, Navarro M, et al. Oxaliplatin/5FU/LV in adju vant colon cancer: Updated efficacy results of the MOSAIC trial, including survi val, with a median follow-up of six years[J]. ASCO Meeting Abstracts, 2007, 25: 4007.

[71] Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer [J]. Gastroenterology, 2008, 134(5): 1296-1310. DOI: 10.1053/j.gastro.2008.02.098.

[72] Samantas E, Dervenis C, Rigatos SK. Adjuvant chemotherapy for colo n cancer: evidence on improvement in survival[J]. Dig Dis, 2007, 25(1): 67-75. D OI: 10.1159/000099172.

[73] Sargent D, Sobrero A, Grothey A, et al. Evidence for cure by adjuv ant therapy in colon cancer: observationsbased on individual patient data from 20 ,898 patients on 18 randomized trials[J]. J Clin Oncol, 2009, 27(6): 872-877. DO I: 10.1200/JCO.2008.19.5362.

[74] André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in

stage Ⅱ or Ⅲ colon cancer in the MOSAIC trial[J]. J Clin Oncol, 2009, 27(19): 3109-3116. DOI: 10.1200/JCO.2008.20.6771.

[75] Rodríguez-Moranta F, Saló J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial[J]. J Clin Oncol, 2006, 24(3): 386-393. DOI: 10.1200/JCO.2005.02.0826.

[76] Goldberg RM. Therapy for metastatic colorectal cancer[J]. Oncologist, 2006, 11(9): 981-987. DOI: 10.1634/theoncologist.11-9-981.

[77] Tveit KM, Wiig JN, Olsen DR, et al. Combined modality treatment including intraoperative radiotherapy in locally advanced and recurrent rectal cancer[J]. Radiother Oncol, 1997, 44(3): 277-282. DOI: 10.1016/s0167-8140(97)00070-4.

[78] Yu TK, Bhosale PR, Crane CH, et al. Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer[J]. Int J Radiat Oncol Biol Phys, 2008, 71(4): 1175-1180. DOI: 10.1016/j.ijrobp.2007.11.018.

[79] Fennell ML, Das IP, Clauser S, et al. The organization of multidisciplinary care teams: modeling internal and external influences on cancer care quality[J]. J Natl Cancer Inst Monographs, 2010, 2010(40): 72-80. DOI: 10.1093/jncimonographs/lgq010.

[80] Rabinowitz B. Interdisciplinary breast cancer care: declaring and improving the standard[J]. Oncology (Williston Park, NY), 2004, 18(10): 1263-1268.

[81] Nordlinger B, Vauthey JN, Poston G, et al. The timing of chemotherapy and surgery for the treatment of colorectal liver metastases[J]. Clin Colorectal Cancer, 2010, 9(4): 212-218. DOI: 10.3816/CCC.2010.n.031.

[82] Jones RP, Vauthey JN, Adam R, et al. Effect of specialist decision-making on treatment strategies for colorectal liver metastases[J]. Br J Surg, 2012, 99(9): 1263-1269. DOI: 10.1002/bjs.8835.

[83] Wright FC, De Vito C, Langer B, et al. Multidisciplinary cancer conferences: a systematic review and development of practice standards[J]. Eur J Cancer, 2007, 43(6): 1002-1010. DOI: 10.1016/j.ejca.2007.01.025.

[84] Jung SM, Hong YS, Kim TW, et al. Impact of a Multidisciplinary Team Approach for Managing Advanced and Recurrent Colorectal Cancer[J]. World J Surg, 2017[Epub ahead of print]. DOI: 10.1007/s00268-017-4409-5.

[85] Davies AR, Deans DA, Penman I, et al. The multidisciplinary team meeting improves staging accuracy and treatment selection for gastro-esophageal cancer[J]. Dis Esophagus, 2006, 19(6): 496-503. DOI: 10.1111/j.1442-2050.2006.00629.x.

[86] Fleissig A, Jenkins V, Catt S, et al. Multidisciplinary teams in cancer care: are they effective in the UK[J]. Lancet Oncol, 2006, 7(11): 935-943. DOI: 10.1016/S1470-2045(06)70940-8.

[87] Gabel M, Hilton NE, Nathanson SD. Multidisciplinary breast cancer clinics. Do they work[J]. Cancer, 1997, 79(12): 2380-2384. DOI: 10.1002/(sici)1097-0142(19970615)79:12<2380::aid-cncr12>3.0.co;2-n.

[88] Abdalla EK. Resection of colorectal liver metastases[J]. J Gastrointest Surg, 2011, 15(3): 416-419. DOI: 10.1007/s11605-011-1429-6.

[89] Carter S. Multidisciplinary team working, clinical networks, and chambers, opportunities to work differently in the NHS[J]. Quality and Safety in Health Care, 2003, 12(90001): 25i-28. DOI: 10.1136/qhc.12.suppl_1.i25.

[90] Rummans TA, Clark MM, Sloan JA, et al. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial[J]. J Clin Oncol, 2006, 24(4): 635-642. DOI: 10.1200/JCO.2006.06.209.

[91] Du CZ, Li J, Cai Y, et al. Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy[J]. World J Gastroenterol, 2011, 17(15): 2013-2018. DOI: 10.3748/wjg.v17.i15.2013.

[92] MacDermid E, Hooton G, MacDonald M, et al. Improving patient survival with the colorectal cancer multi-disciplinary team[J]. Colorectal Dis, 2009, 11(3): 291-295. DOI: 10.1111/j.1463-1318.2008.01580.x.

[93] Obias VJ, Reynolds HL Jr. Multidisciplinary teams in the management of rectal cancer[J]. Clin Colon Rectal Surg, 2007, 20(3): 143-147. DOI: 10.1055/s-2007-984858.

[94] Wanis KN, Pineda-Solis K, Tun-Abraham ME, et al. Management of colorectal cancer with synchronous liver metastases: impact of multidisciplinary case conference review[J]. Hepatobiliary Surg Nutr, 2017, 6(3): 162-169. DOI: 10.21037/hbsn.2017.01.01.

[95] Lan YT, Jiang JK, Chang SC, et al. Improved outcomes of colorectal cancer patients with liver metastases in the era of the multidisciplinary teams[J]. Int J Colorectal Dis, 2016, 31(2): 403-411. DOI: 10.1007/s00384-015-2459-4.

[96] Look Hong NJ, Gagliardi AR, Bronskill SE, et al. Multidisciplinary cancer conferences: exploring obstacles and facilitators to their implementation[J]. J Oncol Pract, 2010, 6(2): 61-68. DOI: 10.1200/JOP.091085.

[97] Bentrem DJ, Dematteo RP, Blumgart LH. Surgical therapy for metastatic disease to the liver[J]. Annu Rev Med, 2005, 56: 139-156. DOI: 10.1146/annurev.med.56.082103.104630.

[98] Abdalla EK. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology[J]. Am J Surg, 2009, 197(6): 737-739. DOI: 10.1016/j.amjsurg.2008.06.029.

[99] Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases[J]. Am J Surg, 2009, 197(6): 728-736. DOI: 10.1016/j.amjsurg.2008.04.013.

[100] Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent[J]. J Gastrointest Surg, 2009, 13(3): 486-491. DOI: 10.1007/s11605-008-0727-0.

[101] Dexiang Z, Li R, Ye W, et al. Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases[J]. Ann Surg Oncol, 2012, 19(9): 2860-2868. DOI: 10.1245/s10434-012-2356-9.

[102] Lochan R, White S A, Manas D M. Liver resection for colorectal liver metastasis[J]. Surg Oncol, 2007, 16(1): 33-45. DOI: 10.1016/j.suronc.2007.04.010.

[103] Adam R. Current surgical strategies for the treatment of colorectal cancer liver metastases[J]. Eur J Cancer Suppl, 2004, 2(7): 21-26. DOI: 10.1016/j.ejcsup.2004.04.011.

[104] Khan AS, Garcia-Aroz S, Ansari MA, et al. Assessment and optimization of liver volume before major hepatic resection: Current guidelines and a narrative review[J]. Int J Surg, 2018, 52: 74-81. DOI: 10.1016/j.ijsu.2018.01.042.

[105] Bégin A, Martel G, Lapointe R, et al. Accuracy of preoperative automatic measurement of the liver volume by CT-scan combined to a 3D virtual surgical planning software (3DVSP)[J]. Surg Endosc, 2014, 28(12): 3408-3412. DOI: 10.1007/s00464-014-3611-x.

[106] Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection

for colorecta l metastases[J]. Ann Surg, 2005, 241(5): 715-722. DOI: 10.1097/01.sla.0000160703. 75808.7d.

[107] Yan TD, Padang R, Xia H, et al. Management of involved or close r esection margins in 120 patients with colorectal liver metastases: edge cryother apy can achieve long-term survival[J]. Am J Surg, 2006, 191(6): 735-742. DOI: 10 .1016/j.amjsurg. 2005.05.055.

[108] Blazer DG 3rd, Kishi Y, Maru DM, et al. Pathologic response to pr eoperative chemotherapy: a new outcome end point after resection of hepatic colo rectal metastases[J]. J Clin Oncol, 2008, 26 (33): 5344-5351. DOI: 10.1200/JCO.2008 .17.5299.

[109] Alberts SR, Wagman LD. Chemotherapy for colorectal cancer liver m etastases[J]. Oncologist, 2008, 13(10): 1063-1073. DOI: 10.1634/theoncologist.200 8-0142.

[110] Jaeck D. The significance of hepatic pedicle lymph nodes metastas es in surgical management of colorectal liver metastases and of other liver mali gnancies[J]. Ann Surg Oncol, 2003, 10(9): 1007-1011. DOI: 10.1245/aso.2003.09.903 .

[111] Pulitanò C, Bodingbauer M, Aldrighetti L, et al. Colorectal live r metastasis in the setting of lymph node metastasis: defining the benefit of su rgical resection[J]. Ann Surg Oncol, 2012, 19(2): 435-442. DOI: 10.1245/s10434-0 11-1902-1.

[112] Jaeck D, Oussoultzoglou E, Rosso E. Hepatectomy for colorectal me tastases in the presence of extrahepatic disease[J]. Surg Oncol Clin N Am, 2007 , 16(3): 507-523, viii. DOI: 10.1016/j. soc.2007.04.010.

[113] Miller G, Biernacki P, Kemeny NE, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases[J] . J Am Coll Surg, 2007, 205(2): 231-238. DOI: 10.1016/j.jamcollsurg.2007.04.039.

[114] Pulitanò C, Bodingbauer M, Aldrighetti L, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis[J]. Ann Surg Oncol, 2011, 18(5): 1380 -1388. DOI: 10.1245/s10434-010-1459-4.

[115] Chua TC, Saxena A, Liauw W, et al. Hepatectomy and resection of c oncomitant extrahepatic disease for colorectal liver metastases--a systematic review[J]. Eur J Cancer, 2012, 48(12): 1757-1765. DOI: 10.1016/j.ejca.2011.10.034 .

[116] Gonzalez M, Ris HB, Krueger T, et al. Colorectal cancer and thora cic surgeons: close encounters of the third kind[J]. Expert Rev Anticancer The r, 2012, 12(4): 495-503. DOI: 10.1586/era. 12.21.

[117] Hao CY, Ji JF. Surgical treatment of liver metastases of colorect al cancer: Strategies and controversies in 2006[J]. Eur J Surg Oncol, 2006, 32(5): 473-483. DOI: 10.1016/j.ejso.2006.02. 016.

[118] Turrini O, Viret F, Guiramand J, et al. Strategies for the treatm ent of synchronous liver metastasis[J]. Eur J Surg Oncol, 2007, 33(6): 735-740. DOI: 10.1016/j.ejso.2007.02.025.

[119] Otchy D, Hyman NH, Simmang C, et al. Practice parameters for colo n cancer[J]. Dis Colon Rectum, 2004, 47(8): 1269-1284. DOI: 10.1007/s10350-004- 0598-8.

[120] Capussotti L, Ferrero A, Viganò L, et al. Major liver resections synchronous with colorectal surgery[J]. Ann Surg Oncol, 2007, 14(1): 195-201. D OI: 10.1245/s10434-006-9055-3.

[121] Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection o f colorectal carcinoma metastases to the liver. A prognostic scoring system to i mprove case selection, based on 1568 patients. Association Fran aise de Chirurgi e[J]. Cancer, 1996, 77(7): 1254-1262.

[122] Nakajima K, Takahashi S, Saito N, et al. Predictive factors for a nastomotic leakage after simultaneous resection of synchronous colorectal liver metastasis[J]. J Gastrointest Surg, 2012, 16(4): 821-827. DOI: 10.1007/s11605-01 1-1782-5.

[123] Schnitzbauer AA, Lang SA, Goessmann H, et al. Right portal vein l igation combined with in situ splitting induces rapid left lateral liver lobe hy pertrophy enabling 2-staged extended right hepatic resection in small-for-siz e settings[J]. Ann Surg, 2012, 255(3): 405-414. DOI: 10.1097/SLA.0b013e31824856f5 .

[124] Roxburgh CSD, Richards CH, Moug SJ, et al. Determinants of short - and long-term outcome in patients undergoing simultaneous resection of color ectal cancer and synchronous colorectal liver metastases[J]. Int J Colorect Di s, 2011, 27(3): 363-369. DOI: 10.1007/s00384-011-1339-9.

[125] Slupski M, Wlodarczyk Z, Jasinski M, et al. Outcomes of simultane ous and delayed resections of synchronous colorectal liver metastases[J]. Can J Surg, 2009, 52(6): E241-E244.

[126] Weber JC, Bachellier P, Oussoultzoglou E, et al. Simultaneous res ection of colorectal primary tumour and synchronous liver metastases[J]. Br J Surg, 2003, 90(8): 956-962. DOI: 10.1002/bjs.4132.

[127] de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience [J]. HPB (Oxford), 2011, 13(10): 745-752. DOI: 10.1111/j.1477-2574.2011.00372.x.

[128] Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy[J]. J Am Coll Surg, 2010, 210(6): 934-941. DOI: 10. 1016/j. jamcollsurg. 2010.02.039.

[129] Cooper AB, Curley SA. Surgical treatment of colorectal liver meta stases[J]. Chin Clin Oncol, 2013, 2(2): 15. DOI: 10.3978/j. issn.2304-3865.2013.03 .02.

[130] Waisberg J, Ivankovics IG. Liver-first approach of colorectal ca ncer with synchronous hepatic metastases: A reverse strategy[J]. World J Hepat ol, 2015, 7(11): 1444-1449. DOI: 10.4254/wjh. v7.i11.1444.

[131] Lam V W T, Laurence J M, Pang T, et al. A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorec tal liver metastases[J]. HPB (Oxford), 2014, 16(2): 101-108. DOI: 10.1111/hpb.120 83.

[132] Van Dessel E, Fierens K, Pattyn P, et al. Defining the optimal th erapy sequence in synchronous resectable liver metastases from colorectal cancer : a decision analysis approach[J]. Acta Chir Belg, 2009, 109(3): 317-320. DOI: 10 .1080/00015458.2009. 11680432.

[133] Kelly ME, Spolverato G, Lê GN, et al. Synchronous colorectal liv er metastasis: A network meta-analysisreview comparing classical, combined, and liver-first surgical strategies[J]. J Surg Oncol, 2014, 111(3): 341-351. DOI: 1 0.1002/jso.23819.

[134] Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year su rvival after resection of colorectal liver metastases defines cure [J]. J Clin Oncol, 2007, 25(29): 4575-4580. DOI: 10.1200/JCO.2007.11.0833.

[135] Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose po sitron emission tomography (FDG-PET) in the management of patients with colorec tal cancer[J]. Eur J Surg Oncol (EJSO), 2007, 33(1): 1-6. DOI: 10.1016/j.ejso.200 6.10.020.

[136] Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predi cts hepatic dysfunction in patients undergoing major liver resection[J]. J Gas trointest Surg, 2003, 7(3): 325-330. DOI:

10.1016/s1091-255x(02)00370-0.

[137] Sarpel U, Bonavia AS, Grucela A, et al. Does anatomic versus nona natomic resection affect recurrence and survival in patients undergoing surgery for colorectal liver metastasis[J]. Ann Surg Oncol, 2009, 16(2): 379-384. DOI: 10 .1245/s10434-008-0218-2.

[138] Clavien PA, Petrowsky H, DeOliveira ML, et al. Strategies for saf er liver surgery and partial liver transplantation[J]. N Engl J Med, 2007, 356 (1 5): 1545-1559. DOI: 10. 1056/NEJMra065156.

[139] Ayez N, Lalmahomed ZS, Eggermont AM, et al. Outcome of microscopi c incomplete resection (R1) of colorectal liver metastases in the era of neoadju vant chemotherapy[J]. Ann Surg Oncol, 2012, 19(5): 1618-1627. DOI: 10.1245/s10434 -011-2114-4.

[140] Yamamoto J, Shimada K, Kosuge T, et al. Factors influencing survi val of patients undergoing hepatectomy for colorectal metastases[J]. Br J Surg , 1999, 86(3): 332-337. DOI: 10.1046/j.1365-2168.1999.01030.x.

[141] Kokudo N, Miki Y, Sugai S, et al. Genetic and histological assess ment of surgical margins in resected liver metastases from colorectal carcinoma: minimum surgical margins for successful resection[J]. Arch Surg, 2002, 137(7): 8 33-840.

[142] Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approa ch for initially unresectable colorectal hepatic metastases [J]. Surg Oncol Cli n N Am, 2007, 16(3): 525-536, viii. DOI: 10.1016/j.soc.2007.04.016.

[143] Homayounfar K, Liersch T, Schuetze G, et al. Two-stage hepatecto my (R0) with portal vein ligation--towards curing patients with extended bilob ular colorectal liver metastases[J]. Int J Colorectal Dis, 2009, 24(4): 409-418. DOI: 10.1007/s00384-008-0620-z.

[144] Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embo lization and neoadjuvant chemotherapy as a treatment strategy for resectable hep atic colorectal metastases[J]. Ann Surg, 2008, 247 (3): 451-455. DOI: 10. 1097/SLA.0b013e31815ed693.

[145] Yamashita S, Hasegawa K, Takahashi M, et al. One-Stage Hepatecto my Following Portal Vein Embolizationfor Colorectal Liver Metastasis[J]. World J Surg, 2012, 37(3): 622-628. DOI: 10.1007/s00268-012-1861-0.

[146] Wicherts DA, de Haas RJ, Andreani P, et al. Impact of portal vein embolization on long-term survival of patients with primarily unresectable col orectal liver metastases[J]. Br J Surg, 2010, 97(2): 240-250. DOI: 10.1002/bjs.67 56.

[147] Torres OJ, Moraes-Junior JM, Lima e Lima NC, et al. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): a new ap proach in liver resections[J]. Braz Arch Dig Surg, 2012, 25(4): 290-292.

[148] Bertens KA, Hawel J, Lung K, et al. ALPPS: challenging the concept of unresectability—a systematic review[J]. Int J Surg, 2015, 13: 280-287. DOI: 10.1016/j.ijsu.2014.12.008.

[149] Oldhafer KJ, Donati M, Jenner RM, et al. ALPPS for patients with colorectal liver metastases: effective liverhypertrophy, but early tumor recurren ce[J]. World J Surg, 2014, 38(6): 1504-1509. DOI: 10.1007/s00268-013-2401-2.

[150] Tanaka K, Matsuo K, Murakami T, et al. Associating liver partitio n and portal vein ligation for staged hepatectomy (ALPPS): Short-term outcome, functional changes in the future liver remnant, and tumor growth activity[J]. Eur J Surg Oncol (EJSO), 2015, 41(4): 506-512. DOI: 10.1016/j.ejso.2015.01.031.

[151] Moris D, Ronnekleiv-Kelly S, Kostakis ID, et al. Operative Resul ts and Oncologic Outcomes of Associating Liver Partition and Portal Vein Ligatio n for Staged Hepatectomy (ALPPS) Versus Two-Stage Hepatectomy (TSH) in Patients with Unresectable Colorectal Liver Metastases: A Systematic Review and Meta-An alysis[J]. World J Surg, 2018, 42(3): 806-815. DOI: 10.1007/s00268-017-4181-6.

[152] Sandstrom P, Rosok B I, Sparrelid E, et al. ALPPS Improves Resect ability Compared With Conventional Two-stage Hepatectomy in Patients With Advan ced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomi zed Controlled Trial (LIGRO Trial)[J]. Ann Surg, 2018, 267(5): 833-840. DOI: 10.1 097/sla.0000000000002511.

[153] Spampinato MG, Mandalá L, Quarta G, et al. One-stage, totally l aparoscopic major hepatectomy and colectomy for colorectal neoplasm with synchro nous liver metastasis: safety, feasibility and short-term outcome[J]. Surgery, 2013, 153(6): 861-865. DOI: 10.1016/j.surg.2012.06.007.

[154] Ratti F, Schadde E, Masetti M, et al. Strategies to Increase the Resectability of Patients with Colorectal Liver Metastases: A Multi-center Case -Match Analysis of ALPPS and Conventional Two-Stage Hepatectomy[J]. Ann Surg Oncol, 2015, 22(6): 1933-1942. DOI: 10.1245/s10434-014-4291-4.

[155] Neeleman N, Andersson R. Repeated liver resection for recurrent l iver cancer[J]. Br J Surg, 1996, 83(7): 893-901. DOI: 10.1002/bjs.1800830705.

[156] Antoniou A, Lovegrove RE, Tilney HS, et al. Meta-analysis of cli nical outcome after first and second liver resection for colorectal metastases[J]. Surgery, 2007, 141(1): 9-18. DOI: 10.1016/j.surg.2006.07.045.

[157] Adam R, Hoti E, Bredt LC. Evolution of neoadjuvant therapy for ex tended hepatic metastases—have we reached our (non-resectable) limit[J]. J S urg Oncol, 2010, 102(8): 922-931. DOI: 10.1002/jso.21727.

[158] Warwick R, Page R. Resection of pulmonary metastases from colorec tal carcinoma[J]. Eur J Surg Oncol, 2007, 33(Suppl 2): S59-S63. DOI: 10.1016/j.ej so.2007.09.018.

[159] Elias D, Benizri E, Pocard M, et al. Treatment of synchronous per itoneal carcinomatosis and liver metastases from colorectal cancer[J]. Eur J S urg Oncol (EJSO), 2006, 32(6): 632-636. DOI: 10.1016/j.ejso.2006.03.013.

[160] Carpizo D R, D'Angelica M. Liver Resection for Metastatic Colore ctal Cancer in the Presence of ExtrahepaticDisease[J]. Ann Surg Oncol, 2009, 16 (9): 2411-2421. DOI: 10. 1245/s10434-009-0493-6.

[161] Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemother apy in the management of resected or resectable colorectal liver metastases: a s ystematic review and meta-analysis of randomized controlled trials[J]. Oncol Rep, 2012, 27(6): 1849-1856. DOI: 10.3892/or.2012.1740.

[162] Ismaili N. Treatment of colorectal liver metastases[J]. World J Surg Oncol, 2011, 9: 154. DOI: 10.1186/1477-7819-9-154.

[163] Cleary JM, Tanabe KT, Lauwers GY, et al. Hepatic toxicities assoc iated with the use of preoperative systemic therapy in patients with metastatic colorectal adenocarcinoma to the liver[J]. Oncologist, 2009, 14 (11): 1095-1105. DOI: 10. 1634/theoncologist.2009-0152.

[164] Nordlinger B, Sorbye H, Collette L, et al. Final results of the EORTC Intergroup randomized phase Ⅲ study40983 [EPOC] evaluating the benefit o f perioperative FOLFOX4 chemotherapy for patients with potentiallyresectable col orectal cancer liver metasta-

ses[J]. J Clin Oncol, 2007, 25(Suppl 18): LBA5.

[165] Tanaka K, Adam R, Shimada H, et al. Role of neoadjuvant chemother apy in the treatment of multiple colorectal metastases to the liver[J]. Br J S urg, 2003, 90(8): 963-969. DOI: 10.1002/bjs.4160.

[166] Leonard G D, Brenner B, Kemeny N E. Neoadjuvant Chemotherapy Befo re Liver Resection for Patients WithUnresectable Liver Metastases From Colorecta l Carcinoma[J]. J Clin Oncol, 2005, 23(9): 2038-2048. DOI: 10.1200/jco.2005.00.34 9.

[167] Benoist S, Brouquet A, Penna C, et al. Complete response of color ectal liver metastases after chemotherapy: does it mean cure [J]. J Clin Oncol, 2006, 24(24): 3939-3945. DOI: 10.1200/JCO.2006.05.8727.

[168] Gruenberger B, Scheithauer W, Punzengruber R, et al. Importance o f response to neoadjuvant chemotherapy in potentially curable colorectal cancer liver metastases[J]. BMC Cancer, 2008, 8: 120. DOI: 10.1186/1471-2407-8-120.

[169] Chiappa A, Bertani E, Makuuchi M, et al. Neoadjuvant chemotherapy followed by hepatectomy for primarily resectable colorectal cancer liver metast ases[J]. Hepatogastroenterology, 2009, 56(91/92): 829-834.

[170] Abdalla EK, Adam R, Bilchik AJ, et al. Improving resectability of hepatic colorectal metastases: expert consensus statement[J]. Ann Surg Oncol, 2006, 13(10): 1271-1280. DOI: 10.1245/s10434-006-9045-5.

[171] Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment o f unresectable colorectal liver metastases: correlation between tumour response and resection rates[J]. Ann Oncol, 2005, 16(8): 1311-1319. DOI: 10.1093/annonc/md i246.

[172] Mentha G, Majno P, Terraz S, et al. Treatment strategies for the management of advanced colorectal liver metastases detected synchronously with t he primary tumour[J]. Eur J Surg Oncol, 2007, 33(Suppl 2): S76-S83. DOI: 10.1016/ j.ejso.2007.09.016.

[173] Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemoth erapy with FOLFOX4 and surgery versus surgery alone for resectable liver metasta ses from colorectal cancer (EORTC Intergroup trial 40983): a randomised controll ed trial[J]. Lancet, 2008, 371: 1007-1016.

[174] Nordlinger B, Van Cutsem E, Gruenberger T, et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of pat ients with colorectal liver metastases: recommendations from an expert panel[J]. Ann Oncol, 2009, 20(6): 985-992. DOI: 10.1093/annonc/mdn735.

[175] Masi G, Loupakis F, Pollina L, et al. Long-term outcome of initi ally unresectable metastatic colorectal cancer patients treated with 5- uoroura cil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surg ery of metastases[J]. Ann Surg, 2009, 249: 420-425.

[176] Kataoka K, Kanazawa A, Nakajima A, et al. Feasibility and potenti al benefit of preoperative chemotherapy for colorectal liver metastasis (CLM): a single-centered retrospective study[J]. Surg Today, 2013, 43(10): 1154-1161. D OI: 10.1007/s00595-012-0410-7.

[177] Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in c olorectal cancer liver metastases[J]. J Clin Oncol, 2006, 24(31): 4983-4990. DOI : 10.1200/JCO.2006.05.8156.

[178] Malik HZ, Farid S, Al-Mukthar A, et al. A critical appraisal of the role of neoadjuvant chemotherapy for colorectal liver metastases: a case-co ntrolled study[J]. Ann Surg Oncol, 2007, 14(12): 3519-3526. DOI: 10.1245/s10434- 007-9533-2.

[179] Welsh FK, Tilney HS, Tekkis PP, et al. Safe liver resection follo wing chemotherapy for colorectal metastases isa matter of timing [J]. Br J Canc er, 2007, 96(7): 1037-1042. DOI: 10.1038/sj.bjc.6603670.

[180] Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperati ve chemotherapy on the risk of major hepatectomy for colorectal liver metastases [J]. Ann Surg, 2006, 243(1): 1-7. DOI: 10.1097/01.sla.0000193603.26265.c3.

[181] Kandutsch S, Klinger M, Hacker S, et al. Patterns of hepatotoxici ty after chemotherapy for colorectal cancer liver metastases[J]. Eur J Surg On col, 2008, 34(11): 1231-1236. DOI: 10.1016/j.ejso.2008.01.001.

[182] Fernandez FG, Ritter J, Goodwin JW, et al. Effect of steatohepati tis associated with irinotecan or oxaliplatin pretreatment on resectability of h epatic colorectal metastases[J]. J Am Coll Surg, 2005, 200(6): 845-853. DOI: 10.1 016/j.jamcollsurg.2005.01.024.

[183] Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen pred icts steatohepatitis and an increase in 90-day mortality after surgery for hepa tic colorectal metastases[J]. J Clin Oncol, 2006, 24(13): 2065-2072. DOI: 10.1200 /JCO.2005.05.3074.

[184] Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome[J]. J Gastrointest Surg, 2007, 11(7): 860-868. DOI: 10.1007/s11605-007- 0149-4.

[185] Gomez D, Malik HZ, Bonney GK, et al. Steatosis predicts postopera tive morbidity following hepatic resection for colorectal metastasis[J]. Br J Surg, 2007, 94(11): 1395-1402. DOI: 10.1002/bjs.5820.

[186] Nakano H, Oussoultzoglou E, Rosso E, et al. Sinusoidal injury inc reases morbidity after major hepatectomy in patients with colorectal liver metas tases receiving preoperative chemotherapy[J]. Ann Surg, 2008, 247(1): 118-124. D OI: 10.1097/SLA.0b013e31815774de.

[187] McCormack L, Petrowsky H, Jochum W, et al. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case-control study[J]. Ann Surg, 2007, 245(6): 923-930. DOI: 10.1097/01.sla.0000 251747.80025.b7.

[188] Kishi Y, Zorzi D, Contreras CM, et al. Extended preoperative chem otherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases[J]. Ann Surg Oncol, 2010, 17(11): 2870-2876. DOI: 10.1245/s10434-010-1166-1.

[189] Adam R, Wicherts DA, de Haas RJ, et al. Complete pathologic respo nse after preoperative chemotherapy for colorectal liver metastases: myth or rea lity[J]. J Clin Oncol, 2008, 26(10): 1635-1641. DOI: 10.1200/JCO.2007.13.7471.

[190] van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colore ctal liver metastases after chemotherapy: should we be concerned[J]. J Gastroi ntest Surg, 2010, 14(11): 1691-1700. DOI: 10.1007/s11605-010-1348-y.

[191] Bischof DA, Clary BM, Maithel SK, et al. Surgical management of d isappearing colorectal liver metastases[J]. Br J Surg, 2013, 100(11): 1414-1420. DOI: 10.1002/bjs.9213.

[192] Kuhlmann K, van Hilst J, Fisher S, et al. Management of disappear ing colorectal liver metastases[J]. Eur J Surg Oncol, 2016, 42(12): 1798-1805. D OI: 10.1016/j.ejso.2016.05.005.

[193] Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectab le colorectal liver metastases downstaged by chemotherapy:

a model to predict lo ng-term survival[J]. Ann Surg, 2004, 240(4): 644-657.

[194] Benoist S, Nordlinger B. Neoadjuvant treatment before resection o f liver metastases[J]. Eur J Surg Oncol, 2007, 33(Suppl 2): S35-S41. DOI: 10.1016 /j.ejso.2007.09.022.

[195] Reddy SK, Barbas AS, Clary BM. Synchronous colorectal liver metas tases: is it time to reconsider traditional paradigms of management[J]. Ann Su rg Oncol, 2009, 16(9): 2395-2410. DOI: 10.1245/s10434-009-0372-1.

[196] Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tu mor in patients with synchronous stage Ⅳ colorectal cancer receiving combinatio n chemotherapy without surgery as initial treatment[J]. J Clin Oncol, 2009, 27(2 0): 3379-3384. DOI: 10.1200/JCO.2008.20.9817.

[197] Mehta NN, Ravikumar R, Coldham CA, et al. Effect of preoperative chemotherapy on liver resection for colorectal liver metastases[J]. Eur J Surg Oncol, 2008, 34(7): 782-786. DOI: 10.1016/j.ejso.2007.09.007.

[198] Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capeci tabine, and oxaliplatin as neoadjuvant therapy for patients with potentially cur able metastatic colorectal cancer[J]. J Clin Oncol, 2008, 26(11): 1830-1835. DOI :10.1200/JCO.2007.13.7679.

[199] Coskun U, Buyukberber S, Yaman E, et al. Xelox (capecitabine plus oxaliplatin) as neoadjuvant chemotherapy of unresectable liver metastases in co lorectal cancer patients[J]. Neoplasma, 2008, 55(1): 65-70.

[200] Cassidy J, Clarke s, Diaz-Rubio D, et al. XELOX vs. FOLFOX4: Eff icacy results from XELOX-1/NO16966, a randomized phase Ⅲ trial in first-line metastatic colorectal cancer[C]. 2007 Gastroimtestinal Cancers Symposium, Abst ract 270.

[201] Pessaux P, Marzano E, Casnedi S, et al. Histological and immediat e postoperative outcome after preoperative cetuximab: case-matched control stud y[J]. World J Surg, 2010, 34(11): 2765-2772.DOI: 10.1007/s00268-010-0731-x.

[202] Pessaux P, Panaro F, Casnedi S, et al. Targeted molecular therapi es (cetuximab and bevacizumab) do not induce additional hepatotoxicity: prelimin ary results of a case-control study[J]. Eur J Surg Oncol, 2010, 36(6): 575-582. DOI: 10.1016/j.ejso.2010.04.010.

[203] Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial[J]. Lancet On col, 2010, 11(1): 38-47. DOI: 10.1016/S1470-2045(09)70330-4.

[204] Pimrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy w ith or without cetuximab in patients with resectablecolorectal liver metastasis: the New EPOC randomised controlled trial[J]. Lancet Oncol, 2014, 15(6): 601-611 . DOI: 10.1016/S1470-2045(14)70105-6.

[205] Umehara M, Umehara Y, Takahashi K, et al. Preoperative Chemothera py with Bevacizumab Extends Disease-free Survival After Resection of Liver Meta stases from Colorectal Cancer[J]. Anticancer Res, 2016, 36(4): 1949-1954.

[206] Kemeny N, Jarnagin W, Paty P, et al. Phase I trial of systemic ox aliplatin combination chemotherapy with hepatic arterial infusion in patients wi th unresectable liver metastases from colorectal cancer[J]. J Clin Oncol, 2005, 23(22): 4888-4896. DOI: 10.1200/JCO.2005.07.100.

[207] Kemeny N, Eid A, Stockman J, et al. Hepatic arterial infusion of floxuridine and dexamethasone plus high-dose Mitomycin C for patients with unre sectable hepatic metastases from colorectal carcinoma[J]. J Surg Oncol, 2005, 91 (2): 97-101. DOI: 10.1002/jso.20286.

[208] Clancy TE, Dixon E, Perlis R, et al. Hepatic arterial infusion af ter curative resection of colorectal cancer metastases: a meta-analysis of pros pective clinical trials[J]. J Gastrointest Surg, 2005, 9(2): 198-206.DOI: 10.1016 /j.gassur.2004.07.004.

[209] Zorzi D, Kishi Y, Maru DM, et al. Effect of extended preoperative chemotherapy on pathologic response and postoperative liver insufficiency after hepatic resection for colorectal liver metastases[J]. J Clin Oncol, 2009: Abstr act 295.

[210] Choti MA. Chemotherapy-associated hepatotoxicity: do we need to be concerned[J]. Ann Surg Oncol, 2009, 16(9): 2391-2394. DOI: 10.1245/s10434-009 -0512-7.

[211] Benoist S, Nordlinger B. The role of preoperative chemotherapy in patients with resectable colorectal liver metastases[J]. Ann Surg Oncol, 2009, 16(9): 2385-2390. DOI: 10.1245/s10434-009-0492-7.

[212] Vadeyar HJ. Current therapeutic options for colorectal liver meta stases[J]. Indian J Gastroenterol, 2007, 26(1): 26-29.

[213] Ychou M, Hohenberger W, Thezenas S, et al. Randomized phase Ⅲ t rial comparing infused 5-fluorouracil/folinic acid (LV5FU) versus LV5FU+irinote can (LV5FU+IRI) as adjuvant treatment after complete resection of liver metastas es from colorectal cancer (LMCRC). (CPT-GMA-301)[J]. J Clin Oncol, 2008, 26(15): LBA4013-LBA4013. DOI: 10.1200/jco.2008.26.15_suppl.lba4013.

[214] Gruenberger T, Kaczirek K, Bergmann M, et al. Progression-free s urvival in a phase Ⅱ study of perioperative bevacizumab plus XELOX in patients with potentially curable metastatic colorectal cancer[J]. J Clin Oncol, 2008, 26 (15): 4073-4073. DOI: 10.1200/jco.2008.26.15_suppl.4073.

[215] Bouganim N, Ang C, Kavan P, et al. Perioperative bevacizumab (Bev) containing chemotherapy for colorectal liver metastases[J]. J Clin Oncol, 200 8, 26(15): 15073-15073.DOI: 10.1200/jco.2008.26.15_suppl.15073.

[216] Adam R, Bhangui P, Poston G, et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases[J]. Ann Surg, 2 010, 252(5): 774-787. DOI: 10.1097/SLA.0b013e3181fcf3e3.

[217] Goéré D, Benhaim L, Bonnet S, et al. Adjuvant chemotherapy afte r resection of colorectal liver metastases in patients at high risk of hepatic r ecurrence: a comparative study between hepatic arterial infusion of oxaliplatin and modern systemic chemotherapy[J]. Ann Surg, 2013, 257(1): 114-120. DOI: 10.109 7/SLA.0b013e31827b9005.

[218] House MG, Kemeny NE, G nen M, et al. Comparison of adjuvant syste mic chemotherapy with or without hepatic arterial infusional chemotherapy after hepatic resection for metastatic colorectal cancer[J]. Ann Surg, 2011, 254(6): 85 1-856. DOI: 10.1097/SLA.0b013e31822f4f88.

[219] Kemeny N E, Jarnagin W R, Capanu M, et al. Randomized Phase Ⅱ Tr ial of Adjuvant Hepatic Arterial Infusionand Systemic Chemotherapy With or Witho ut Bevacizumab in Patients With Resected Hepatic Metastases FromColorectal Cance r[J]. J Clin Oncol, 2011, 29(7): 884-889. DOI: 10.1200/jco.2010.32.5977.

[220] Adam R. Chemotherapy and surgery: new perspectives on the treatme nt of unresectable liver metastases[J]. Ann Oncol, 2003, 14(Suppl 2): ii13-6. DO I: 10.1093/annonc/mdg731.

[221] Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and

irinotecan or infu sed fluorouracil plus leucovorin and oxaliplatin in patients with previously unt reated metastatic colorectal cancer: a North American Intergroup Trial[J]. J C lin Oncol, 2006, 24(21): 3347-3353. DOI: 10.1200/JCO.2006.06.1317.

[222] Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOL FOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study[J]. J Clin Oncol, 2004, 22(2): 229-237. DOI: 10.1200/JCO.2004.05.113.

[223] Cals L, Rixe O, Fran ois E, et al. Dose-finding study of weekly 24-h continuous infusion of 5-fluorouracil associated with alternating oxalipl atin or irinotcan in advanced colorectal cancer patients[J]. Ann Oncol, 2004, 15(7): 1018-1024. DOI: 10.1093/annonc/mdh259.

[224] Falcone A, Ricci S, Brunetti I, et al. Phase Ⅲ trial of infusio nal fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared w ith infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest[J]. J Clin Oncol, 2007, 25(13): 1670-1676. DOI: 10.1200/JCO.2006.09.0928.

[225] Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy o f oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first -line treatment of metastatic colorectal cancer: results of the TREE Study[J]. J Clin Oncol, 2008, 26(21): 3523-3529. DOI: 10.1200/JCO.2007.15.4138.

[226] Mahnken AH, Pereira PL, de Baère T. Interventional oncologic app roaches to liver metastases[J]. Radiology, 2013, 266(2): 407-430. DOI: 10.1148/radiol.12112544.

[227] Goéré D, Deshaies I, de Baere T, et al. Prolonged survival of i nitially unresectable hepatic colorectal cancer patients treated with hepatic ar terial infusion of oxaliplatin followed by radical surgery of metastases[J]. A nn Surg, 2010, 251(4): 686-691. DOI: 10.1097/SLA.0b013e3181d35983.

[228] Nishiofuku H, Tanaka T, Aramaki T, et al. Hepatic arterial infusi on of 5-fluorouracil for patients with liver metastases from colorectal cancer refractory to standard systemic chemotherapy: a multicenter, retrospective analy sis[J]. Clin Colorectal Cancer, 2010, 9(5): 305-310. DOI: 10.3816/CCC.2010.n.044.

[229] Van Cutsem E, K hne CH, Hitre E, et al. Cetuximab and chemotherap y as initial treatment for metastatic colorectal cancer[J]. N Engl J Med, 2009, 360(14): 1408-1417. DOI: 10.1056/NEJMoa0805019.

[230] Kabbinavar FF, Schulz J, McCleod M, et al. Addition of Bevacizum ab to Bolus Fluorouracil and Leucovorin in First-Line Metastatic Colorectal Can cer: Results of a Randomized Phase Ⅱ Trial[J]. J Clin Oncol, 2005, 23(16): 3697- 3705. DOI: 10.1200/jco.2005.05.112.

[231] Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combina tion with oxaliplatin-based chemotherapy as first-line therapy in metastatic c olorectal cancer: a randomized phase Ⅲ study[J]. J Clin Oncol, 2008, 26(12): 201 3-2019. DOI: 10.1200/JCO.2007.14.9930.

[232] Fraker DL, Soulen M. Regional therapy of hepatic metastases[J]. Hematol Oncol Clin North Am, 2002, 16(4): 947-967. DOI: 10.1016/s0889-8588(02)000 39-4.

[233] Nitzkorski JR, Farma JM, Watson JC, et al. Outcome and natural hi story of patients with stage Ⅳ colorectal cancer receiving chemotherapy without primary tumor resection[J]. Ann Surg Oncol, 2012, 19(2): 379-383. DOI: 10.1245/s 10434-011-2028-1.

[234] Cirocchi R, Trastulli S, Abraha I, et al. Non-resection versus r esection for an asymptomatic primary tumour in patients with unresectable stage Ⅳ colorectal cancer[J]. Cochrane Database Syst Rev, 2012 (8): CD008997. DOI: 10. 1 002/14651858. CD008997.pub2.

[235] Colucci G, Gebbia V, Paoletti G, et al. Phase Ⅲ randomized tria l of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a mu lticenter study of the Gruppo Oncologico Dell'Italia Meridionale[J]. J Clin O ncol, 2005, 23(22): 4866-4875. DOI: 10.1200/JCO.2005.07.113.

[236] Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of his tological tumor response assessment in predicting the outcome in patients with c olorectal liver metastases treated with neo-adjuvant chemotherapy followed by l iver surgery[J]. Ann Oncol, 2007, 18(2): 299-304. DOI: 10.1093/annonc/mdl386.

[237] Yu Q, Zhang L, Fan S, et al. The significance of transarterial ch emoembolization combined with systemic chemotherapy for patients with KRAS wild -type unresectable metachronous colorectal carcinoma with liver metastases[J]. J Cancer Res Ther, 2016, 12(Suppl): C205-C211. DOI: 10.4103/0973-1482.200603.

[238] Zelek L. Multimodal therapy with intravenous biweekly leucovorin, 5-fluorouracil and irinotecan combined with hepatic arterial infusion pirarubic in in non-resectable hepatic metastases from colorectal cancer (a European Asso ciation for Research in Oncology trial)[J]. Ann Oncol, 2003, 14(10): 1537-1542. DOI: 10.1093/annonc/mdg404.

[239] Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal[J]. A nn Surg Oncol, 2001, 8(4): 347-353. DOI: 10.1245/aso.2001.8.4.347.

[240] Suzuki C, Blomqvist L, Sundin A, et al. The initial change in tum or size predicts response and survival in patients with metastatic colorectal ca ncer treated with combination chemotherapy[J]. Ann Oncol, 2012, 23(4): 948-954. DOI: 10.1093/annonc/mdr350.

[241] Ye LC, Wei Y, Zhu DX, et al. Impact of early tumor shrinkage on c linical outcome in wild-type-KRAS colorectal liver metastases treated with cet uximab[J]. J Gastroenterol Hepatol, 2015, 30(4): 674-679. DOI: 10.1111/jgh.12847.

[242] Piessevaux H, Buyse M, Schlichting M, et al. Use of early tumor shri nkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab[J]. J Clin Oncol, 2013, 31(30): 3764-3775. DOI: 10.1200/JCO.2012.42.85 32.

[243] Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorour acil, and leucovorin for patients with unresectable liver-only metastases from c olorectal cancer: a North Central Cancer Treatment Group phase Ⅱ study[J]. J Clin Oncol, 2005, 23(36): 9243-9249. DOI: 10.1200/JCO.2005.07.740.

[244] Quenet F, Nordlinger B, Rivoire M, et al. Resection of previously un resectable liver metastases from colorectal cancer (LMCRC) after chemotherapy (C T) with CPT-11/L-OHP/LV5FU (Folfirinox): A prospective phase Ⅱ trial[J]. J Clin Oncol, 2004, 22(14): 3613-3613. DOI: 10.1200/jco.2004.22.14_suppl.3613.

[245] Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of p atients with unresectable colorectal cancer liver metastases following infusiona l chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery[J]. An n Oncol, 1999, 10(6): 663-669. DOI: 10.1023/a:1008347829017.

[246] Bruera G, Santomaggio A, Cannita K, et al. "Poker" association of weekly alternating 5-fluorouracil, irinotecan, bevacizumab and oxaliplatin (FIr -B/FOx) in first line treatment of metastatic colorectal cancer: a phase Ⅱ stu dy[J]. BMC Cancer, 2010(1): 567. DOI: 10.1186/1471-2407-10-567.

[247] Wong R, Cunningham D, Barbachano Y, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patient s with poor-risk colorectal liver-only metastases not selected for upfront res ection[J]. Ann Oncol, 2011, 22(9): 2042-2048. DOI: 10.1093/annonc/mdq714.

[248] Van Cutsem E, Lenz HJ, Kohne CH, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximabtreatment and RAS mutations in colorectal cancer[J]. J Clin Oncol, 2015, 33(7): 692-700. DOI: 10.1200/JCO.2014.59.4812.

[249] Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of Subs equent Therapies on Outcome of the FIRE-3/AIO KRK0306 Trial: First-Line Therap y With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With KRAS Wild-Type Tu mors in Metastatic Colorectal Cancer[J]. J Clin Oncol, 2015, 33(32): 3718-3726. DOI: 10.1200/JCO.2015.61.2887.

[250] Azadeh P, Mortazavi N, Tahmasebi A, et al. Cetuximab Plus Various Ch emotherapy Regimens for Patients with KRAS Wild-Type Metastatic Colorectal Canc er[J]. Chemotherapy, 2016, 61(1): 51-56. DOI: 10.1159/000440693.

[251] Cassidy J, Cunningham D, Berry S R, et al. Surgery with curative int ent in patients (pts) treated with first-line chemotherapy (CT) + bevacizumab (BEV) for metastatic colorectal cancer (mCRC): First BEAT and NO16966[J]. J Cli n Oncol, 2008, 26(15): 4022-4022. DOI: 10.1200/jco.2008.26.15_suppl.4022.

[252] Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucov orin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer[J]. J Clin Oncol, 2009, 27(5): 663 - 671. DOI: 10.12 00/JCO.2008.20.8397.

[253] Douillard JY, Siena S, Cassidy J, et al. Randomized, phase Ⅲ trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX 4) versus FOLFOX4 alone as first-line treatment in patients with previously unt reated metastatic colorectal cancer: the PRIME study[J]. J Clin Oncol, 2010, 28(31): 4697-4705. DOI: 10.1200/JCO.2009.27.4860.

[254] Basso M, Dadduzio V, Ardito F, et al. Conversion Chemotherapy for Te chnically Unresectable Colorectal Liver Metastases: A Retrospective, STROBE-Comp liant, Single-Center Study Comparing Chemotherapy Alone and Combination Chemothe rapy With Cetuximab or Bevacizumab[J]. Medicine (Baltimore), 2016, 95(20): e3722. DOI: 10.1097/MD.0000000000003722.

[255] Karapetis CS, Jonker D, Daneshmand M, et al. PIK3CA, BRAF, and PT EN status and benefit from cetuximab in the treatment of advanced colorectal can cer—results from NCIC CTG/AGITG CO.17[J]. Clin Cancer Res, 2014, 20(3): 744-753. DOI: 10.1158/1078-0432.CCR-13-0606.

[256] Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fl uorouracil and irinotecan) as first-line treatment in metastatic colorectal can cer (MCC): a multicentre randomised phase Ⅲ trial from the Hellenic Oncology Re search Group (HORG)[J]. Br J Cancer, 2006, 94(6): 798-805. DOI: 10.1038/sj.bjc.660 3011.

[257] Garufi C, Torsello A, Tumolo S, et al. Cetuximab plus chronomodul ated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemo therapy in colorectal liver metastases: POCHER trial[J]. Br J Cancer, 2010, 103(10): 1542-1547. DOI: 10.1038/sj.bjc.6605940.

[258] Stein A, Atanackovic D, Hildebrandt B, et al. Upfront FOLFOXIRI+b evacizumab followed by fluoropyrimidin and bevacizumab maintenance in patients w ith molecularly unselected metastatic colorectal cancer[J]. Br J Cancer, 2015, 1 13(6): 872-877. DOI: 10.1038/bjc.2015.299.

[259] Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus beva cizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients wit h metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study[J]. Lancet Oncol, 2015, 16(13): 1306-1315. DOI: 10.1016/S1470-2045(15)00122-9.

[260] Tomasello G, Petrelli F, Ghidini M, et al. FOLFOXIRI Plus Bevaciz umab as Conversion Therapy for Patients With Initially Unresectable Metastatic C olorectal Cancer: A Systematic Review and Pooled Analysis[J]. JAMA Oncol, 2017, 3(7): e170278. DOI: 10.1001/jamaoncol.2017.0278.

[261] Esin E, Yalcin S. Maintenance strategy in metastatic colorectal c ancer: A systematic review[J]. Cancer TreatRev, 2016, 42: 82-90. DOI: 10.1016/j.c trv.2015.10.012.

[262] Hegewisch-Becker S, Graeven U, Lerchenmüller CA, et al. Mainten ance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevaciz umab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non -inferiority, open-label, phase 3 trial[J]. Lancet Oncol, 2015, 16(13): 1355-136 9. DOI: 10.1016/S1470-2045(15)00042-X.

[263] Simkens LH, von Tinteren H, ven Tiji A, et al. Maintenance treatm ent with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal CancerGroup[J]. Lancet oncol, 2015, 385: 1843-1852.

[264] Goey KKH, Elias SG, van Tinteren H, et al. Maintenance treatment with capecitabine and bevacizumab versus observation in metastatic colorectal ca ncer: updated results and molecular subgroup analyses of the phase 3 CAIRO3 stud y[J]. Ann Oncol, 2017, 28(9): 2128-2134. DOI: 10.1093/annonc/mdx322.

[265] Stein A, Schwenke C, Folprecht G, et al. Effect of Application an d Intensity of Bevacizumab-based Maintenance After Induction Chemotherapy With Bevacizumab for Metastatic Colorectal Cancer: A Meta-analysis[J]. Clin Colore ctal Cancer, 2016, 15(2): e29-e39. DOI: 10.1016/j.clcc.2015.12.005.

[266] Xu RH, Muro K, Morita S, et al. Modified XELIRI (capecitabine plu s irinotecan) versus FOLFIRI (leucovorin, fluorouracil, and irinotecan), both eithe r with or without bevacizumab, as second-line therapy for metastatic colorectal cancer (AXEPT): a multicentre, open-label, randomised, non-inferiority, phase 3 trial[J]. Lancet Oncol, 2018, 19(5): 660-671. DOI: 10.1016/S1470-2045(18)30140 -2.

[267] Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combin ation chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-0 5): an open-label, randomised, phase 3 trial[J]. Lancet Oncol, 2011, 12(11): 103 2-1044. DOI: 10.1016/S1470-2045(11)70199-1.

[268] Koopman M, Antonini NF, Douma J, et al. Sequential versus combina tion chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colo rectal cancer (CAIRO): a phase Ⅲ randomised controlled trial[J]. Lancet, 2007, 370(9582): 135-142.

[269] Seymour MT, Maughan TS, Ledermann JA, et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis adv anced colorectal cancer (MRC FOCUS): a randomised controlled trial[J]. Lancet, 2007, 370(9582): 143-152. DOI: 10.1016/S0140-6736(07)61087-3.

[270] Grothey A, Cutsem EV, Sobrero A, et al. Regorafenib monotherapy f or previously treated metastatic colorectal cancer (COR-

RECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial[J]. Lancet, 2013, 381(9 863): 303-312. DOI:10.1016/s0140-6736(12)61900-x.

[271] Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial[J]. Lancet Oncol, 2015, 16(6): 619-629. DOI: 10.1016/S1470-2045(15)70156-7.

[272] Bennouna J, Borg C, Delord JP, et al. Bevacizumab combined with chemotherapy in the second-line treatment of metastatic colorectal cancer: results from the phase Ⅱ BEVACOLOR study[J]. Clin Colorectal Cancer, 2012, 11(1): 38-44. DOI: 10.1016/j.clcc.2011.05.002.

[273] Iwamoto S, Hazama S, Kato T, et al. Multicenter phase Ⅱ study of second-line cetuximab plus folinic acid/5-fluorouracil/irinotecan (FOLFIRI) in KRAS wild-type metastatic colorectal cancer: the FLIER study[J]. Anticancer Res, 2014, 34(4): 1967-1973.

[274] Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer[J]. N Engl J Med, 2004, 350(23): 2335-2342. DOI:10.1056/NEJMoa032691.

[275] Chan DL, Alzahrani NA, Morris DL, et al. Systematic review and meta-analysis of hepatic arterial infusion chemotherapy as bridging therapy for colorectal liver metastases[J]. Surg Oncol, 2015, 24(3): 162-171. DOI:10.1016/j.suronc.2015.06.014.

[276] D'Angelica MI, Correa-Gallego C, Paty PB, et al. Phase Ⅱ trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes[J]. Ann Surg, 2015, 261(2): 353-360. DOI: 10.1097/SLA.0000000000000614.

[277] McAuliffe JC, Qadan M, D'Angelica MI. Hepatic resection, hepatic arterial infusion pump therapy, and genetic biomarkers in the management of hepatic metastases from colorectal cancer[J]. J Gastrointest Oncol, 2015, 6(6): 699-708. DOI: 10.3978/j.issn.2078-6891.2015.081.

[278] Liu DM, Thakor AS, Baerlocher M, et al. A review of conventional and drug-eluting chemoembolization in the treatment of colorectal liver metastases: principles and proof[J]. Future Oncol, 2015, 11(9): 1421-1428. DOI:10.2217/fon.15.3.

[279] Nosher JL, Ahmed I, Patel AN, et al. Non-operative therapies for colorectal liver metastases[J]. J Gastrointest Oncol, 2015, 6(2): 224-240. DOI: 10.3978/j.issn.2078-6891.2014.065.

[280] Mocellin S, Pasquali S, Nitti D. Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer[J]. Cochrane Database Syst Rev, 2009(3): CD007823. DOI: 10.1002/14651858.CD007823.pub2.

[281] Kemeny NE, Melendez FDH, Capanu M, et al. Conversion to Resectability Using Hepatic Artery InfusionPlus Systemic Chemotherapy for the Treatment of Unresectable Liver Metastases From Colorectal Carcinoma[J]. J Clin Oncol, 2009, 27(21): 3465-3471. DOI:10.1200/jco.2008.20.1301.

[282] Hammill CW, Billingsley KG, Cassera MA, et al. Outcome after laparoscopic radiofrequency ablation of technically resectable colorectal liver metastases[J]. Ann Surg Oncol, 2011, 18(7): 1947-1954. DOI:10.1245/s10434-010-1535-9.

[283] Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study[J]. Radiology, 2003, 226(2): 441-451. DOI:10.1148/radiol.2262012198.

[284] Feliberti EC, Wagman LD. Radiofrequency ablation of liver metastases from colorectal carcinoma[J]. Cancer Control, 2006, 13(1): 48-51. DOI:10.1177/107327480601300107.

[285] Siperstein AE, Berber E, Ballem N, et al. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience[J]. Ann Surg, 2007, 246(4): 559-565. DOI: 10.1097/SLA.0b013e318155a7b6.

[286] Berber E, Tsinberg M, Tellioglu G, et al. Resection Versus Laparoscopic Radiofrequency Thermal AblationOf Solitary Colorectal Liver Metastasis[J]. J Gastrointest Surg, 2008, 12(11): 1967-1972. DOI:10.1007/s11605-008-0622-8.

[287] Knudsen AR, Kannerup AS, Mortensen FV, et al. Radiofrequency ablation of colorectal liver metastases downstaged by chemotherapy[J]. Acta Radiol, 2009, 50(7): 716-721. DOI:10.1080/02841850902991634.

[288] Brouquet A, Andreou A, Vauthey JN. The management of solitary colorectal liver metastases[J]. Surgeon, 2011, 9(5): 265-272. DOI:10.1016/j.surge.2010.12.005.

[289] Kawaguchi Y, Hasegawa K, Saiura A, et al. Surgical resection for local recurrence after radiofrequency ablation for colorectal liver metastasis is more extensive than primary resection[J]. Scandinavian Journal ofGastroenterology, 2014, 49(5): 569-575. DOI:10.3109/00365521.2014.893013.

[290] Bilchik AJ, Wood TF, Allegra DP. Radiofrequency ablation of unresectable hepatic malignancies: lessonslearned[J]. Oncologist, 2001, 6(1): 24-33. DOI:10.1634/theoncologist.6-1-24.

[291] Curley SA, Izzo F. Radiofrequency ablation of hepatocellular carcinoma[J]. Minerva Chir, 2002, 57(2): 165-176. DOI:10.1007/0-387-21598-0_6.

[292] Lu DS, Raman SS, Limanond P, et al. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors[J]. J Vasc Interv Radiol, 2003, 14(10): 1267-1274. DOI:10.1097/01.rvi.0000092666.72261.6b.

[293] Elias D, Di Pietroantonio D, Gachot B, et al. Liver abscess after radiofrequency ablation of tumors in patients with a biliary tract procedure[J]. Gastroenterol Clin Biol, 2006, 30(6/7): 823-827. DOI:10.1016/s0399-8320(06)73327-9.

[294] Zhang X, Zhou L, Chen B, et al. Microwave ablation with cooled-tip electrode for liver cancer: an analysis of 160 cases[J]. Minim Invasive Therapy Allied Technol, 2008, 17: 303-307.

[295] Shono Y, Tabuse K, Tsuji T, et al. Microwave coagulation therapy for unresectable colorectal metastatic liver tumor[J]. Gan To Kagaku Ryoho, 2002, 29(6): 856-859. DOI: 10.3380/jmicrowavesurg.18.17.

[296] Grundmann RT, Hermanek P, Merkel S, et al. Diagnosis and treatment of colorectal liver metastases-workflow[J]. Zentralbl Chir, 2008, 133(3): 267-284. DOI:10.1055/s-2008-1076796.

[297] Seifert JK, Junginger T. Prognostic factors for cryotherapy of colorectal liver metastases[J]. Eur J Surg Oncol, 2004, 30(1): 34-40. DOI:10.1016/j.ejso.2003.10.009.

[298] Chen YY, Perera DS, Yan TD, et al. Applying Fong's CRS liver score in patients with colorectal liver metastases treated by cryotherapy[J]. Asian J Surg, 2006, 29(4): 238-241. DOI: 10.1016/S1015-9584(09)60095-6.

[299] Seifert JK, Junginger T. Cryotherapy for liver tumors: current status, perspectives, clinical results, and review of literature[J]. Technol Cancer Res Treat, 2004, 3(2): 151-163. DOI:10.1177/153303460400300208.

[300] Gignoux BM, Ducerf C, Mabrut JY, et al. Cryosurgery of primary and metastatic cancers of the liver[J]. Ann Chir, 2001, 126

(10):950-959. DOI:10.1 016/s0003-3944(01)00637-x.

[301] Austin-Seymour MM, Chen GT, Castro JR, et al. Dose volume histog ram analysis of liver radiation tolerance[J]. Int J Radiat Oncol Biol Phys,198 6,12(1):31-35. DOI:10.1016/0360-3016(86)90412-8.

[302] Eble MJ, Gademann G, Wannenmacher M. The value of radiotherapy fo r liver metastases[J]. StrahlentherOnkol, 1993, 169(8):459-468.

[303] INGOLD JA, REED GB, KAPLAN HS, et al. RADIATION HEPATITIS[J]. A m J Roentgenol Radium Ther Nucl Med, 1965,93:200-208.

[304] Yeo SG, Kim DY, Kim TH, et al. Whole-liver radiotherapy for end -stage colorectal cancer patients with massive liver metastases and advanced he patic dysfunction[J]. Radiat Oncol, 2010, 5(1):97. DOI:10.1186/1748-717x-5-97 .

[305] Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-Institutiona l Phase Ⅰ/Ⅱ Trial of Stereotactic BodyRadiation Therapy for Liver Metastases[J]. J Clin Oncol, 2009, 27(10):1572-1578. DOI:10.1200/jco.2008.19.6329.

[306] Mohiuddin M, Chen E, Ahmad N. Combined liver radiation and chemot herapy for palliation of hepatic metastases from colorectal cancer[J]. J Clin Oncol,1996,14(3):722-728. DOI:10.1200/JCO.1996.14.3.722.

[307] Collettini F, Schnapauff D, Poellinger A, et al. Percutaneous CT -guided high-dose brachytherapy (CT-HDRBT) ablation of primary and metastatic lung tumors in nonsurgical candidates[J]. Rofo,2012,184(4):316-323. DOI:10.1 055/s-0031-1299101.

[308] Comito T, Cozzi L, Clerici E, et al. Stereotactic Ablative Radiot herapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a sa fe and effective approach[J]. BMC Cancer, 2014,14:619. DOI:10.1186/1471-2407- 14-619.

[309] Filippi AR, Badellino S, Guarneri A, et al. Outcomes of single fr action stereotactic ablative radiotherapy for lung metastases[J]. Technol Canc er Res Treat,2014,13(1):37-45. DOI:10.7785/tcrt.2012.500355.

[310] Tselis N, Ferentinos K, Kolotas C, et al. Computed tomography-gu ided interstitial high-dose-rate brachytherapy in the local treatment of prima ry and secondary intrathoracic malignancies[J]. J Thorac Oncol, 2011, 6(3): 545- 552. DOI: 10. 1097/JTO.0b013e318208c7a3.

[311] Peters N, Wieners G, Pech M, et al. CT-guided interstitial brach ytherapy of primary and secondary lung malignancies: results of a prospective ph ase Ⅱ trial[J]. Strahlenther Onkol, 2008, 184(6):296-301. DOI:10.1007/s00066- 008-1718-5.

[312] Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation th erapy for liver metastases[J]. Eur J Cancer, 2009, 45(17):2947-2959. DOI:10.101 6/j.ejca.2009.08.011.

[313] Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualiz ed stereotactic body radiotherapy of liver metastases[J]. J Clin Oncol,2009,27 (10):1585-1591. DOI:10.1200/JCO.2008.20.0600.

[314] Agolli L, Bracci S, Nicosia L, et al. Lung Metastases Treated Wit h Stereotactic Ablative Radiation Therapyin Oligometastatic Colorectal Cancer Pa tients: Outcomes and Prognostic Factors After Long-Term Follow-Up[J]. Clin C olorectal Cancer,2017,16(1):58-64. DOI:10.1016/j.clcc.2016.07.004.

[315] Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiothe rapy for colorectal liver metastases: a pooled analysis[J]. Cancer,2011,117(17):4060-4069. DOI:10.1002/cncr.25997.

[316] Hong TS, Ritter MA, Tomé WA, et al. Intensity-modulated radiati on therapy: emerging cancer treatment technology[J]. Br J Cancer, 2005, 92 (10): 1819-1824. DOI: 10. 1038/sj. bjc.6602577.

[317] Meyer J, Czito B, Yin FF, et al. Advanced radiation therapy techn ologies in the treatment of rectal and anal cancer: intensity-modulated photon therapy and proton therapy[J]. Clin Colorectal Cancer,2007,6(5):348-356. DOI: 10.3816/CCC.2007.n.003.

[318] Topkan E, Onal HC, Yavuz MN. Managing liver metastases with confo rmal radiation therapy[J]. J Support Oncol,2008,6(1):9-13, 15.

[319] Schefter TE, Kavanagh BD, Timmerman RD, et al. A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases[J]. Int J Rad iat Oncol Biol Phys,2005,62(5):1371-1378. DOI:10.1016/j.ijrobp.2005.01.002.

[320] Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies[J]. Int J Radiat Oncol Biol Phys,2010,78(2):486-493. DOI:10.1016/j.ijrobp.2009.08. 020.

[321] Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stere otactic body radiation therapy (SBRT) for limited hepatic metastases[J]. Int J Radiat Oncol Biol Phys,2007,67(3):793-798. DOI:10.1016/j.ijrobp.2006.10.025.

[322] Gruenberger B, Tamandl D, Puhalla H, et al. Bevacizumab plus XEL OX as neoadjuvant chemotherapy for patients with potentially curable metastatic colorectal cancer[J]. J Clin Oncol,2007,25(18 Suppl):179s.

[323] Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorect al cancer: results from a large observational cohort study (BRiTE)[J]. J Clin Oncol,2008,26(33):5326-5334. DOI:10.1200/JCO.2008.16.3212.

[324] Welch S, Spithoff K, Rumble RB, et al. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: a systematic review[J]. Ann Oncol, 2010, 21(6):1152-1162. DOI:10.1093/annonc/mdp533.

[325] Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and c etuximab in metastatic colorectal cancer[J]. N Engl J Med,2009,360(6):563-572 . DOI:10.1056/NEJMoa0808268.

[326] Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase Ⅲ B tr ial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy a nd bevacizumab alone for metastatic colorectal cancer[J]. J Clin Oncol, 2009, 2 7(5):672-680. DOI: 10.1200/JCO.2008.19.8135.

[327] Spigel DR, Greco FA, Waterhouse D, et al. Phase Ⅱ trial of FOLFO X6, bevacizumab, and cetuximab in the first-line treatment of metastatic colore ctal cancer[J]. Clin Adv Hematol Oncol,2010,8(7): 480-485. DOI:10.3816/ccc.20 10.n.014.

[328] Sato Y, Matsusaka S, Suenaga M, et al. Cetuximab could be more ef fective without prior bevacizumab treatment in metastatic colorectal cancer pati ents[J]. OncoTargets and Therapy,2015,8:3329-3336.DOI: 10.2147/OTT.S89241.

[329] Raoul JL, Van Laethem JL, Peeters M, et al. Cetuximab in combinat ion with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) in the initial treatm ent of metastatic colorectal cancer: a multicentre two-part phase Ⅰ/Ⅱ study[J]. BMC Cancer,2009,9:112. DOI:10.1186/1471-2407-9-112.

[330] Van Cutsem E, Kohne CH, Láng I, et al. Cetuximab plus irinotecan , fluorouracil, and leucovorin as first-line treatment for metastatic colorecta l cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status[J]. J Clin Oncol,2011,29(15):2011-2019. DOI:10.1200/JCO.2010. 33.5091.

[331] Pietrantonio F, Cremolini C, Petrelli F, et al. First-line anti-EGFR monoclonal antibodies in panRAS wild-type metastatic colorectal cancer: A systematic review and meta-analysis[J]. Crit Rev Oncol Hematol, 2015, 96(1): 1 56-166. DOI: 10.1016/j.critrevonc.2015.05.016.

[332] De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type s tate predicts survival and is associated to early radiological response in metas tatic colorectal cancer treated with cetuximab [J]. Ann Oncol, 2008, 19(3): 508-5 15. DOI: 10.1093/annonc/mdm496.

[333] Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutation s and benefit from cetuximab in advanced colorectal cancer [J]. N Engl J Med, 20 08, 359(17): 1757-1765. DOI: 10.1056/NEJMoa0804385.

[334] Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required f or panitumumab efficacy in patients with metastatic colorectal cancer[J]. J Cl in Oncol, 2008, 26(10): 1626-1634. DOI: 10.1200/JCO.2007.14.7116.

[335] Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of KRAS an d BRAF in stage Ⅱ and Ⅲ resected colon cancer: results of the translational st udy on the PETACC-3, EORTC 40993, SAKK 60-00 trial[J]. J Clin Oncol, 2010, 28(3): 466-474. DOI: 10.1200/JCO.2009.23.3452.

[336] Price TJ, Hardingham JE, Lee CK, et al. Impact of KRAS and BRAF G ene Mutation Status on Outcomes From the Phase Ⅲ AGITG MAX Trial of Capecitabin e Alone or in Combination With Bevacizumab and Mitomycin in Advanced Colorectal Cancer [J]. J Clin Oncol, 2011, 29(19): 2675-2682. DOI: 10.1200/JCO.2010.34.5520.

[337] Saridaki Z, Papadatos-Pastos D, Tzardi M, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic c olorectal patients′ outcome[J]. Br J Cancer, 2010, 102(12): 1762-1768. DOI: 10.1 038/sj.bjc.6605694.

[338] Tveit K, Guren T. randomized phase Ⅲ study of 5-Fluorouracil/fo linate/oxaliplatin given continously or intermittently with or without cetuximab , as firstline treatment of metastatic colorectal cancer: The NORDIC Ⅶ study (N CT00145314)[J]. Ann Oncol, 2010, 21: LBA 20.

[339] Package Insert. Cetuximab (Erbitux)[M]. Branchburg, NJ: ImClone Systems Incorporated, 2013.

[340] Hoff PM, Eng C, Adinin RB, et al. Preliminary results from a phas e Ⅱ study of FOLFIRI plus bevacizumab as rst-linetreatment for metastatic colo rectal cancer (mCRC)[J]. J Clin Oncol, 2006, 24 Suppl: 165S.

[341] Van Cutsem E, Rivera F, Berry S, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metas tatic colorectal cancer: the BEAT study [J]. Ann Oncol, 2009, 20(11): 1842-1847. DOI: 10.1093/annonc/mdp233.

[342] López R, Salgado M, Reboredo M, et al. A retrospective observati onal study on the safety and efficacy of first-line treatment with bevacizumab combined with FOLFIRI in metastatic colorectal cancer[J]. Br J Cancer, 2010, 103 (10): 1536-1541. DOI: 10.1038/sj.bjc.6605938.

[343] Chaudhury P, Hassanain M, Bouganim N, et al. Perioperative chemot herapy with bevacizumab and liver resection for colorectal cancer liver metastas is[J]. HPB (Oxford), 2010, 12(1): 37-42. DOI: 10.1111/j.1477-2574.2009.00119.x.

[344] Jang HJ, Kim BJ, Kim JH, et al. The addition of bevacizumab in th e first-line treatment for metastatic colorectal cancer: an updated meta-analy sis of randomized trials[J]. Oncotarget, 2017, 8(42): 73009-73016. DOI: 10.18632/ oncotarget.20314.

[345] Cartwright TH, Yim YM, Yu E, et al. Survival outcomes of bevacizu mab beyond progression in metastatic colorectal cancer patients treated in US co mmunity oncology[J]. Clin Colorectal Cancer, 2012, 11(4): 238-246. DOI: 10.1016/j .clcc.2012.05.005.

[346] Hamamoto Y, Yamaguchi T, Nishina T, et al. A phase Ⅰ/Ⅱ study of XELIRI plus bevacizumab as second-linechemotherapy for Japanese patients with metastatic colorectal cancer (BIX study)[J]. Oncologist, 2014, 19(11): 1131-1132 . DOI: 10.1634/theoncologist.2014-0159.

[347] Masi G, Salvatore L, Boni L, et al. Continuation or reintroductio n of bevacizumab beyond progression to first-line therapy in metastatic colorec tal cancer: final results of the randomized BEBYP trial[J]. Ann Oncol, 2015, 26(4): 724-730. DOI: 10.1093/annonc/mdv012.

[348] Bennouna J, Phelip JM, André T, et al. Observational Cohort Stud y of Patients With Metastatic Colorectal Cancer Initiating Chemotherapy in Combi nation With Bevacizumab (CONCERT)[J]. Clin Colorectal Cancer, 2017, 16(2): 129-1 40.e4. DOI: 10.1016/j.clcc.2016.07.013.

[349] Yin C, Ma G, Rong Y, et al. The Efficacy of Bevacizumab in Differ ent Line Chemotherapy for Chinese Patients with Metastatic Colorectal Cancer[J]. J Cancer, 2016, 7(13): 1901-1906. DOI: 10.7150/jca.15802.

[350] D′Angelica M, Kornprat P, Gonen M, et al. Lack of evidence for i ncreased operative morbidity after hepatectomy with perioperative use of bevaciz umab: a matched case-control study[J]. Ann Surg Oncol, 2007, 14(2): 759-765. DO I: 10.1245/s10434-006-9074-0.

[351] Reddy S K, Morse M A, Hurwitz H I, et al. Addition of Bevacizumab to Irinotecan- and Oxaliplatin-BasedPreoperative Chemotherapy Regimens Does N ot Increase Morbidity after Resection of Colorectal LiverMetastases[J]. J Am C oll Surg, 2008, 206(1): 96-106. DOI: 10.1016/j.jamcollsurg.2007.06.290.

[352] Starlinger P, Alidzanovic L, Schauer D, et al. Neoadjuvant bevaci zumab persistently inactivates VEGF at the time of surgery despite preoperative cessation[J]. Br J Cancer, 2012, 107(6): 961-966. DOI: 10.1038/bjc.2012.342.

[353] Shitara K, Yamazaki K, Uetake H, et al. Randomized phase Ⅱ study of regorafenib followed by cetuximab versus reverse sequence for wild-type KRA S metastatic colorectal cancer previously treated with fluoropyrimidine, oxalipl atin, and irinotecan (REVERCE)[J]. J Clin Oncol, 2018, 32(15 Suppl): TPS3662-TPS .

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