

TACE 联合索拉非尼治疗肝细胞癌的影像学分析

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[摘要] **目的** 分析TACE联合索拉非尼治疗肝细胞癌(HCC)的影像学表现, 评估联合治疗的疗效, 寻找索拉非尼治疗HCC可能的影像学证据。**方法** 2008年8月至2010年10月收治的30例HCC患者, 男性25例, 女性5例, 年龄30~68岁, 平均年龄56岁。患者接受TACE联合索拉非尼治疗。影像学(CT/MR)随访6~20个月, 平均9个月, 分析影像学表现, 根据实体肿瘤RECIST修订标准进行疗效评估。**结果** 根据病灶碘油沉积的分布将病灶的CT图像表现分为四型。I型——病灶无碘油沉积, 全部或部分呈低密度。II型——病灶中心碘油沉积, 周围呈低密度。III型——病灶碘油致密沉积。IV型——病灶碘油沉积区与低密度区混杂分布。30例患者中出现I型表现5例, II型表现3例, III型表现6例, IV型表现15例, 一周后因严重腹痛停药1例。结合CT和MR动态增强扫描图像将病灶进一步分为肿瘤有存活及无存活两种类型。其中, I型表现的5例患者肿瘤存活3例, 无肿瘤存活2例, 低密度区无肿瘤存活。II型表现的3例患者中, 肿瘤存活2例, 无肿瘤存活1例。III型表现6例患者中肿瘤存活者2例, 无肿瘤存活者4例。IV型表现15例患者中肿瘤存活15例。出现I型表现的时间为2~8个月, 平均5.3个月。随访第5个月, 根据实体肿瘤RECIST修订标准评估疗效, 29例患者出现CR 3例, PR 6例, SD 11例, PD 9例, DCR 68.97%。**结论** 影像学可反映TACE联合索拉非尼治疗HCC的疗效, I型表现中病灶无碘油沉积的坏死性低密度区可能体现索拉非尼参与治疗的结果。

[关键词] 肝动脉化疗栓塞; 索拉非尼; 肝细胞癌; 联合治疗; CT/MR

Imaging analysis of hepatocellular carcinoma treated by TACE combined with sorafenib

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[Abstract] **Objective** To analyze imaging manifestation of hepatocellular carcinoma treated by TACE combined with sorafenib, assess the curative effect of combined therapy and find out the possible imaging evidence of sorafenib for HCC. **Methods** From August 2008 to October 2010, 30 cases (mean age, 56 years; range, 30 ~ 68 years) of HCC were treated by TACE combined with sorafenib. Follow-up was performed by CT/MR from 6 to 20 months, mean 9 months. Follow-up images were analyzed. **Results** Four types of CT imaging were found according to the distribution of lipiodol deposition in the lesion. Type I—the lesion displayed complete or partial low density without lipiodol deposition. Type II—the lesion displayed peripheral low density with central lipiodol deposition. Type III—the lesion displayed compact lipiodol deposition. Type IV—low density areas intermingled with lipiodol deposition areas in the lesion. Type I (n=5), Type II (n=3), Type III (n=6), and Type IV (n=15) were found in 29 cases. One patient stopped taking sorafenib after one week due to severe abdominal pain. The patients were divided into viable group and inviable group based on the dynamic contrast enhanced CT or MR imaging. Three patients had viable tumor and 2 patients had inviable tumor in Type I. The low density areas in Type I was inviable. Two patients had viable tumor and 1 patient had inviable tumor in Type II. Two patients had viable tumor and 4 patients had inviable tumor in Type III. All patients in Type IV had viable tumor. The low density areas in Type I were formed in the second to eighth follow-up month, mean 5.3 months. At the fifth follow up month, CR (n=3), PR (n=6), SD (n=11) and PD (n=9) were found in 29 cases on the basis of revised RECIST. The DCR was 68.97%. **Conclusion** CT and MR images can reflect curative effect of hepatocellular carcinoma treated by TACE combined with sorafenib. The low density area which is completely necrotic without lipiodol deposition in Type I may be caused by sorafenib.

[Key words] Transcatheter arterial chemoembolization; Sorafenib; Hepatocellular; Carcinoma combined therapy; CT/MR

2008年肝细胞肝癌(hepatocellular carcinoma, HCC)巴塞罗那临床肝癌分级(Barcelona clinic liver cancer staging classification, BCLC)及治疗策略中, B期患者首选经导管肝动脉化疗栓塞治疗(transcatheter arterial chemoembolization, TACE), 而C期患者则推荐使用“甲磺酸索拉非尼片”(多吉美)治疗^[1]。但TACE往往使肿瘤难以完全坏死, 侧支动脉形成导致的肿瘤残留、复发和远处转移仍是TACE治疗的难题。本研究采用TACE联合多吉美治疗30例

HCC患者, 应用CT/MR定期随访, 探讨TACE联合多吉美治疗HCC的疗效, 现报告如下。

1 资料与方法

1.1 临床资料

2008年8月至2010年10月我科收治的30例HCC患者, 男性25例, 女性5例, 年龄30~68岁, 平均年龄56岁。所有患者结合病史、实验室及影像学检查临床诊断为HCC。根据BCLC分期指导原则, AFP阴性(<400ng/ml)、乙肝阳性患者, 有两个以上影像学证据(CT、MR)支持HCC诊断。30例患者肝功能Child-Pugh分级A级18例, B级12例。BCLC分期A期5例, B期12例, C期13例。所有患者乙肝表面抗原阳性。AFP阳性(≥400ng/ml)21例, 阴性9例(<400ng/ml)。合并胸椎

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转移1例, 双肺转移6例, 下腔静脉癌栓2例, 肝静脉癌栓6例, 门静脉主干癌栓5例。

2 方法

2.1 介入治疗方法

患者完善相关检查及术前准备, 仰卧DSA手术床接受TACE治疗。使用22G穿刺针采用Seldinger法穿刺右侧股动脉, 穿刺成功后置入5F导管鞘(COOK公司, 美国)。0.035inch导丝(Terumo公司, 日本)引导下, 使用5F普通RH导管(COOK公司, 美国)插管至腹腔干动脉, 肝总动脉及肝固有动脉造影。造影明确肿瘤供血动脉及肿瘤染色范围, 了解有无肝外肿瘤供血动脉, 有无肝动脉-门静脉/肝静脉分流。利用同轴导管技术使用3F微导管(SP, Terumo公司, 日本)超选择性插管至肿瘤供血动脉行TACE治疗。先行表柔吡星30mg+洛铂50mg+5-氟尿嘧啶1.0缓慢肿瘤动脉灌注后, 再用丝裂霉素10mg+超液化碘油10~20ml(混合乳剂)经导管注入行肿瘤血管栓塞。对合并肝动脉-门静脉/肝静脉分流者, 采用PVA颗粒(500 μ g~700 μ g)闭塞分流道后再行化疗栓塞。

2.2 术后治疗及影像学随访

术后12h内监测生命体征, 常规给予护肝、止痛、抗病毒(HBV DNA定量>500)、制酸、预防感染、增强免疫及对症治疗。术后恶心呕吐反应消失即开始口服多吉美治疗, 服用剂量为400毫克/次, 2次/日。术后复查肝功能及生化指标, 达到出院标准者准予出院。出院后所有患者继续口服护肝、抗病毒药物及多吉美治疗。患者前3个月每月接受1次CT/MR随访, 发现肝内病灶复发或病灶碘油沉积不全者根据病情给予第二次或多次TACE治疗。3个月后每两个月接受1次CT/MR随访。随访及再次TACE治疗期间无特殊情况不间断或减少多吉美的服用量。患者死亡或终止服药视为随访终点。

2.3 影像学分型及评估

首先依据病灶碘油沉积的分布进行病灶CT图像分型, 结合CT和MR增强扫描图像将病灶进一步分为肿瘤有存活及无存活两种类型。根据2008年美国肝脏病协会提出的RECIST(Response Evaluation Criteria in Solid Tumors)修订标准进行疗效评估。即: 完全缓解(Complete response, CR)指所有目标病灶动脉期的增强显影均消失; 部分缓解(Partial response, PR)为目标病灶(动脉期增强显影)的直径总和缩小 $\geq 30\%$; 病灶进展(Progressive disease, PD)为目标病灶(动脉期增强显影)的直径总和增加 $\geq 20\%$ 或出现新病灶; 病灶稳定(Stable disease, SD)为缩小未达PR或增加未到PD者。疾病稳定率(disease control rate, DCR)=(CR+PR+SD)/总数。

3 结果

3.1 介入治疗结果

30例患者共接受106次TACE治疗。第一次介入术后开始服用多吉美22例患者, 非第一介入术后开始服用多吉美8例患者。合并胸椎转移的1例患者随访第5个月时行胸椎转移灶栓塞治疗1次。合并下腔静脉癌栓的1例患者随访第6个月行下腔静脉“Z”型支架成形术。合并肝动脉-门静脉/肝静脉分流6例, 分别给予PVA颗粒(500 μ g~700 μ g)栓塞治疗。CT/MR随访6~20个月, 平均随访9个月。随访期间16例患者死亡, 1例死于下腔静脉癌栓脱落导致的肺栓塞, 1例死于心肌梗死, 3例死

于上消化道大出血, 11例死于肝肾功能衰竭。

3.2 CT/MR随访结果(见表1)

对影像学随访结果进行分析总结, 根据病灶碘油沉积的分布将CT图像分为四型。I型——病灶无碘油沉积, 全部或部分呈低密度(如图1、图2)。II型——病灶中心碘油沉积, 周围呈低密度(图3、图4)。III型——病灶碘油致密沉积(图5、图6)。IV型——病灶碘油沉积区与低密度区混杂分布(图7)。30例患者中出现I型表现5例, II型表现3例, III型表现6例, IV型表现15例, 一周后停药1例。根据CT和MR增强扫描图像将病灶进一步分为肿瘤有存活及无存活两种类型。其中, I型

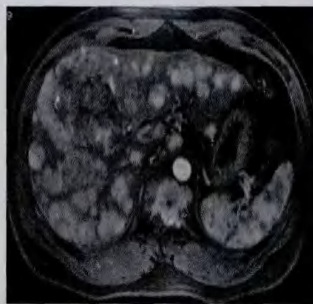


图1

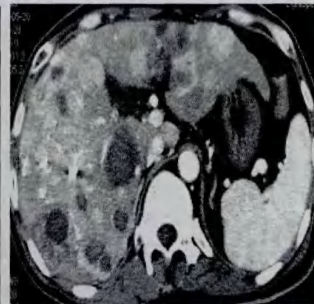


图2

I型。图1、图2为同一病例。男性, 41岁。图1: TACE联合多吉美治疗前MR增强扫描提示肝内多发病灶。图2: 随访第八个月, 患者共接受五次TACE治疗。CT扫描显示肝内多发低密度改变病灶(黑色箭头所示), 增强扫描动脉期低密度区不强化, 病灶内部及周边无碘油沉积。

Type I. Figure 1 and figure 2 were the same case. Male, 41. Figure 1: Dynamic contrast enhanced MR image showed multiple lesions in the liver before combined therapy. Figure 2: Multiple hepatic lesions became low density without lipiodol deposition. Dynamic contrast enhanced CT image showed low density areas had no enhancement on artery phase at the eighth month during follow up period. The patient received five times of TACE.



图3



图4

II型。图3、图4为同一病例。男性, 53岁。图3: TACE联合多吉美治疗前MR增强扫描提示肝S8段肝癌。图4: 随访第4个月, 患者共接受两次TACE治疗。CT显示病灶较前缩小, 中心碘油沉积, 周围呈低密度无强化区(白色箭头所示)。

Type II. Figure 3 and figure 4 were the same case. Male, 53. Figure 3: Dynamic contrast enhanced MR image showed HCC in S8 section of the liver before combined therapy. Figure 4: The lesion displayed peripheral low density with central lipiodol deposition on dynamic contrast enhanced CT image at the fifteenth follow up month. The patient received twice TACE. The size of the lesion was reduced.

表现的5例患者肿瘤存活3例,无肿瘤存活2例,低密度区无肿瘤存活(图8~图10)。II型表现的3例患者中,肿瘤存活2例,无肿瘤存活1例。III型表现6例患者中肿瘤存活2例,无肿瘤存活者4例。IV型表现15例患者中肿瘤存活15例。出现I型表现的时间为2~8个月,平均5.3个月。I型表现5例患者的生存期12~20个月,平均16.5个月。随访第5个月,根据实体肿瘤RECIST修订标准评估疗效,29例患者出现CR3例,PR 6例,SD 11例,PD 9例,DCR 68.97%。

表1 影像学随访结果

分型	例数	肿瘤存活	无肿瘤存活	随访5个月				
				CR	PR	SD	PD	DCR
I型	5	3	2	1	1	1	2	
II型	3	2	1	1	1	0	1	
III型	6	2	4	1	2	2	1	
IV型	15	15	0	0	2	8	5	
合计 (例)	29	22	7	3	6	11	9	68.97%

3.3 多吉美相关不良反应

服用多吉美期间,常见的不良反应有手足反应,腹泻,脱

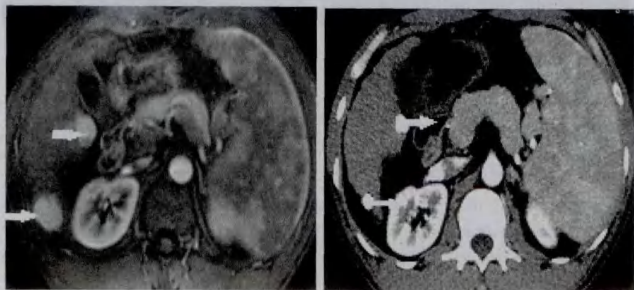


图5

图6

III型。图5、图6为同一患者。男性,35岁。图5:TACE联合多吉美治疗前MR增强扫描提示肝S6、S7段肝癌。图6:随访第八个月,患者共接受两次TACE治疗。CT显示病灶明显缩小,碘油沉积致密(白色箭头所示)。

Type III. Figure 5 and figure 6 were the same case. Male, 35. Figure 5: Dynamic contrast enhanced MR image showed lesions in S6 and S7 section of the liver before combined therapy. Figure 6: The lesions showed compact lipiodol deposition on dynamic contrast enhanced CT image at the eighth month. The patient received twice TACE. The sizes of the lesions were remarkably reduced.

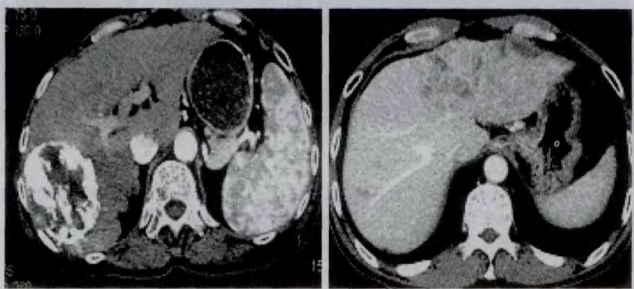


图7

图8

IV型。女性,60岁。图7:TACE联合多吉美治疗1个月后随访CT提示病灶内碘油沉积区与低密度区混杂分布(黑色箭头所示)。

Type IV. Female, 60. Low density areas intermingled with lipiodol deposition areas in the lesion on dynamic contrast enhanced CT image at the first month during follow up period.



图9

图10

图11

I型。图8~图10为同一患者。男性,53岁。图8:TACE联合多吉美治疗前CT增强扫描提示肝左叶肝癌。图9、图10:随访第六个月,患者共接受三次TACE治疗。CT和MR扫描提示病灶周边及内部出现多发无碘油沉积的低密度区(黑色箭头所示),CT和MR增强扫描均证实低密度区完全坏死。

Type I. Figure 8, figure 9 and figure 10 were the same case. Male, 53. Figure 8: Dynamic contrast enhanced CT image showed HCC in the left lobe of the liver before combined therapy. Figure 9 and Figure 10: Peripheral and inside necrotic low density areas were found on dynamic contrast enhanced CT and MR images at the sixth month during follow up period. The patient received three times of TACE.

发,皮疹等。以手足反应及腹泻最为常见。1例患者服药后产生严重腹痛于一周后停止服药。3例患者因不能耐受手足反应减半量服药(400毫克/次,1次/日)。1例患者因介入伤口愈合不良停药2周。其余患者给予相应的治疗及护理后不良反应都能耐受。

4 讨论

4.1 TACE联合多吉美治疗HCC的理论基础

BCLC分期B期患者的中位生存期约16个月,而TACE可以使中位生存期延长至19~20个月^[2]。但TACE在治疗HCC的过程中存在栓塞不完整,栓塞后肿瘤容易建立侧支循环,术后患者血浆及肿瘤内血管内皮生长因子(VEGF)高表达等问题^[3]。最近对HCC的生物学研究表明^[4],在HCC的发生和发展过程中,由表皮生长因子受体(EGFR)、血管内皮生长因子受体(VEGFR)、血小板源性生长因子受体(PDGFR)介导的血管生成信号传导通路起着重要作用^[5],成为重要的HCC分子治疗靶点。索拉非尼(多吉美)是一种口服的多激酶抑制剂,其主要作用靶点为VEGFR-2、VEGFR-3、PDGFR- β 。全球随机、双盲、安慰剂-对照试验研究表明,多吉美可以延长HCC患者肿瘤无进展期(Time to tumor progression, TTP)及总体生存期(Overall survival, OS)^[6-7]。因此,理论上TACE联合多吉美治疗HCC有望取得更好的疗效。

4.2 影像学反映联合治疗的疗效,体现多吉美治疗HCC的可能证据

影像学检查是实体肿瘤RECIST评估的重要环节^[8],2008年美国肝脏病协会提出了存活肿瘤的概念,把肿瘤是否有存活作为疗效评估的一个重要环节。即“目标病灶动脉期的增强显影的变化情况作为判断肿瘤大小变化的标准”。根据这一标准,本组29例患者随访第5个月出现CR3例,PR6例,SD11例,PD9例,DCR达68.97%,生存期均超过6个月。临床常用的影像学检查方法为CT和MR。CT具有较高的密度分辨率,因此可以很好的显示病灶碘油分布情况。但同时由于高密度碘油产生的伪影,当存活肿瘤体积较小并且靠近碘油或位于碘油中央时,影响肿瘤复发的判断^[9-10]。MR具有较高的敏感性,T2WI, DWI及T1WI增强扫描序列可较准确评估TACE术后有无肿瘤

复发^[11-12]。因此我们采用CT检查显示病灶碘油分布的同时,结合CT动态增强扫描,必要时结合MR的T2WI, DWI及T1WI增强扫描序列判断肿瘤有无存活及复发。

根据随访图像所得的四种CT分型中, I型中病灶无任何碘油沉积。同时CT/MR证实低密度区病灶没有活性, 即低密度区呈完全性的坏死, 不同于单纯TACE的临床随访CT表现。肝癌病灶出现坏死的病理生理学机制有两种情况。第一, 肿瘤体积较大, 血供丰富, 肿瘤细胞生长旺盛, 肿瘤中心相对供血不足发生坏死。第二, 肿瘤供血动脉被阻断, 肿瘤缺血, 发生坏死。TACE治疗HCC的理论基础是由于肿瘤组织缺乏枯否细胞及淋巴系统, 碘油可以较长时间沉积于肝癌病灶内, 导致肿瘤缺血, 从而抑制肿瘤的生长, 导致肿瘤死亡。通过CT和MR图像可以看出, I型病灶低密度区内任何碘油沉积, 低密度区位于病灶的周边和内部, 并且呈多中心性融合的趋势。这些影像学表现提示我们病灶出现的坏死并不是由于病灶生长迅速或肿瘤供血动脉被阻断导致的相对或绝对缺血造成的, 可能是多吉美靶向治疗的结果。

回顾分析出现I型CT表现的5例患者的临床资料。5例患者肝内的病灶多为富血供型, BCLC分期C期2例, B期3例, 肝功能Child-Pugh分级A级4例, B级1例。第一次TACE治疗后开始多吉美治疗。治疗过程中无间断或减量服药。出现低密度区的时间多在三个月以后。5例患者的生存期均超过1年, 但出现此种类型的表现对患者的总体生存期有无影响尚待进一步论证。由于病例数目偏少, 无法进行统计学分析。

综上所述, TACE联合多吉美可有效治疗HCC。虽然多吉美治疗肝细胞癌的分子机制已有较多报道, 但相关的影像学研究报告不多。我们通过30例患者的影像学分析, 发现病灶呈现无碘油沉积的完全坏死这一相对特异的影像学表现, 推测其可能为索拉非尼治疗的结果。

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