



· 论 著 ·

胃癌同时性肝转移肝切除的疗效及预后分析

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[摘要] 背景与目的: 胃癌同时性肝转移 (gastric cancer with synchronous liver metastases, GCLM) 患者是否接受肝切除仍存在争议。本研究通过分析GCLM患者的临床病理学特征及治疗方式, 探究其与患者预后的关系, 希望为该病的临床治疗及预后评价提供参考依据。方法: 回顾性分析2006年3月—2018年8月复旦大学附属肿瘤医院收治的经术后病理学检查诊断为胃腺癌, 影像学检查提示伴有肝转移的患者资料, 包括性别、年龄、原发灶大小、部位、浸润深度、淋巴结转移、分化程度、肝转移灶大小、分布、数目、治疗方法及甲胎蛋白 (alpha fetoprotein, AFP)、癌胚抗原 (carcinoembryonic antigen, CEA) 等肿瘤标志物水平, 并进行随访。采用Kaplan-Meier生存曲线分析患者的总生存期 (overall survival, OS), 用log-rank检验进行单因素分析, COX回归模型进行多因素分析, 探究影响GCLM患者生存的独立预后因素, 通过亚组分析筛选最佳的肝切除对象。结果: 79例纳入本研究的GCLM患者的中位发病年龄为63岁, 男女比例为5.58:1.00。中位OS为11个月, 1、3和5年OS率分别为46.0%、23.3%和6.9%。单因素分析结果显示, 影响OS的因素包括胃原发灶大小、分化程度、肝转移灶的分布、确诊时血清AFP水平及肝切除。多因素分析结果显示, 影响OS的独立危险因素为双叶肝转移 (HR=37.253, $P=0.008$), 保护因素为肝切除 (HR=0.149, $P=0.044$)。进一步亚组分析显示, 对转移灶最大直径 ≤ 3 cm、单发肝转移灶、单叶转移、确诊时血清AFP及CEA水平正常者, 肝切除有可能改善其OS。结论: 回顾性研究表明肝切除有可能改善部分GCLM患者的预后。

[关键词] 胃癌; 同时性肝转移; 肝切除; 预后

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Analysis of efficacy of hepatectomy and prognostic risk factors in patients with gastric cancer with synchronous liver metastasis ZOU Ting, LIU Xiaowen (Department of Gastric Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)

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[Abstract] **Background and purpose:** Whether patients with gastric cancer with synchronous liver metastases (GCLM) receive hepatectomy remains controversial. In this study, we analyzed the clinicopathological characteristics and treatment modalities of patients with GCLM to investigate their relationship with prognosis, hoping to provide a reference basis for the clinical treatment and prognostic evaluation of this disease. **Methods:** The patients admitted to the Fudan University Shanghai Cancer Center from March 2006 to August 2018 who were diagnosed with gastric adenocarcinoma by postoperative pathology and liver metastases by imaging examination were retrospectively analyzed, including gender, age, primary tumor size, location, depth of invasion, lymph node metastasis, differentiated degree, metastatic tumor size, distribution, number, the treatment, serum alpha fetoprotein (AFP) and carcinoembryonic antigen (CEA) level at diagnosis, and combined with follow-up investigation. The Kaplan-Meier method was used to analyze the overall survival (OS) of the patients, log-rank test was applied for univariate analysis, and the COX regression model was used for multifactorial analysis to explore the independent prognostic factors affecting the OS of patients with GCLM. The best target for hepatectomy was screened by further subgroup analysis. **Results:** The median age of onset in 79 patients with GCLM admitted to this study was 63 years, and the male to female ratio was 5.58 vs 1.00. The median OS was 11 months, the 1-year, 3-year and 5-year OS rates were 46.0%, 23.3%, and 16.9%, respectively. The results of the univariate analysis showed that the factors affecting OS include primary tumor size, differentiated degree, hepatic tumor distribution, serum AFP level at diagnosis and hepatectomy. The results of multivariate analysis showed that the independent risk factor affecting OS was bilateral liver metastasis

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(HR=37.253, $P=0.008$), and the protective factor was hepatectomy (HR=0.149, $P=0.044$). Further subgroup analysis showed that hepatectomy improved OS in the subgroup with metastatic tumor size ≤ 3 cm, single liver metastasis, unilateral metastasis and normal serum AFP and CEA levels at diagnosis. **Conclusion:** Retrospective study suggests that hepatectomy may improve the prognosis of some patients with GCLM.

[**Key words**] Gastric cancer; Synchronous liver metastases; Hepatectomy; Prognosis

在全球范围内,胃癌是癌症相关死亡的主要原因之一^[1]。因为缺乏特异性的症状,许多患者在初诊时已是晚期^[2-4]。肝脏是胃癌最常见的远处转移部位,美国国家综合癌症网络(National Comprehensive Cancer Network, NCCN)指南推荐了许多替代疗法及多学科治疗方案,包括系统性化疗、肝动脉化疗栓塞、射频消融、分子靶向治疗、支持治疗及其他姑息治疗。最近一些证据表明,对胃癌和肝转移同时进行R0切除能够提高胃癌同时性肝转移(gastric cancer with synchronous liver metastases, GCLM)患者的生存率^[5-6]。目前,对GCLM患者是否进行肝切除仍存在争议^[7],因为GCLM患者都有其各自的临床病理学特点,存在其他远处转移、广泛淋巴结转移、双侧多发转移或严重内科合并症的GCLM患者不适合肝切除^[8]。因此,筛选最佳的肝切除对象尤为关键。本研究回顾性分析79例GCLM患者的临床病理学资料,探讨影响预后的因素及肝切除的疗效,旨在为GCLM的治疗模式探索提供参考。

1 资料和方法

1.1 一般资料

收集复旦大学附属肿瘤医院2006年3月—2018年8月收治的GCLM患者的临床资料并进行分析。纳入标准:①病理学检查确诊为胃腺癌,经影像学或病理学检查证实为肝转移;②临床诊疗记录及后续随访资料完整。排除标准:①胃癌除肝转移外还伴有其他脏器转移,如肺、卵巢、腹膜转移(纳入的患者均在术中或探查后发现无腹膜转移);②患有其他部位原发性肿瘤;③其他病理学类型的胃癌(图1)。

1.2 观察指标和治疗情况

观察指标包括性别、年龄、胃癌原发灶大小及部位、分化程度、淋巴结转移、浸润深度、肝转移灶大小及分布、是否肝切除等。术后TNM分期参照美国癌症联合会(American Joint Committee on Cancer, AJCC)/国际抗癌联盟(Union for International Cancer Control, UICC)胃癌第8版TNM分期标准。79例GCLM患者中,胃切除联合肝切除者34例(43%),单纯胃切除者22例(28%),开腹探查者23例(29%)。参照NCCN胃癌临床实践指南(2022年第2版),患者术后均根据其身体情况行化疗、肝动脉化疗栓塞、射频消融或分子靶向治疗等综合治疗,小部分患者行新辅助化疗,化疗方案以铂类药物、5-氟尿嘧啶及紫杉类药物为主。

1.3 随访

通过术后定期复查、电话或短信的方式随访,随访起始时间定义为首次诊断为胃癌同时性肝转移的时间,随访时间截至2020年9月或患者死亡。

1.4 统计学处理

所有数据采用SPSS 25.0软件进行统计分析,采用log-rank检验进行生存分析,Kaplan-Meier法进行单因素分析,COX比例风险回归模型进行多因素分析。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 临床病理学特征

成功纳入的患者共79例,男性67例(85%),女性12例(15%)。中位发病年龄为63(42~79)岁,其中 ≤ 60 岁的为31例(39%), > 60 岁的为48例(61%)。肝切除患者34例(43%),未行肝切除患者45例

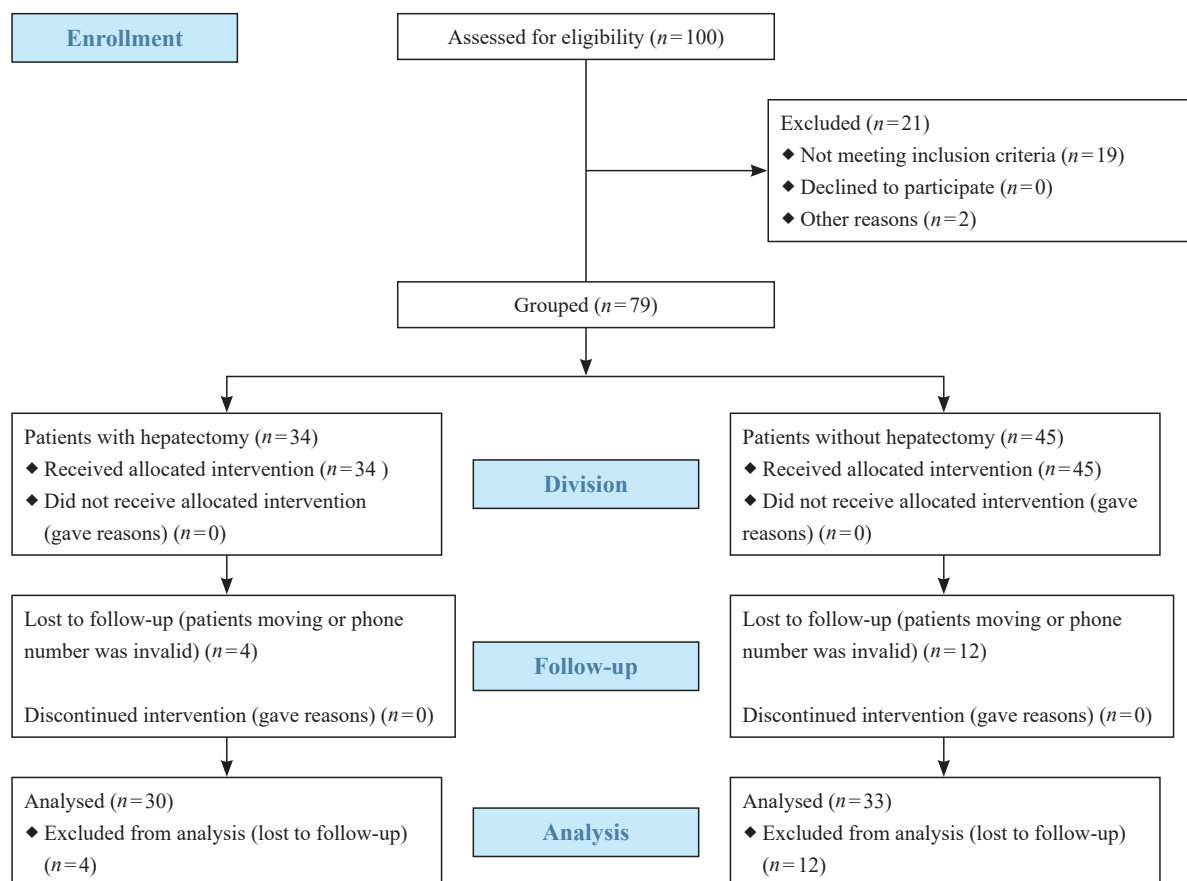


图1 研究设计及患者筛选流程图

Fig. 1 The flow chart of study design and patient inclusion

(57%)。所有患者均为同时性肝转移，无腹膜转移。患者的临床病理学特征见表1。

2.2 GCLM患者预后相关因素分析

79例GCLM患者中位总生存期(overall survival, OS)为11个月,1、3和5年OS率分别为46.0%、23.3%和6.9%。单因素分析显示,影响预后的因素包括原发灶大小($P=0.046$)、分化程度($P=0.001$)、肝转移灶的分布($P=0.038$)、确诊时血清甲胎蛋白(alpha fetoprotein, AFP)水平($P<0.001$)及肝切除($P<0.001$),而年龄、性别、原发灶的部位、浸润深度、淋巴结转移、肝转移灶的大小和数目以及确诊时血清癌胚抗原(carcinoembryonic antigen, CEA)水平与GCLM患者预后无关($P>0.05$)。多因素分析显示,肝转移灶的分布($HR=37.253$, $P=0.008$)及肝切除($HR=0.149$, $P=0.044$)是影响GCLM患者OS

的独立预后因素(表2,图2)。

2.3 肝切除对GCLM患者预后的影响

根据是否行肝切除将79例患者分为两组,肝切除组34例和非肝切除组45例。肝切除组与非肝切除组患者1、3及5年OS率分别为63.3%、45.7%、32.0%和30.3%、9.1%、3.0%,两组患者中位OS分别为35和8个月。亚组分析结果显示,转移灶的最大直径 ≤ 3 cm、单发肝转移灶、单叶转移、确诊时血清AFP及CEA水平正常的亚组,肝切除有可能改善其OS(图3)。

3 讨论

随着胃镜筛查的普及和治疗手段的发展,胃癌患者的预后有了显著改善。胃癌同时性肝转移发生率为2.0%~9.6%,低于结直肠癌。胃癌肝转移目前有手术、姑息化疗、射频消融等治

表1 79例胃癌同时性肝转移患者临床病理学特征

Tab.1 Clinicopathological data of 79 patients with gastric cancer with synchronous liver metastases

Factor	n (%)	Factor	n (%)
Gender		Hepatic tumor distribution	
Male	67 (85)	Unilateral	50 (63)
Female	12 (15)	Bilateral	28 (36)
Age/year		NA	1 (1)
≤60	31 (39)	Metastatic tumor number	
>60	48 (61)	Single	41 (52)
Primary tumor size D/cm		Multiple	37 (47)
≤5	37 (47)	NA	1 (1)
>5	37 (47)	Hepatectomy	
NA	5 (6)	Yes	34 (43)
Location		No	45 (57)
Upper-middle	37 (47)	Peritoneal metastasis	
Lower	39 (49)	Yes	0 (0)
NA	3 (4)	No	79 (100)
Depth of invasion		Serum AFP level at diagnosis	
T ₁₋₂	7 (9)	Normal	50 (63)
T ₃₋₄	42 (53)	Elevated	7 (9)
NA	30 (38)	NA	22 (28)
Lymph node metastasis		Serum CEA level at diagnosis	
N ₀₋₁	14 (18)	Normal	32 (40)
N ₂₋₃	35 (44)	Elevated	25 (32)
NA	30 (38)	NA	22 (28)
Differentiated degree		Synchronous liver metastases	
Well/moderate	25 (32)	Yes	79 (100)
Poor	30 (38)	No	0 (0)
NA	24 (30)		
Metastatic tumor size D/cm			
≤3	41 (52)		
>3	7 (9)		
NA	31 (39)		

AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen; NA: Not accessed.

疗方法, 但大多数患者的治疗效果并不理想。REGATTA试验结果表明, 与单纯化疗相比, 姑息性切除加化疗并不能提高IV期胃癌患者的

OS率, 这让人质疑手术在转移性胃癌中的价值^[9]。鉴于新出现的证据证明肝转移灶切除对少数转移性胃癌患者有益^[4, 10-13], 我们对胃癌

表2 影响胃癌同时性肝转移患者OS的单因素及多因素分析

Tab. 2 Univariate and multivariate analysis of OS in patients with gastric cancer with synchronous liver metastases

Data	Univariate analysis		Multivariate analysis	
	<i>P</i> value	HR	95% CI	<i>P</i> value
Gender	0.992			
Age/year	0.879			
Primary tumor size <i>D</i> /cm	0.046	0.662	0.164-2.666	0.562
Location	0.136			
Depth of invasion	0.087			
Number of lymph nodes	0.087	2.055	0.359-11.746	0.418
Differentiated degree	0.001	0.185	0.034-1.011	0.052
Metastatic tumor size <i>D</i> /cm	0.360	0.593	0.092-3.812	0.582
Hepatic tumor distribution	0.038	37.253	2.577-538.447	0.008
Metastatic tumor number	0.456	1.790	0.303-10.581	0.521
Hepatectomy	0.000	0.149	0.023-0.948	0.044
Serum AFP level at diagnosis	0.000	8.554	0.851-86.032	0.068
Serum CEA level at diagnosis	0.149			

CEA: Carcinoembryonic antigen; AFP: Alpha-fetoprotein; HR: Hazard ratio; CI: Confidence intervals.

同时性肝转移患者进行了回顾性分析。

研究^[5-6]表明,胃癌同时性肝转移患者接受肝切除后的OS率显著提高。本研究34例GCLM患者同时行根治性胃切除和肝切除,中位生存时间为35个月,1、3及5年的OS率分别为63.3%、45.7%和32.0%。多因素分析发现,肝切除及肝转移灶的部位是GCLM患者的独立预后因素。值得注意的是,目前的研究结果应该考虑到它的局限性。在本研究中,我们仅根据患者是否行肝切除分为肝切除组和非肝切除组,未考虑新辅助化疗或胃切除等混杂因素对研究结果的影响。

由于肝切除并不适用于所有的GCLM患者,因此,患者筛选在GCLM治疗中尤为关键。由于缺乏胃癌肝转移手术治疗的随机对照临床研究,目前还没有明确的患者选择标准。我们的亚组分析结果显示,单个肝转移灶、肝转移灶直径 ≤ 3 cm及单叶分布的患者更适合行肝切除。Ochiai等^[14]报道,在没有原发胃癌浆膜侵犯的患者中,应该尝试肝切除。就肝转移病灶的数量和大小而言,文献^[15-16]报道,孤立转移或直径

< 3 cm的肝转移瘤患者可能会有更好的OS率。有研究^[17]推荐对单发肝转移伴原发灶淋巴结转移分期 N_0 或 N_1 期的患者行肝切除治疗。在本研究中,由于 T_1 或 T_2 、 N_0 或 N_1 期的样本量过小,未对该因素进行亚组分析。当然,行同步肝切除的患者,必须原发灶可切除、无肝外转移以及具有良好的器官功能储备^[18]。总的来说,在考虑行同步肝切除时,原发肿瘤侵犯浆膜或较高的原发肿瘤 N 分期、肝转移灶多发或直径 ≥ 3 cm和不能R0切除可能是非肝切除的选择标准^[15, 19-21]。

肝转移灶的局部治疗方式还包括射频消融(radiofrequency ablation, RFA),用于治疗因肿瘤数量、位置或大小等因素限制而无法切除的肝转移灶。存在以下情况时不推荐RFA,一种是远端胆道梗阻,导致胆管内压力过高,增加病灶胆汁渗漏风险。其次,靠近肝包膜的病变,特别是位于膈下间隙的病变,因为这些患者在RFA治疗后很可能发生腹腔出血。此外,位于尾状叶及胆囊或肝血管附近(距离小于10 mm)的肿瘤也不适合做RFA^[22]。对于多发肝转移瘤,可考虑

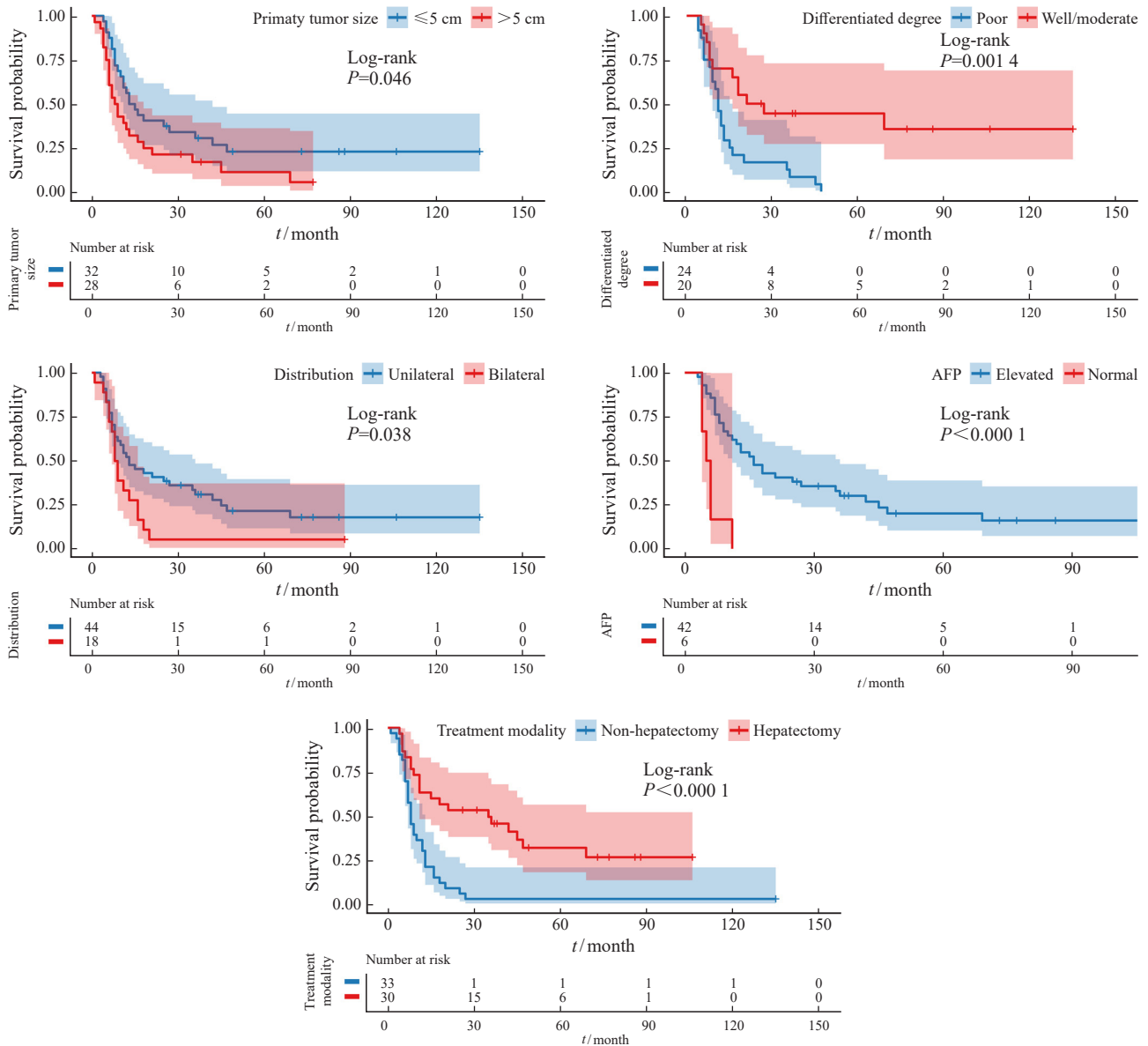


图2 部分预后变量的生存曲线

Fig. 2 Survival curves for several prognostic variables

RFA联合肝切除。

在本研究中,小部分患者行术前化疗,我们未就术前化疗进一步探究其对GCLM患者预后的影响。专家共识^[23]建议,对于I型胃癌肝转移(live metastasis from gastric cancer, LMGC),可预先同时切除或术前化疗后同时切除,I型LMGC是指仅限于技术上可切除的1~3个肝转移瘤,其最大直径不超过4 cm,或位于单侧肝脏而不累及主要血管或胆管的LMGC。根据一项国际调查,对于同时患有LMGC的患者,欧洲更常推荐术前化疗,而在日本,前期手术是首选方

法^[24]。目前,由于缺乏比较研究,术前化疗的真正益处还不清楚。术前化疗最重要的优势似乎是更好地选择患者^[8],因为化疗应答者的无进展生存(progression-free survival, PFS)率高于无应答的患者^[25]。除化疗外,近期有研究^[26]表明,免疫治疗对胃癌肝转移患者也有一定的疗效。

这是一项回顾性研究,部分患者临床病理学资料不够完整,可能对研究结果造成影响。此外,样本量相对较小也局限了本次研究结果,目前发表的大多数相关研究也只有少量的病例,这

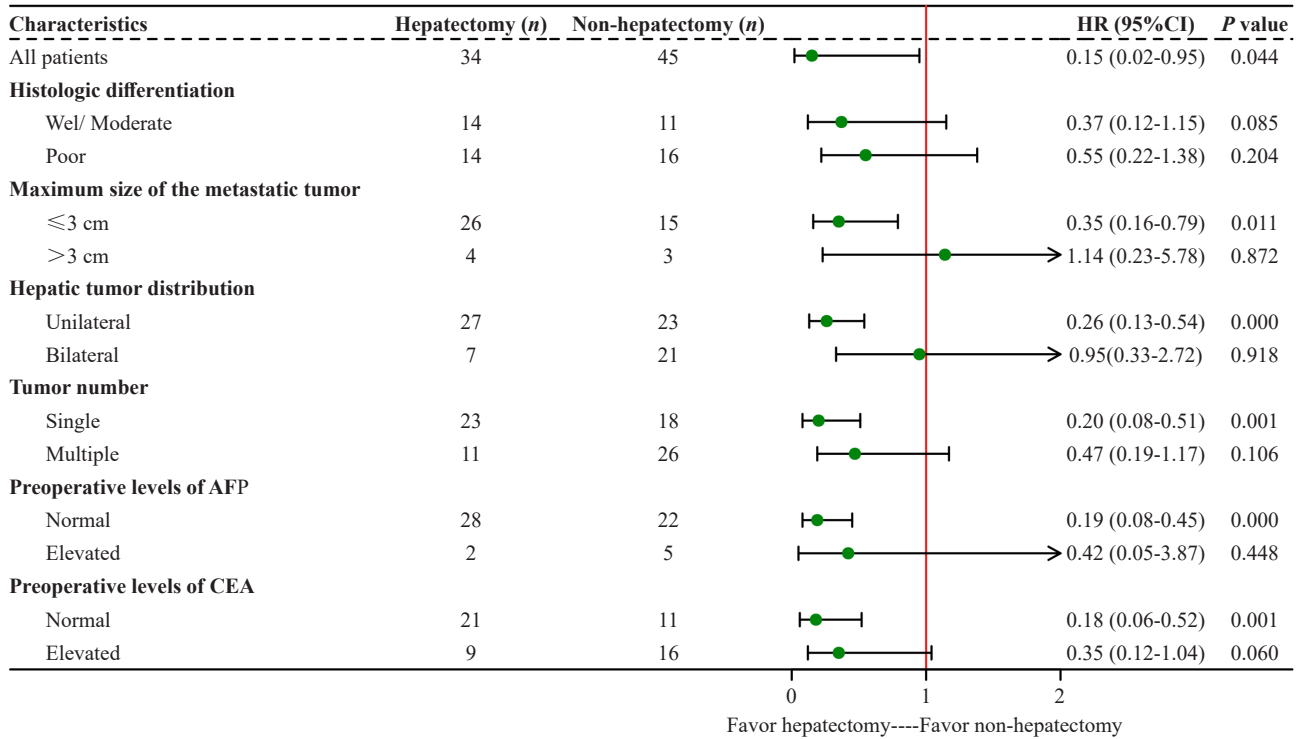


图3 79例胃癌同时性肝转移患者预后的亚组分析

Fig. 3 Overall survival by subgroup analysis of 79 patients with gastric cancer with synchronous liver metastases

既反映了本研究相对严格的纳入标准，也反映了接受肝切除的患者数量较少。因此，我们应当谨慎看待研究结果。为了克服这些局限性，需要未来开展多中心研究，或更好的随机对照临床研究，评估积极的手术方法对这些患者预后的影响。

利益冲突声明：所有作者均声明不存在利益冲突。

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《中国癌症杂志》被国内外著名数据库收录最新进展

截至2023年6月,《中国癌症杂志》已被《中文核心期刊要目总览(2020年版)》、中国科技论文统计源期刊(中国科技核心期刊)数据库、中文生物医学期刊文献数据库(CMCC)、中国生物医学期刊引文数据库(CMCI)、中国生物文献数据库、《科技期刊世界影响力指数(WJCI)报告(2021年版)》、DOAJ数据库、SCOPUS数据库、EMBASE数据库、《化学文摘》(CA)、JST数据库、Index of Copernicus以及WHO西太平洋地区医学索引(WPRIM)等数据库收录。2012年被评为《复旦大学学位与研究生教育国内期刊指导目录》A类期刊。

《中国癌症杂志》编辑部