

早期预测肝细胞癌微血管侵犯的研究进展

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【摘要】 肝细胞癌微血管侵犯(MVI)是影响肝细胞癌(HCC)患者预后的重要组织病理学因素。MVI常需术后病理检查确诊,如何建立MVI的早期预测模型是目前的研究热点。近年来不少学者对MVI的预测因素进行了相关研究,致力于建立一个能达成共识的早期预测模型。本文就早期预测MVI的研究进展进行多方面综述。

【关键词】 肝细胞癌;微血管侵犯;早期预测;预测模型;研究进展

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Research progress in early prediction of microvascular invasion in hepatocellular carcinoma. CAI Yu-sen, ZHANG Zeng-rui, GU Yong-xin, ZHU Wen-dian. Guangdong Medical University, Zhanjiang 524000, Guangdong, CHINA

【Abstract】 Microvascular invasion (MVI) is an important histopathological factor affecting the prognosis of patients with hepatocellular carcinoma (HCC). MVI usually requires postoperative pathological examination to confirm the diagnosis, and how to establish an early prediction model of MVI is a current research hotspot. In recent years, many scholars have conducted relevant studies on the predictive factors of MVI, and are committed to establishing an early prediction model that can reach a consensus. This article reviews the research progress of early prediction of MVI in many aspects.

【Key words】 Hepatocellular carcinoma; Microvascular invasion; Early prediction; Prediction model; Research progress

原发性肝癌是目前我国第4位常见恶性肿瘤及第3位肿瘤致死病因,严重威胁我国人民的生命和健康^[1]。即使目前对肝细胞癌得诊疗手段不断提高,但患者预后并不乐观。肝细胞癌(hepatocellular carcinoma, HCC)的大小与数量、分化程度、血管侵犯等诸多因素降低了肝癌患者的预后。近年来,部分学者以肝细胞癌的微血管侵犯(microvascular invasion, MVI)作为研究的突破口,发现MVI是影响肝细胞癌患者预后的重要因素,MVI阳性患者的术后复发率可达阴性患者的两倍之高^[2-3]。MVI需要术后的病理检查确诊,如何在术前精准预测MVI的存在,目前学者们并未达到共识。对MVI进行早期预测并提供相应的个体化治疗方案,是改善肝癌患者远期疗效瓶颈的重要切入点^[4]。本文以近年国内外与MVI相关的文献报道进行综合,展开综述。

1 MVI的概念

相关研究指出MVI的阳性率为15%~57.1%^[5],这可能由于病源、取材、诊断等多方面的差异造成。我国《肝癌病理诊疗规范(2017年版)》^[1]中指出:微血管侵犯,即原发性肝癌在显微镜下于被内皮细胞衬覆的血管腔内见到癌细胞巢团。有学者指出,E-黏附蛋白的低表达,降低了细胞之间的黏附性,使组织完整性缺失,进一步促使了肿瘤的侵袭^[5]。而黏附蛋白Kindlin-2的高表达与MVI相关,促进肿瘤侵袭性增加^[6]。越来越多基础研究在揭示着MVI的形成机制,如蛋白质精氨酸甲基转移酶1(PRMT1)^[7]、长链非编码

RNA-AWPPH^[8]、Metadherin蛋白(MTDH)^[9]等在体内的高表达与MVI有着高相关性。

2 MVI对预后影响

MVI是大血管侵犯的前期阶段,严重制约了患者术后预后的改善。SHEN等^[10]发现肝切除后MVI阳性患者肝内及肝外复发率均高于阴性患者。即便是小肝癌,MVI阳性患者行肝切除的术后复发率、无瘤生存率等也会受到显著影响^[2,11]。CHEN等^[12]的一项荟萃分析指出MVI阳性组患者术后的总体生存率明显低于MVI阴性组。MVI危险分级越高预后越差,赵晖等^[13]发现无MVI组术后1、3、5年无瘤生存率分别为79.5%、57.2%、48.9%,低危组为75.5%、45.0%、31.5%,高危组为50.0%、23.7%、15.8%,差异均有统计学意义。尽管国外学者对MVI的分级与我国有所差异,但均指出MVI危险分级越高,病理分型越差,患者术后预后则越差^[14-16]。针对MVI分级进行进一步研究,完善个体化治疗方案,是目前研究的新方向。

3 MVI对治疗方式的影响

POMMERGAARD等^[17]通过23 124例肝移植病例发现,MVI阴性患者无论肿瘤结节大小和数量其5年总生存率为73.2%,即便是在米兰标准外及Up-to-seven标准外进行肝移植,MVI阴性患者的5年生存率也高达65.8%,而MVI阳性患者仅为58.8%。部分学者也指出MVI阳性是肝移植术后肝癌复发的独立危险因素^[18-19]。若能早期预测MVI,那么对于MVI阴性患者能否放宽肝移植的标准,使患者的预后得到改善?肝癌切

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除术是临床最常用的治疗手段,行解剖性肝切除的患者的预后较行非解剖性肝切除的患者有显著的提高,特别是合并MVI的患者,而采取肿瘤宽切缘(≥ 1 cm)相对于窄切缘也能改善患者的预后^[20-22]。相关研究表明合并MVI的肝癌患者术后早期辅助经导管动脉化疗栓塞(TACE)治疗也可以获得较好的预后^[23-24]。目前有研究指出TACE联合索拉非尼治疗中晚期肝癌能取得较为满意的疗效^[25]。LI等^[26]发现对于合并乙肝的MVI患者,若术后DNA载量高于2 000 IU/ml,患者的总体生存率(OS)及无病生存率(DFS)会下降。手术前后有效的抗病毒治疗是否能改善MVI患者的预后,值得学者们进行更深一步的研究。

4 MVI的早期预测

4.1 肿瘤的大体形态与MVI的相关性 PAWLIK等^[27]指出瘤体越大,肿瘤分化程度越低,MVI发生率越高,当肿瘤 ≤ 3 cm时MVI发生率为25%;3.1~5 cm时为40%;5.1~6.5 cm时为55%; >6.5 cm时为63%。EGUCHI等^[28]指出当瘤体 ≥ 5 cm时是MVI的独立预测因子,而瘤体 <5 cm时,瘤体外单发结节及连续多发结节的出现更容易发生MVI。

4.2 术前影像学预测MVI 我国台湾学者CHOU等^[29-30]将增强CT下肿瘤形态分为3种亚型:单结节型、单结节外生型、多结节外生型,前者归为光滑边缘,后两者归为非光滑边缘,他指出肿瘤边缘不光滑与MVI的出现有显著相关性。REGINELLI等^[31]指出增强CT下肿瘤边缘不光滑和肿瘤包膜的不完整均与MVI的存在相关。ZHANG等^[32]通过增强CT上发现肝包膜侵犯预测MVI的敏感性为78.9%,特异性为81.6%,准确率为80.6%,肿瘤边缘不光滑预测MVI的敏感性、特异性和准确率分别为59.6%、79.6%和72.5%。HU等^[33]通过Meta分析发现肿瘤边缘不光滑预测MVI的DOR可达21.30,曲线下面积(AUC)可达0.90,其另一项Meta分析指出增强MRI下癌周强化与MVI之间存在显著的相关性^[34]。KIM等^[35]将增强MRI下的癌周强化征象分为楔形及不规则两种形态,并指出不规则的癌周强化征象预测MVI的敏感性为74.3%、特异性为82.9%,阳性预测值为81.3%、阴性预测值为76.3%。而ZHANG等^[36]发现术前增强MRI下动脉期肿瘤边缘强化和肝胆期肿瘤周围楔形低密度影是MVI的独立危险因素,当这两个因素同时存在时,其预测MVI阳性的特异性可达95.15%。瘤内动脉和肿瘤低密度信号环征象的出现被定义为TTPVI (two-trait predictor of venous invasion),这可能是由于肿瘤压迫周围肝组织致其纤维化,形成低衰减或低水平的光晕,同时,瘤内大量新生血管的形成导致肿瘤内血管征象的出现。ZHANG等^[37]发现增强CT及增强MRI下TTPVI的出现是MVI的独立预测因子(OR: 4.802, 95%CI: 1.037~22.233, $P=0.045$)。BANERJEE等^[38]提出了静脉侵犯放射学基因(radiogenomic venous invasion, RVI)的定义,其为增强CT下一

种来自肝细胞癌91基因并与MVI相关的生物标记物。RVI主要由三方面组成:静脉期肿瘤内部动脉、门脉期肿瘤低密度晕圈及门脉期肿瘤-肝脏差异,上述任一征象出现时可判定为RVI阳性。其预测MVI的诊断准确性,敏感性和特异性分别为89%、76%和94%。此外,ZHANG等^[39]也发现RVI的存在与肝癌患者预后不良相关。近年来,不少学者通过纹理分析技术对MVI进行预测研究。WILSON等^[40]通过增强MRI发现门脉期肿瘤瘤及T1加权成像上肿瘤平均值与MVI的出现相关,其最佳截断值分别为5.73和23.41,灵敏度分别为0.68和0.5,特异性分别为0.64和0.86;当两个标准都满足时,MVI阳性预测率可高达87%。NEBBIA等^[41]利用SVM算法得出,肿瘤在增强MRI中显像灰度的不均匀,及非光滑的肿瘤边缘与MVI阳性相关,结合T2加权像及门脉期征象预测MVI阳性的AUC为86.69%。马萧虹等^[42]发现利用增强MRI动脉期中灰度共生矩阵相关性、灰度共生矩阵对比度及灰度共生矩阵熵和来预测MVI的诊断准确率为83.30%。但是由于ROI是由影像医师在二维图像上选取肿瘤最大截面,其对于评判肿瘤的三维空间有着一定的限制性。LIM等^[43]指出PET/CT阳性,即指肿瘤对FDG的摄取显著高于周围肝组织,是MVI的独立预测因子,其敏感性、特异性、准确性、阳性预测值、阴性预测值分别为62%、76%、71%、53%、81%。AHN等^[44]在PET/CT中得出肿瘤和正常肝脏的目标体积(VOI),并在每种VOI中测出标准摄取值(SUV),肿瘤VOI中的最大SUV定义为 $TSUV_{max}$,正常肝脏VOI中的平均SUV定义为 $LSUV_{mean}$;当 $TSUV_{max}/LSUV_{mean} \geq 1.2$ 时与MVI有着显著相关性,odds=14.218 ($P=0.001$)。

4.3 血清生化标志物 ZHANG等^[45]发现当甲胎蛋白AFP >232.2 $\mu\text{g/L}$ 时,AFP预测MVI的敏感性、特异性和准确率分别为56.1%、66.0%和62.5%。脱- γ -羧基凝血酶原(DCP),又称PIVKA-II,是HCC细胞自分泌的一种异常凝血酶原,具有刺激肝癌细胞恶性增殖作用和促进肿瘤微血管生长作用。POTE等^[46]发现PIVKA-II水平 >90 mAU/mL是MVI的独立预测因子,同时也指出组织PIVKA-II的高表达与MVI存在显著相关。如果将PIVKA-II免疫染色与其血清水平相结合,其诊断效能可以得到提升。汪宇等^[47]发现外周血循环肿瘤细胞CTC阳性、AFP >400 $\mu\text{g/L}$ 及DCP >40 mAU/mL是MVI存在的独立危险因素。部分研究对于AFP及DCP预测MVI的最佳截断值有一定差异,且除肝癌患者之外,在肝炎患者中,AFP及DCP也会有一定程度的异常升高,相关研究也需将这一部分因素考虑在内。蔡尚坤等^[48]指出血清中高谷氨酰转氨酶(GGT)水平与肿瘤大小有关,其可能与肝实质受压产生炎症,使GGT合成增加相关,而术前低GGT组的MVI患者更少,术后生存率更高。ZHU等^[49]发现碱性磷酸酶计数和淋巴细胞计数是MVI的独立预测因子,

并得出碱性磷酸酶与淋巴细胞比率(ALR)评分,高评分与MVI的存在呈正相关,并指出高ALR评分患者的不良生存结局与肿瘤中CD8⁺T细胞浸润减少有关。ZHANG等^[50]发现术前国际标准化比值(INR)高低与MVI相关,低INR患者更容易出现MVI,INR水平的高低是MVI患者术后无瘤生存率及总体生存率的独立危险因素,血液高凝状态可能与微血管中癌细胞的积聚有关,而具体的相关性需进一步研究去证实。WEI等^[51]的一项研究中发现,相对于MVI阴性组及轻度MVI组,重度MVI组中患者患有乙肝的比例更高,乙型肝炎病毒感染后的细胞活跃复制可能与MVI的形成相关。MA等^[52]发现术前血清高磷酸化蛋白1(STP1)水平是MVI的独立危险因素,并与HCC患者长期预后不良相关。DING等^[53]发现血清中对氧磷酶1(PON1)水平与MVI呈负相关,其最佳诊断临界值为191.12 ng/mL。WANG等^[54]发现患者血液里循环肿瘤DNA(ctDNA)的等位基因突变频率(AF)达到0.83%时与MVI的存在高度相关,其在验证队列中的敏感性为78.6%、特异性为81.8%。ctDNA中最常见的突变基因包括TP53、TERT、AXIN1、LRP1B和CTNNB1等。也有学者通过质谱鉴定发现血清中针对热休克蛋白hsp70和烯醇化酶(Eno-1)的抗体是肝癌切除前预测MVI的潜在生物标志物,MVI阴性患者抗hsp70抗体滴度明显高于MVI阳性患者;MVI阴性患者抗Eno-1抗体滴度明显低于MVI阳性患者^[55]。

4.4 MVI早期预测模型 联合相关预测因子建立可靠的MVI早期预测模型是目前的研究热点与难点。NITTA等^[19]发现AFP \geq 100 ng/mL、肿瘤直径 \geq 4 cm、肿瘤边缘不光滑、中性粒细胞/淋巴细胞比值(NLR) \geq 3.2以及天冬氨酸转氨酶计数(AST) \geq 62 U/L是MVI的危险因素;当所有危险因素均无时,MVI发生率为17%,当所有危险因素都存在时MVI发生率可达86.9%。他们将50%的MVI可能性作为有无MVI的截断值,发现接受肝切除患者的5年OS和RFS在有无MVI时分别为38.4% vs 66.1%和15.8% vs 28.6%,肝移植患者的5年OS和RFS在有无MVI时分别为51.4% vs 80.6%和60.9% vs 89.9%。胡月雷等^[56]对利用患者年龄 \geq 60岁、肿瘤最大直径 \geq 5 cm、血小板/淋巴细胞比值 \geq 72.30、中性粒细胞/淋巴细胞比值 \geq 1.83这四个危险因素建立了评分系统,当危险评分为0~1.5分、2.0~3.5分和4.0~5.0分时,患者MVI阳性率分别为18.6%、42.9%、78.3%,ROC曲线分析此危险评分模型预测MVI的最佳临界值为2.75分。LEI等^[57]通过研究发现肿瘤最大直径、肿瘤多发结节、包膜不完整、AFP \geq 20 ng/mL、血小板计数 \leq 10.0 \times 10³/ μ L、乙肝病毒载量 $>$ 104 IU/mL及增强MRI典型的征象的出现是乙肝肝癌MVI阳性患者的独立危险因素;结合以上因素,作出列线图模型并发现此模型预测MVI具有良好的效能,其列线图总得分的最佳截断值为200分。目前

不少诊断效能较佳的预测模型逐渐被发现,但学者们对各模型内相关指标及阈值的见解并未得到统一。

5 展望

MVI是提高HCC患者预后道路上的绊脚石,如何精准地预测MVI的存在是学者们迫切需要解决的难点。作为非侵入性的检查,血清学及影像学检查最常被临床所利用。由于肿瘤的进展是一个侵袭性的过程,不同的时间点所获得的检查数据存在这一定的差异,关于早期预测模型的研究需要在一定的时间内获取相关资料。同时,目前许多基础研究由于耗材及耗时等方面的原因,并不能完全适用于临床。在寻找预测因子的同时,尽量减少误差的产生及提高适用性,是不可忽略的一部分。学者们应进行更多的研究为MVI预测模型的建立而铺路,并以此进行一系列临床研究,规范围手术期处理及术后综合治疗方案,改善肝癌患者的预后。

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人工颈椎间盘临床应用现状和发展前景

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【摘要】 传统颈椎手术会导致颈椎活动度下降和“邻椎病”等情况,人工椎间盘置换术是解决这些并发症的重要手段。从 Fernstrom 创造第一代人工椎间盘,到改良后的 Bristol-Cummins/Frenchay/Prestige 人工颈椎间盘,再到使用较多的 Bryan 金属-聚乙烯人工颈椎间盘,都存在诸多问题。人工颈椎间盘的旋转中心选择、表面材料性质、关节面数量、运动限制的类型、固定方式、材料性质都影响人工颈椎间盘的中、长期稳定性。人工颈椎间盘理论上保留了椎体的活动度,最大限度模拟了颈椎的活动度,减少“邻椎病”发生。至今为止其表现出来的缺点包括不合适尺寸的假体会导致假体松动、脱位以及金属板损坏;手术难度大,导致减压不彻底,手术效果欠佳;脊髓或神经根损伤;血肿和感染等。人工颈椎间盘置换术作为一种高难度的手术,无论是手术本身还是器械都存在较多的问题,现今研究的热点主要集中在新结构设计、面向种群设计和材料改进方面。

【关键词】 人工颈椎间盘;研究前沿;优缺点;设计理念;新型材料;颈椎病

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Clinical application status and development prospect of artificial cervical intervertebral disc. DENG De-jun, LI Xian-kun. Spinal surgery, Huizhou Third People's Hospital, Huizhou 516002, Guangdong, CHINA

【Abstract】 Traditional cervical spine surgery can lead to the decline of cervical mobility and "adjacent segment disease". Artificial disc replacement is an important means to solve these complications. From the first-generation artificial cervical disc created by Fernstrom, to the improved Bristol-Cummins/French/prestige artificial cervical disc, to the more used Bryan metal-polyethylene artificial cervical disc, there are still many problems. The selection of rotation center, the properties of surface materials, the number of articular surfaces, the types of motion limitation, the fixation methods, and the properties of materials all affect the medium and long-term stability of the artificial cervical disc. Theoretically, the artificial cervical disc retains the mobility of the vertebral body, simulates the mobility of the cervical spine to the maximum extent, and reduces the occurrence of "adjacent segment disease". So far, its disadvantages include prosthesis loosening, dislocation, and metal plate damage caused by improperly sized prosthesis; incomplete decompression, poor surgical effects caused by difficult operation; spinal cord or nerve root injury; hematoma and infection. Artificial cervical disc replacement, as a highly difficult operation, has many problems in both the operation itself and the instruments. Current research hotspots mainly focus on new structure design, population-oriented design and material improvement.

【Key words】 Artificial cervical disc; Research frontier; Advantages and disadvantages; Design concept; New material; Cervical spondylosis

人工颈椎间盘置换术是一种快速发展的手术方式,用于治疗颈椎退变性椎间盘疾病。颈椎前路减压植骨融合内固定术作为颈椎病主流治疗方法拥有超

50 年的历史,但其融合了椎间隙,牺牲了颈椎活动度,增加临近椎体的压力,加速临近椎体的退变,导致“邻椎病”发生,一直受到临床医生诟病^[1-2]。人工颈椎间

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