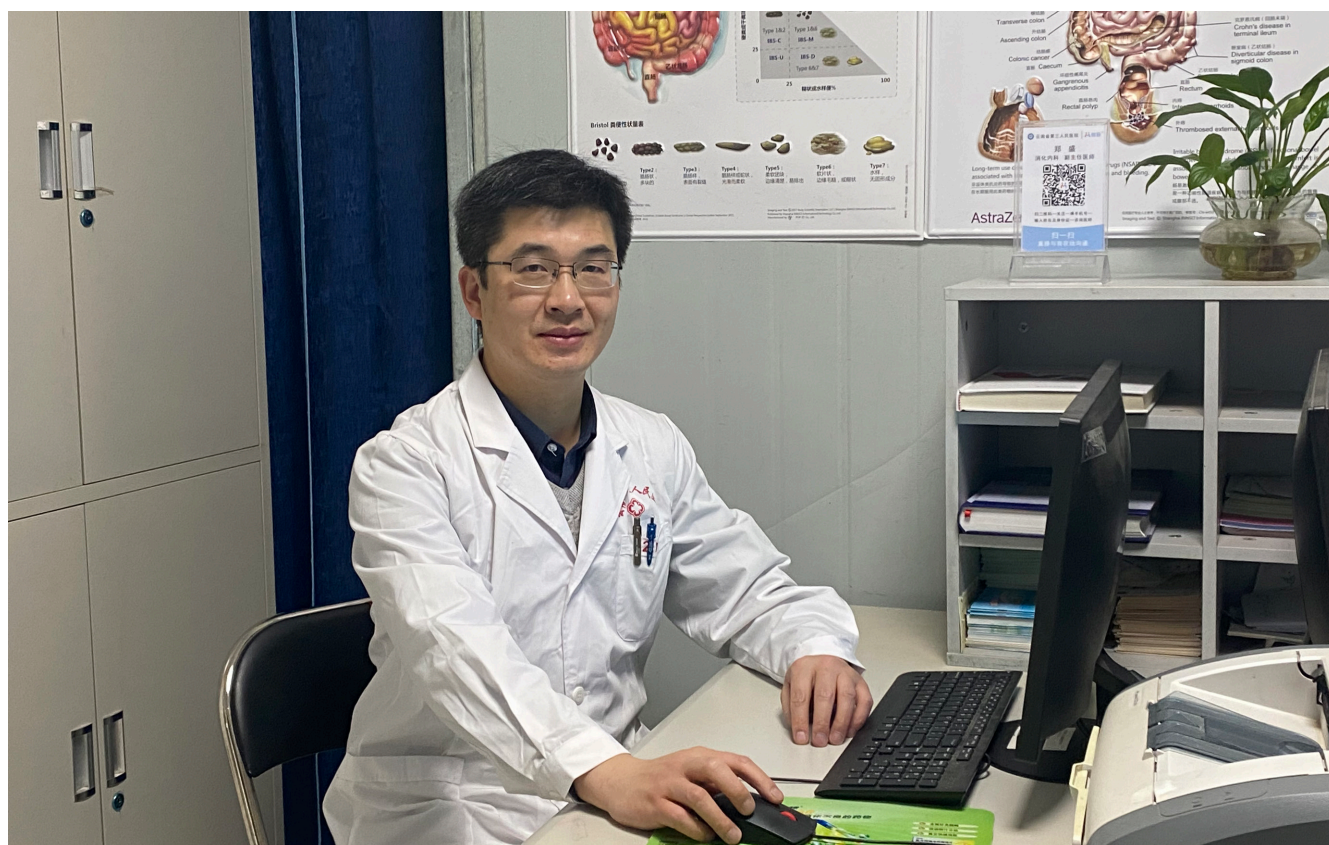


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射频消融治疗肝细胞癌的预后因素及研究新进展

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Radiofrequency ablation of hepatocellular carcinoma: Prognostic factors and recent advances

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Abstract

With the improvement of technology and diagnostic level, radiofrequency ablation (RFA) has made rapid progress in the treatment of primary hepatocellular carcinoma (HCC) in the past two decades. Especially, the overall survival after the treatment of small HCCs by RFA can be comparable to that achieved by hepatic resection. The 10-year survival rates of RFA for HCC were 27.3%-46.1%, and for solitary HCC less than 3 cm, the 10-year survival rate is about 74.0%. RFA combined with other therapies can expand the indications of RFA treatment and benefit the survival of patients with HCC. The prognostic model of RFA for HCC provides a powerful tool for individualized clinical diagnosis and treatment.

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Key Words: Primary hepatocellular carcinoma; Radiofrequency ablation; Prognostic nomogram; Prognostic factors

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摘要

随着医学诊疗水平的提高, 射频消融在治疗原发性肝癌的临床应用和基础研究方面都取得飞速进展, 发挥着越来越重要的作用: (1)射频消融治疗原发性肝癌的10年总生存率为27.3%-46.1%, 对于肿瘤单发且最大径 ≤ 3 cm的HCC患者, 10年总生存率可达74%, 生存结果与手术切除相似; (2)射频消融联合其他治疗等可以扩大消融治疗的适应证, 使患者生存获益; (3)建立预测射频消融治疗原发性肝癌的预后模型, 可指导制定治疗和随访策略, 为临床个体化诊疗提供重要依据。

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关键词: 原发性肝细胞癌; 射频消融; 预测模型; 预后因素

核心提要: 射频消融治疗原发性肝癌是一种临床应用越来越广泛的微创治疗手段, 本文对这一治疗方法的长期生存及其预后因素进行回顾阐述, 以期对临床实际工作提供参考和理论支持。

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0 引言

肝癌是全球第五大常见癌症, 是一个重大的全球卫生问题^[1]. 在我国, 肝癌是导致癌症相关死亡的第二大原因^[2]. 肝细胞癌(hepatocellular carcinoma, HCC)约占肝癌的90%, 由于部分患者就诊时肿瘤分期较晚, HCC患者整体预后仍然较差, 5年总体生存率约10%-12%^[3]. 早期肝癌根治性治疗后5年总生存率可达50%-70%^[4-6], 如肝切除术、肝移植和肿瘤消融术. 目前, 肝切除术、消融(射频消融, radiofrequency ablation, RFA; 微波消融)、肝移植是肝癌的主要根治方法. 中晚期肝癌治疗方法包括肝动脉化疗栓塞术(trans-arterial chemoembolization, TACE)、放疗、免疫治疗、靶向治疗等^[8,9]. RFA是目前国际上应用最广泛、发表研究论文最多的局部消融治疗方法, 由于其微创、费用低、并发症少、恢复快等特点, 在根治性治疗HCC中占据了重要的地位^[6,10-13]. 多项研究均表明对于早期HCC和复发性HCC, 尤其是直径 ≤ 3 cm的肿瘤, 射频消融治疗后整体生存期与手术切除的效果相似^[14-21].

在过去的几十年里, 外科手术技术和三维立体定位放疗的改进, 使肝切除术及放疗等治疗方式的适应证得以扩大, 这样的进步令射频治疗肝癌的优势受到了挑战^[22-27]. 射频消融联合其他治疗是目前治疗肝癌的一个热点. 越来越多研究表明, 射频消融联合介入治疗可提高患者的生存期或与手术切除效果相似^[28-30]. 此外, 射频消融后局部肿瘤复发率较高的风险仍然是一个需要解决的难题^[6,31].

本文通过检索Pub-Med及CNKI等数据库, 将RFA治疗HCC相关研究进行了深入分析, 阐述射频消融治疗手段的创新及进步, 分析肝癌患者的长期预后, 对今后的临床实际工作提供参考和理论支持.

1 总生存期、无瘤生存期及局部肿瘤进展率

据多项临床研究报道^[17,32-34], RFA治疗HCC的10年总生

存率为27.3%-46.1%. 对于肿瘤单发且最大径 ≤ 3 cm的HCC患者, RFA治疗后10年总生存率可高达74%^[6,35], 与手术切除效果相似. 然而, 对于有肝硬化背景且肿瘤最大径为3-5 cm的HCC, 选择局部消融还是肝部分切除术仍存在争议. 对于直径为3-5 cm的肿瘤患者, 目前的研究认为手术切除的远期总生存期比RFA略好^[20]. 对于特殊人群, 如年龄 ≥ 75 岁的老年人, 老年人受肝功能及其他基础病的影响, 与年轻患者不同, RFA治疗较手术切除是相对有效和安全的^[36]. 同样, 在HCC合并肝硬化的患者中, 常常伴有门脉高压, 由于肝部分切除术后可能出现肝失代偿、肝衰及出血等, RFA是首选治疗方式.

总体而言, RFA治疗小肝癌的总生存期是与手术相当的, 与手术切除相比, 经皮RFA的侵袭性更小, 并发症风险更低, 这对于肝切除效果不佳的肝硬化患者比较适用. 但是对于中等或大肿瘤的HCC治疗决策, RFA可能不是最佳的适应证. 由于较大肿瘤周围伴有微血管浸润, 这是决定治疗后早期复发和生存的关键因素^[37]. 因此, RFA治疗较大肿瘤时, 虽然可以进行多次重复RFA, 由于肿瘤周围的微血管侵犯, 如果局部消融不彻底, 不能完全达到消融安全范围, 早期复发率要略高于手术切除, 这将影响患者的预后.

RFA治疗HCC的早期复发率较手术切除稍高, 但总体生存期无统计学差异. Pompili等人^[38]进行倾向评分匹配分析了RFA与肝切除术治疗早期小肝癌(≤ 2 cm)的疗效和安全性. 结果显示4年局部肿瘤复发率RFA组高于手术切除组, 差异具有统计学意义(20.5% vs 0.4%, $P < 0.001$); 4年总生存期RFA组与手术切除组无显著差异(66.2% vs 74.4%, $P = 0.353$). 另外, RFA治疗^[12]明显降低了治疗相关死亡率(发生率0% vs 8.0%, $P < 0.001$), 缩短了住院时间(RFA: 1天 vs 手术切除: 5天, $P < 0.001$), 在微创治疗的优势是明显优于手术切除的.

一项荟萃分析^[39]纳入4项随机对照研究和10项队列研究比较RFA与微波消融(MWA)治疗肝癌的疗效. 结果表明, 经皮MWA和RFA在肿瘤灭活率、局部肿瘤复发、无瘤生存期、总生存期和主要并发症发生率没有显著差异. 同样, 经皮消融治疗对 ≥ 3 cm的肝癌, MWA和RFA的肿瘤灭活率和局部肿瘤复发率无统计学差异. 经腹腔镜消融, MWA组局部肿瘤复发率明显降低(OR = 2.16, 95%CI: 1.16-4.02, $P = 0.01$), 但MWA治疗后主要并发症发生率较高(OR = 0.21, 95%CI: 0.04-1.03, $P = 0.05$); 两组间肿瘤灭活率、无瘤生存期、总生存期无明显统计学差异.

根据早期HCC的治疗策略, 在肝源短缺的情况下, RFA治疗HCC为肝移植提供更多的缓解时间, 可作为肝移植的桥梁^[40,41]. 在长达10年的肝移植术后随访中^[40], 肝

移植前经过RFA治疗, 移植后的肝内肿瘤复发率为5.6%。移植后5年和10年的总生存率分别为75.8%和42.2%, 无复发生存率分别为71.1%和39.6%。因此, 在肝癌患者等待肝移植过程中, RFA可作为一种过渡性治疗, 提高肝移植患者生存期, 减少移植后肿瘤复发。

由于RFA本身是局部治疗方式, 消融范围有一定限制, 在未来治疗肝癌的领域中需要发展更多新技术并联合其他治疗, 突破局限性, 发挥RFA微创治疗的优势, 提高患者生存期及生活质量的同时, 最大程度减少局部肿瘤复发。

2 影响预后因素

相关研究^[14-20,42]已经证实了影响肝癌射频治疗的预后因素主要有肿瘤的大小、数目、肿瘤分期、肝功能、甲胎蛋白等。在RFA治疗HCC的早期临床研究中, 肿瘤大小是一个非常重要的决策因素。随着RFA技术及联合治疗的应用, 临床上的降期治疗让部分较大肿瘤和中晚期患者可以获得局部治疗的机会, 一定程度上RFA可作为姑息治疗或联合治疗的一部分, 从而提高患者治疗后的生存质量, 延长患者的生存期。

流行病学研究^[43-45]显示, 肿瘤筛查以及重点人群的随访监测、抗病毒治疗的规范应用, 使肝癌患者的生存期较10年前得到了提高。近年的研究发现^[46-48], 抗病毒治疗可有效预防肿瘤复发, 有助于肝癌消融后整体预后的改善。据Sohn等^[47]人报道, 228例伴有乙型肝炎的HCC患者经射频消融治疗后非抗病毒治疗组5年肝癌复发率为43.8%, 抗病毒治疗组为14.7%, 差异具有统计学意义($P = 0.001$); 非抗病毒治疗组5年总生存率为77.2%, 抗病毒治疗组为93.5%($P = 0.002$)。研究结果显示, RFA后口服抗病毒治疗可显著降低肿瘤复发和死亡风险。

HCC是一种复杂的恶性肿瘤, 确诊时常伴有较差的肝功能, 在治疗后仍有复发的趋势, 多学科联合治疗(MDT)对于HCC患者提供最佳治疗方案十分重要。最近一项回顾性研究表明^[49], MDT组的5年生存率明显高于对照组(71.2% vs 49.4%, $P < 0.001$)。因此, MDT方法可能改善患者生存及预后, 可以进行前瞻性研究进一步验证。

最近的研究报道了白蛋白(albumin, ALB)/碱性磷酸酶(ALP)比值(albumin-to-alkaline phosphatase ratio, AAPR)可作为肿瘤复发和预后的预测因子^[50]。在临床上, 肝功能储备是影响HCC预后的一个重要因素。高水平的ALP提示预后不良; ALP与HCC中上皮间质转化表型相关(上皮间质转化是肿瘤侵袭或转移的重要步骤)。白蛋白是血清蛋白的重要成分, 炎症和营养不良是导致ALB水平降低的重要因素, 在肿瘤患者中, 尤其是慢性肝炎感染, 持续的炎症反应会导致ALB的丢失, 进一步

导致肿瘤患者预后不良。低AAPR的患者与高AAPR的患者相比, 无瘤生存期和总生存期显著降低。低AAPR组的5年无瘤生存率分别为7.3%, 而高AAPR组为28.6%; 低AAPR组的5年总体生存率为51.1%, 而高AAPR为76.7%。研究结果认为AAPR是肝癌RFA患者独立的预后指标, 其鉴别效果优于其他肝功能指标。

3 预后模型的建立

近年来, 采用Cox回归建立模型预测肿瘤的预后成为热点^[51-58]。这些模型根据临床、影像学 and 实验室检查指标进行构建列线图, 在RFA前可预测患者RFA后的总生存率和肿瘤复发率, 指导制定治疗和随访策略。Takuma^[52]研究构建了预测RFA治疗早期HCC总生存期和无进展生存期的模型。预测无进展生存期的模型纳入肿瘤大小、肿瘤数目、天冬氨酸转氨酶、白蛋白、年龄、和甲胎蛋白六个因素; 预测总生存期模型纳入肿瘤大小、终末期肝病模型评分、天冬氨酸转氨酶和白蛋白四个因素。两种模型在训练集中均具有良好的校准和预测能力, c指数分别为0.640和0.692; 在验证集中, 分别为0.614和0.657。Ding等人的研究^[57]显示, 多因素分析发现射频前其他治疗、肿瘤标记物(AFP、CEA、CA19-9)、肝功能分级、肿瘤数目、肿瘤大小是影响总生存的独立预后因素。基于这七个变量建立模型。预测生存率的校准曲线显示, 训练集(c指数: 0.699)和验证集(c指数: 0.734)曲线拟合较好, 表明了模型预测能力较好, 为临床个体化治疗提供了有力工具。

肝癌肝切除术后早期复发对生存率的影响已经有报道^[59,60]。Poon等人^[60]报道了肝癌根治性切除后1年内肿瘤复发和未复发的3年总生存率分别为29.7%和48.3%。Zhou等人^[51]将早期复发纳入模型, 研究探讨消融治疗后早期肿瘤复发与长期生存率的关系。早期复发(≤ 2 年)作为一个独立预后因素纳入模型的构建, 以及纳入肿瘤数量、AFP水平、肝功能这三个指标。用于构建基线列线图的分变量的风险比为1.62-2.67, 而早期复发的风险比为6.34, 远高于其他纳入模型的因素。结果表明早期复发对RFA治疗HCC患者的生存率有显著影响, 模型的c指数为0.81。此模型将早期复发作为危险因素, 在评估患者生存率有较好的预测能力, 从而优化随访和治疗策略。

综上所述, RFA前根据患者的重要临床和实验室指标, 建立模型可较准确预测RFA后肿瘤复发和总体生存情况。这些预测模型是可行的量化评分方式, 它结合了多种因素对患者进行综合评估, 对预后的评判较为直观, 为临床个体化治疗提供参考, 对中有中高风险肿瘤复发的患者制定合适的随访监测, 从而可进行提前干预, 改善患者的生存结果。但是这些预测模型也有其局限

性, 目前尚无法满足所有类型患者的临床需求, 相关研究仍有待进一步探索。

4 RFA在联合治疗中的应用

RFA新技术及联合治疗降低了并发症及局部肿瘤复发, 提高了患者的整体生存期。经动脉化疗栓塞(TACE)联合RFA已被证实可以改善大肿瘤HCC患者的预后^[28,61,62]。对于单发、中等大小(3.1-5.0 cm)的肝癌, TACE联合RFA的10年总体生存率均高于单纯TACE及RFA(41.8% vs 28.4% vs 11.9%, $P=0.022$)^[61]。因为TACE阻塞了肿瘤动脉供血, 增加了RFA的凝固坏死作用, 减少了RFA热损失。另一方面, RFA热效应引起的反应性充血促进了TACE释放化疗药物, 增加了瘤组织中的药物浓度, 增加了细胞对药物的敏感性。最近的一项荟萃分析显示^[63], RFA联合TACE的1年总体生存率高于手术切除($OR=0.50$, 95%CI: 0.30-0.84, $P=0.009$)。这些技术上的联合, 降低了单纯RFA治疗单发较大肿瘤的局部复发率。如前所述, 由于较大肿瘤周围伴有微血管浸润, 联合介入或介入加靶向治疗可以更有效控制复发, 从而提高患者的生存期, 改善患者预后。

随着免疫治疗时代的到来, 消融与免疫系统之间关系的研究不断涌现, RFA联合免疫治疗成为新模式^[64,65]。消融治疗会释放免疫相关抗原, 引发过渡性免疫反应。同样地, 肝癌分子靶向治疗的发展为局部治疗开拓了新的途径^[66,67]。Fukuda等^[68]发现在RFA之前使用索拉非尼可以减少HCC肿瘤和非肿瘤区域的血流量, 增加RFA引起的凝固坏死的程度。Feng等^[69]报道索拉非尼与RFA联合治疗早期肝癌或复发性肝癌患者, 术后复发率较低, 生存率较单纯RFA提高。随着RFA应用的增多, 临床中还存在不规范使用的问题, RFA结合其他治疗手段如TACE、免疫治疗、靶向治疗的治疗时机及应用顺序方面仍缺乏明确的科学证据, 需要进一步探讨和验证。

5 展望

在过去的20年里, RFA治疗HCC取得了实质性的进步, 临床应用日益广泛, 融合图像、超声造影引导和抗病毒治疗方面的技术进步, 提高了局部肿瘤控制的有效率, 改善了RFA治疗HCC的预后。RFA技术操作简单, 通过规范的培训相关人员, 适合在基层医院开展, 在肿瘤早筛开展的同时, 可惠及更多的肝癌患者。

通过使用新技术或联合TACE等其他方法的综合治疗方案, RFA也被提议可治疗更大的肿瘤, 扩大了RFA治疗适应证范围。然而, RFA仍然存在一定的局部和肝内肿瘤复发的风险, 这是目前射频消融遇到的瓶颈。即使一些新的消融技术和新的联合治疗模式已被提出, 今后需要在随机对照试验中进行严格的验证, 也是未来临

床研究工作中需要关注和解决的重点。

6 结论

综上所述, 射频消融治疗肝癌安全有效, 对于早期HCC、老年患者及部分肝功能差的患者是合理的治疗选择。早期肝癌经射频消融治疗的10年生存结果是令人满意的。目前, 如何降低局部复发率是一个挑战, 需要充分发挥射频消融微创、有效的优势, 探索新的治疗技术及联合其他治疗方式弥补其不足, 才能在肝癌的治疗中发挥重要的作用。

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• 消息 •

书 讯

本刊讯 由池肇春教授主编的《腹痛的诊断、鉴别诊断与治疗》已由人民卫生出版社出版发行。

腹痛是消化系统最常见的症状之一,可引起腹痛的疾病很多,容易发生误诊或漏诊,以致患者得不到及时的诊治。本书由全国著名消化内科及相关学科专业学者共同执笔,为近年在腹痛诊疗方面的最新代表作。精装,图文并茂,内容新颖实用,全书2014千字,分上下两篇,上篇为总论,包括腹痛的病理生理学、腹痛的病因与发病机制、腹痛的临床诊断、腹痛的内镜与影像诊断与鉴别诊断、腹痛的实验室诊断、腹痛的治疗等11章。下篇为各论,分别介绍腹痛疾病的鉴别诊断与治疗。从第12章至第15章分别介绍腹腔脏器炎症、阻塞、扭转、穿孔、破裂、血管疾病、心肺疾病、妇科疾病、急性中毒等引起急性腹痛的鉴别诊断与治疗。从第17章至第29章分别介绍胃肠、胰、肾、感染、肿瘤引起的慢性腹痛鉴别诊断与治疗。从第30章至第36章分别介绍肝胆系统疾病和系统疾病引起腹痛的鉴别诊断与治疗。最后一章为经典案例53例,分别介绍了不同案例的诊治体会、经验与教训。

全书以症状鉴别诊断为中心,与治疗并重,均作了全面与详尽的阐述,是一部有关腹痛诊治的新作,有较高的学术水平和参考价值,可为消化内科、普外科、小儿科、感染科、肿瘤科、影像科和妇产科等学科医师学习与参考。每册定价188元,购书热线 010-59787592, 010-59787584, 010-65264830, 人卫智慧服务商城(人卫社官方购书网站)、当当、京东、天猫等网店均可搜索购书,欢迎选购。



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