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World Chin J Digestol 2004 June;12(6):1422-1426
世界华人消化杂志 ISSN 1009-3079 CN 14-1260/R

• 文献综述 •

肝动脉化疗栓塞治疗肝癌

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收稿日期: 2003-09-15 接受日期: 2004-02-09

摘要

肝动脉化疗栓塞(TACE)是不能手术切除肝癌的首选治疗方法, 该技术诞生 30 a 来不断的完善和提高, 目前已在全球得到广泛应用, 尤其是近年来TACE技术有了长足的发展. 螺旋CT的临床应用为TACE术前病情分析及制定切实可行的方案提供了有力的保障, 同时也为TACE术后疗效判断和进一步治疗提供了理论指导. 在具体操作上, 个体化、大剂量的碘油可明显提高 TACE 治疗肝癌的疗效, 改善患者的预后. 经过长期的临床观察和经验积累, 大家已经认识到由于肝癌血供丰富, TACE后新生血管的产生, 侧支循环地建立等因素的制约, 单纯的TACE不容易达到理想的治疗效果, 综合治疗才是TACE 技术的发展方向, 例如配合经皮肝穿刺乙醇注射可明显提高治疗效果. 同时基础研究是TACE技术进一步完善的前提, 动物模型地建立为血管生成抑制剂的试用提供了机会, TACE后肝癌特异性蛋白质地检测, 如Bax与Bcl-2、PCNA等, 为临床工作指明了努力的方向. 历史已经证明, 经过大家的不断努力, TACE技术正在逐渐完善和提高.

冯勇, 刘君. 肝动脉化疗栓塞治疗肝癌. 世界华人消化杂志 2004;12(6):1422-1426
http://www.wjgnet.com/1009-3079/12/1422.asp

0 引言

1974 年 Doyou 首先报道运用肝动脉栓塞术治疗肝癌, 这一技术随着在临床工作中的实际应用, 日趋完善和提高, 已发展成为肝动脉化疗栓塞(transcatheter hepatic arterial chemoembolization, TACE)技术, 并在全球得到了广泛开展和应用, 成为不能手术切除肝癌的首选治疗方法, 同时也取得了较好的疗效[1-10]. 但是由于各种原因的影响, 如肝癌的多重血供、侧支循环的建立等, TACE 治疗肝癌仍是一种姑息性方法, 远期疗效不理想[11-20]. 所以 30 a 来大家一直在不断探索, 试图努力完善和提高 TACE 技术. 近年来由于检查手段的提高, 临床经验的积累, 基础研究的深入, 在TACE 治疗肝癌方面有了长足的发展, 综述如下:

1 螺旋 CT 促进了 TACE 的发展

近几年来螺旋 CT 在临床上的应用为 TACE 治疗肝癌提供了强有力的支持[21-23]. TACE治疗肝癌的主要机制是通过栓塞剂(如碘油等)来栓塞肿瘤的血管, 使其血液供应障碍, 引起肿瘤缺血、缺氧而坏死. 因此, 肝癌行 TACE治疗前了解和掌握其血液供应情况对制定具体方案非常必要. 此前这一工作均在 TACE 的同时完成, 即肝动脉插管成功后先进行数字减影肝动脉造影(digital subtraction angiography, DSA), 来了解肝癌的血液供应等情况, 也非常直观和实用, 对TACE 实施有很好的指导意义. 但也存在不足, 肝癌80%以上血供来自动脉, 其余来自门静脉, 所以这种检查方法不能反应门静脉参与肿瘤供血的情况, 门静脉供血的存在是TACE 治疗肝癌坏死不完全的原因之一, 而螺旋 CT 的出现正弥补了这一不足. 运用螺旋CT双期扫描技术可分别显示肝癌动脉和门静脉的供血情况, 方法是: 用高压注射器经前臂静脉注入对比剂, 如碘普胺 80-100 mL (300 mgI/mL)等, 注入的速度为 3 mL/s, 而后进行螺旋 CT 双期延迟扫描, 注药后 18-25s 扫描为肝动脉期, 60 s 为门静脉期. 若在门静脉期肿瘤有强化, 即说明该肿瘤存在门静脉供血, 对这样的肝癌行单纯 TACE 治疗效果不理想.

肝癌发生肝动脉-门静脉分流(arterioportal shunt, APS)的机会很大, 尤其是肿瘤累及门静脉时发生率为 63%. APS 严重影响 TACE 治疗肝癌的效果, 同时其自身也引起严重的门静脉高压症状, 如腹水、上消化道出血等, 直接影响患者的预后. 以往 APS 的诊断主要依靠于 DSA, 虽然其是一种非常有效的检查方法, 但是, 这是一种有创的检查手段, 在一定程度上限制了其临床使用, 使不少肝癌患者失去了治疗机会. 已经证实螺旋 CT 诊断肝癌合并 APS 与 DSA 具有同样理想的效果[24-26], 甚至优于 DSA, 尤其是对近端的 APS, 敏感度为 100.0%, 准确度达 96.4%, 并且具有方便、快捷、无创的优点, 这对肝癌患者进行 TACE 治疗有很好的指导意义. 对于这样的肝癌患者行 TACE 治疗时, 应首先进行 APS 的栓塞, 栓塞剂可用明胶海绵、弹簧圈等, 而后再行TACE 灌注化疗药物和碘油, 既能纠正患者门脉高压的症状, 又能起到较好治疗肝癌的作用. 螺旋 CT 检查近端 APS 的直接征象是: 肝动脉期门静脉主干和/或第一级分支提早显影, 其门静脉显影密度大于脾静脉或肠系膜上静脉, 甚至接近于主动脉. 间接征象为: 肝动脉期肿瘤所在的非癌肝实质强化, 门静脉期该区域密度与其他部位非癌肝组织一致.

肝癌在TACE之前行螺旋CT双期检查有很好的使用价值，同样肝癌TACE之后行该检查也有非常好的临床意义[21]，对于判断TACE的治疗效果，指导进一步的治疗，估计患者的预后都很有帮助. 肝癌经TACE治疗后行螺旋CT肝双期扫描，不但可观察到肿瘤非坏死区域的低密度区，还可观察到该部位的血液供应情况. 已证实肝癌TACE后螺旋CT双期扫描发现，残留的非坏死癌组织中94.1%有动脉供血存在，50.0%有门静脉供血. 前者我们在分析原因时要想到，可能存在有肿瘤肝外动脉供血的情况[27-28]，且可根据其部位来估计肝外供血的血管，例如肿瘤位于肝脏的右下脏面时要想到胃十二指肠动脉，位于左叶时可能是胃左动脉、左膈动脉等，对以后的TACE具有很好的指导作用，针对性强，可明显提高治疗效果. 对残癌中存在有门静脉供血者，可配合其他治疗来提高疗效.

螺旋CT在肝癌的TACE治疗中有很好的指导作用，与DSA相比有方便、快捷、无创的特点，但仍有不足. 虽然他能通过对肝脏的双期扫描显示肝癌的动脉供血情况，但是肝癌存在许多肝外动脉供血，螺旋CT不能明确诊断. 因此，在螺旋CT肝双期检查的基础上，配合TACE时的DSA检查，对TACE治疗肝癌能起到更好的作用.

2 大剂量碘油能提高TACE的疗效

目前临床上TACE治疗肝癌主要还是用碘油作为栓塞剂，实践证明是非常有效的，现在看来采用个体化、大剂量的碘油作栓塞剂的治疗效果明显优于常规小剂量[22, 29-30]. 临床研究已经证实，将不能手术切除的大肝癌患者473例分为两组，A组216例采用大剂量碘油20-53 mL，平均28.3 mL; B组257例采用常规小剂量5-15 mL，平均11.8 mL. 结果A组手术切除率和肿瘤完全坏死率均高于B组(P <0.05)，同时生存率也高于B组(P <0.01). 所以，大剂量碘油(20-40 mL)经TACE治疗大肝癌且血管丰富者，与常规小剂量比较其治疗效果是肯定的，但要求患者肝功能child's A级，或ICG-R < 20%，否则会增加TACE后发生肝功能衰竭的危险性. 该方法不但可以阻塞肿瘤的动脉供血，同时还阻塞了肿瘤的门静脉供血，起到双重栓塞的作用，引起的肿瘤坏死更完全，相应的治疗效果更好. 原理是肝动脉与门静脉存在吻合支，一般情况下动脉压高于门脉压8倍，并在此水平保持平衡，且呈关闭状态，只有当二者任何一方压力升高时该吻合才开放. 在行大剂量碘油肝动脉灌注时，可使该吻合开放，碘油就由动脉端进入到对侧的小门静脉，即起到双重栓塞的功效.

TACE大剂量碘油治疗肝癌时一定要个体化，做到因人而异，制定个体化的治疗方案，不能一概而论，判断的依据除根据肿瘤的大小外，还要看肿瘤的血液供应情况. 根据肿瘤的血供可将肝癌分为4型[21]，(1)多血供型，螺旋CT肝双期扫描动脉期与门静脉期强化均明显，示肿瘤的血供丰富; (2)少血供型，表现为双期强化均不明显; (3)混合性血供型，肿瘤内既有多血供区，也有少血供区，二者混合存在; (4)合并有动静脉瘘的肝癌患者. 具体操作时，多血供者碘油灌注量为肿瘤最大径的2-3倍，即肿瘤10 cm，碘油用量20-30 mL; 少血供型碘油的用量与肿瘤的最大径一致; 其他两型都视情况而定.通过这种方法治疗肝癌患者的有效率为84.0%，明显高于对照组(46.0%)，多血供型的肝癌占75.0%，这部分患者TACE治疗的预后好[31].

自TACE用于肝癌治疗以来，为了提高疗效，栓塞剂的应用也很多，但经得起时间考验的仍是碘油. 近来美国学者用聚乙烯乙醇做栓塞剂取得了很好的疗效[32]. 另外，国内有学者用聚乳酸/羟乙酸同样效果不错[33].

3 综合治疗是TACE的发展方向

由于肝癌存在肝外动脉、门静脉供血，TACE治疗肝癌仍不能达到根治目的，单纯TACE不能解决这些问题. 有不少学者认为TACE配合其他治疗手段[12, 19, 34-36]具有较好的治疗效果.

TACE配合经皮乙醇注射(percutaneou ethanol injection，PEI)对肝癌的治疗效果明显优于单纯TACE. 在这方面，日本学者在小肝癌的研究上做了大量的工作[37-38]. 研究证实,直径小于3 cm的肝癌经TACE+PEI治疗后，残留非坏死癌组织为3.7%，对照组高达34.2%，且3 a后复发率分别是19.3%和80.1%，5 a生存率是50.0%，而单纯TACE组只有24.0%，没有出现严重的并发症.同时我国大陆和台湾的学者也做了类似的研究[39-40]，得到的结果也是一致的，均证实TACE+PEI治疗肝癌比单纯的TACE效果要好，但要注意患者肝功能情况，还提示肿瘤大于5 cm时远期疗效不好.

肝癌存在的门静脉供血是制约TACE疗效提高的重要因素之一，为解决该问题近来有报道，采用B超引导下经皮肝穿刺门静脉栓塞(portal vein embolization，PVE)配合TACE治疗肝癌[41]，较单纯TACE可明显改善肝癌患者的预后.因此，认为TACE+PVE是治疗肝癌的有效方法.

TACE治疗肝癌远期疗效不好，与TACE后侧支循环建立有直接关系，包括肝内侧支循环与肝外侧支循环两部分，TACE配合手术切除是解决这一难题的有效方法. 不能手术切除的大肝癌经TACE后肿瘤坏死并缩小，使之得到二期手术切除的机会，为这部分患者的治疗开辟了一条很好的途径[42-43]，同时也有效减少和避免了TACE后的复发和转移. 因为TACE往往不能使全部肿瘤坏死，致使残留的癌细胞附着能力下降，并且肿瘤血管结构不完整，易发生转移[44-45]. 同时要注意，对于能手术切除的肝癌要及时进行切除，不可行TACE后再二期手术[46-47]，除了有上述不利因素外，还增加了手术难度. 还有文献介绍，包括肝硬化伴小肝癌的患者进行肝移植等外科手术，配合TACE治疗肝癌已在临

床上开展[48-50]，并取得了较好的疗效.

也有资料介绍TACE配合冷冻疗法、经皮微波凝固、放疗等也能改善肝癌患者的预后[51-54]. 因此，我们可推断单纯的TACE治疗肝癌存在有明显不足，配合其他治疗措施是非常必要的.但一定要注意患者肝功能的情况[55-57].

4 基础研究促进了TACE的提高

近几年来TACE在基础研究方面取得的成绩，对临床上应用该技术治疗肝癌起到了很好的指导作用，发现了一些存在的问题，明确了努力的方向. 用walker-256肿瘤细胞株建立的Wistar大鼠肝肿瘤模型，与人肝肿瘤生长模式非常接近，血管造影观察到该肿瘤血管丰富，与人类的肝癌一样也是以肝动脉供血为主[58]，这种肝肿瘤的动物模型能够进行TACE的实施，为TACE的基础研究提供了保障. 另外，用VX2肿瘤细胞株建立的兔肝肿瘤模型也可进行TACE操作[59]，由于兔相对较大，肝动脉内径比大鼠的要大的多，具体操作起来相对简单.

TACE治疗肝癌继发的新生血管产生，侧支循环的建立是一个非常棘手的问题. 血管的增生与血管内皮生长因子(vascular endothelial growth factor，VEGF)的关系非常密切，而TACE引起肝癌血供障碍、缺氧及肿瘤坏死，同时缺氧和坏死组织均能刺激VEGF的产生，继之促进新生血管的产生[60-62]，这是TACE治疗肝癌不彻底的原因之一. VEGF还有增加血管通透性的作用，再加上肿瘤血管结构不完整等因素，有利于肿瘤细胞进入血液循环发生转移，这与临床观察结果相一致[63]. 血管生成抑制剂TNP-470为这一难题的解决提供了强有力的武器[64-65]，动物试验证明[58, 66]，配合应用血管生成抑制剂TNP-470肝动脉灌注，能有效消除上述不良影响，对试验肿瘤有很好的治疗作用.

细胞凋亡(apoptosis)是细胞接受刺激信号后一种主动的，并由相关基因控制的细胞程序性死亡，其中Bcl-2蛋白是一种公认的细胞凋亡抑制基因[67-68]，而Bax是Bcl-2的同源蛋白，Bcl-2与Bax二者的比率决定着细胞凋亡的速率. 有文献[69]介绍，肝癌经TACE治疗后二期手术切除，用免疫组化技术观察到，肿瘤细胞的凋亡指数(apoptotic index, AI)和Bax表达水平均升高，而Bcl-2，Bcl-2与Bax的比值却有明显的降低，与单存手术切除组有明显差异(P<0.05).所以TACE治疗肝癌有促进肿瘤细胞凋亡的作用.

但是，也有研究观察到TACE有促进肝癌细胞增生的作用.TACE治疗肝癌使肿瘤不同程度的坏死、缩小，这是非常好的一面，可同时也发现残留的癌细胞增生细胞核抗原(proliferating cell nuclear antigen，PCNA)的表达却增强了[46, 70]. PCNA是一种公认的反映细胞增生状态的指标蛋白，该蛋白量增大，肿瘤发生浸润生长与转移的能力就强. 因为PCNA是真核细胞DNA聚合酶的辅助蛋白，主要存在于S期，在一定程度上PCNA的表达与肝癌的恶性程度密切相关[71-72]，可用来判断肿瘤患者的预后. TACE致使PCNA高表达的原因可能是，肝癌经TACE治疗后肿瘤组织大量坏死，少量残留的癌细胞本能性的代偿性增生，使G0期细胞进入到S期，这些肿瘤细胞增生活跃，也就表现为PCNA的高表达，从一个侧面可解释肝癌患者TACE治疗远期疗效不好的原因. 所以TACE后适时的二期手术切除是非常必要的，不能手术切除的大肝癌正是由于TACE治疗，使肿瘤坏死、缩小，纤维组织增生，包膜甚至包囊形成，使二期手术方有机会实施. 但是我们也清楚的看到，大肝癌TACE后二期切除的机率还很低，约10%左右，还有待进一步提高.

为了了解TACE治疗肝癌对患者预后的影响，所以就TACE对抑癌基因p53及nm23的表达也进行了研究观察[46, 70]，nm23是一种公认的转移抑制基因，TACE对这两种基因表达没有显著性影响，这可能与TACE后到二期手术切除的时间有关，由于这段时间较长，原来基因的表达物质逐渐被代谢，同时随着时间的推移,该基因的表达又恢复原来的水平，所以会有上述结果.

虽然TACE治疗肝癌还存在不少问题，但仍不失是一种有效的治疗手段，尤其是对不能手术切除的大肝癌更有意义. 30 a来TACE技术已在全球得到广泛开展应用，我们相信经过大家的不懈努力，TACE技术将发展的更加完善.

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