

肝细胞癌自发性破裂的介入治疗及其研究进展

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摘要

肝细胞癌自发性破裂(ruptured hepatocellular carcinoma, rHCC)是一种危及肝细胞癌(hepatocellular carcinoma, HCC)患者生命的严重并发症, 而且rHCC还有可能升高腹腔播散率, 并对生存产生负面影响。目前rHCC的治疗主要包括急诊手术止血、介入治疗以及姑息治疗。本文描述了rHCC的临床表现、预后、并发症、介入治疗和目前已有的研究证据, 总结了介入治疗止血对于大多数rHCC患者的必要性, 甚至对一些Child-Pugh分级为C级的患者也是如此。根据目前所报道的临床证据, TAE/TACE联合分期肝切除术是一种较为有效的治疗rHCC的方法, 对于大多数rHCC的患者, 首选介入治疗能提供更多的后续分期手术的机会, 预后也更好。

关键词

肝细胞癌破裂, 介入治疗, 肝动脉灌注化疗栓塞术, 经导管血管栓塞术, 射频消融, 预后

Interventional Therapies of Ruptured Hepatocellular Carcinoma and Its Research Progress

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Abstract

Rupture of HCC (rHCC) is a life-threatening complication of hepatocellular carcinoma (HCC), and

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rHCC may lead to a high rate of peritoneal dissemination and affect survival negatively. We described clinical presentation, prognosis, complication, interventional management, and current evidence of rHCC from the perspective of interventional radiologists. Overall, our review summarized that interventional therapies are necessary for most patients with rHCC to achieve hemostasis, even in some patients with Child-Pugh C. Moreover, TAE/TACE followed by staged hepatectomy is a beneficial treatment for rHCC according to current clinical evidence. TAE/TACE is the first choice for most patients with rHCC, and appropriate interventional treatment may provide staged surgery opportunities.

Keywords

Rupture of Hepatocellular Carcinoma, Interventional Therapy, Transarterial Chemoembolization (TACE), Transarterial Embolization (TAE), Radio Frequency Ablation (RFA), Prognosis

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1. 引言

原发性肝癌主要包括肝细胞癌(hepatocellular carcinoma, HCC)、肝内胆管癌(intrahepatic cholangiocarcinoma, ICC)和混合型肝细胞癌-胆管癌(combined hepatocellular-cholangiocarcinoma, cHCC-CCA)三种不同病理学类型, 三者 in 发病机制、生物学行为、病理组织学、治疗方法以及预后等方面差异较大, 其中 HCC 占 75%~85%、ICC 占 10%~15% [1]。肝细胞癌(hepatocellular carcinoma, HCC)是全球第六大癌症, 也是癌症相关死亡的第四大病因[2]。大多数 HCC 的病因包括乙型肝炎病毒(hepatitis B virus, HBV)和丙型肝炎病毒(hepatitis C virus, HCV)感染, 其余主要包括过度饮酒、非酒精性脂肪性肝炎、其他原因引起的肝硬化以及有肝癌家族史等人群[3] [4]。HCC 自发破裂(ruptured hepatocellular carcinoma, rHCC)是一种危及患者生命的并发症, 估计在 HCC 患者中的发生率为 3%~26% [5] [6], 死亡率在 25%到 75%之间 [7] [8] [9] [10]。此外, 即使肿瘤破裂出血得到完全控制, rHCC 也可能导致腹膜播散率升高并对患者的生存产生负面影响[11], 因此 rHCC 患者术后复发风险高且预后不良[12]。所以对于自发性 rHCC 患者来说, 主要手术目标仍然是预防低血容量休克及稳定病情[13] [14]; 因此治疗方案应该根据患者的情况、肿瘤分期、肝功能、切除的可行性等进行讨论。自发性 rHCC 的治疗方案主要包括急诊手术、介入治疗和姑息治疗。然而是否选择急诊手术治疗仍有争议, 因为一些研究认为自发性 rHCC 患者最初应采用非外科手术治疗[15]。此外, 对与一些身体状况较差的患者或老年患者, 急诊手术的风险较高[16], 急诊手术治疗 rHCC 还有可能增加腹腔出血、感染、肝功能衰竭、胆漏的风险, 因此我们应该仔细评估 rHCC 患者对急诊手术是否耐受。同时, 急诊手术可能会延长一些患者的总体生存时间, 但可能会增加一些患者的肿瘤转移风险[17] [18]。对于一些经过临床治疗, 包括介入治疗和急诊手术治疗等 12 小时无明显改善的 rHCC 患者, 支持性护理可作为一种在垂死病人出血失控时的选择[19]。自发性 rHCC 的初始治疗是包括多学科的综合方法, 治疗的主要目标是患者的生存, 不全是 rHCC 的治疗, 而介入治疗正好能够满足患者快速止血的需要。

介入治疗包括肝动脉灌注化疗栓塞术(transarterial chemoembolization, TACE)、经导管血管栓塞术(transarterial embolization, TAE)、经肝动脉放射栓塞术(transarterial radioembolization, TARE)、微波消融

(microwave ablation, MVA)、射频消融(radiofrequency ablation, RFA), 以上数种都是微创治疗肝癌的方法, 同样适用于那些已经发生了肝外转移的患者[5]。TAE/TACE 可以通过栓塞 rHCC 的供血动脉来达到止血的效果, 并且对比外科开放手术其可应用的条件也更为宽泛, 对于一些不能耐受外科开放手术的患者, 可以采取消融术、TAE/TACE 等术式以达到快速止血的目的[20]。本文也旨在阐明 rHCC 的临床表现、预后、并发症和 TAE/TACE 治疗的优势和目前支持的实验证据, 对现在应用较少的消融术仅作介绍。

2. 肝细胞癌破裂的病理生理及其危险因素

目前关于 HCC 破裂的发病机制和预后分析现仍然存在很多争议, 被广泛接受的假设是: HCC 在破裂之前通常肿瘤组织多表现为快速的扩张, 肿瘤实质内部出血坏死, 同时由于肿瘤侵袭和压迫导致肝静脉流出道阻塞, 继而引起肿瘤内高压, 最终导致肿瘤破裂。也有部分研究报道肿瘤的位置、大小、高血压、肝硬化与 HCC 破裂高度相关, 随着肿瘤的进展, 当肿瘤侵犯肝动脉及门静脉时, 肿瘤内部压力升高, 从而导致 rHCC [21] [22] [23]。

肿瘤的大小与 HCC 破裂之间的关系是存在争议的, Li 等[24]的一项病例对照研究指出虽然肿瘤的大小与肿瘤内血管内压力相关, 但肿瘤的大小并不是 HCC 破裂的显著危险因素。然而 Chen 和 Zhu [22] [25] 等人的研究指出 HCC 大于 5 厘米的患者是发生 rHCC 的高危人群。但不可否认的是, 肿瘤的大小仍是评估患者总生存期以及无病生存期的独立危险因素[26] [27]。如上所述, 如果肿瘤体积增加过快, 内部发生坏死, 可能会导致肿瘤表面发生塌陷继而增加破裂出血的可能。虽然肿瘤的大小是研究 HCC 破裂的重要因素, 临床医生也不能简单地仅通过肿瘤的大小来预测 HCC 是否会发生破裂。

既往研究发现, rHCC 的出现可能与肿瘤内部血管的损伤相关。朱等[28]的研究发现与未破裂的 HCC 患者相比, rHCC 患者的血管损伤更为频繁。Zhu 等[29]的研究发现包括乙型肝炎 e1 抗原和补体 c1q 在内的抗原抗体复合物在血管以及损伤的血管壁上的表达主要出现在 rHCC 的患者身上。他们的结论同时也解释了为什么 rHCC 患者在亚洲比在欧洲更加常见, 因为亚洲的慢性 HBV 发病率最高, 尤其是在中国 [30]。此外, 由于肿瘤的侵袭性生长和压迫, 肝静脉系统充血, 静脉内压力可能也会随之升高, 继而导致肝静脉破裂出血。

此外, HCC 是否破裂还与患者的肝功能、是否伴有门静脉癌栓、位置等因素有关。根据 Monroe 等 [31]的报道, 肝功能越差的患者整体预后也会越差, 同时发生 rHCC 的风险也会越大。位于肝包膜下的浅表肿瘤, 可能更容易受到外力的影响继而发生破裂。

3. 肝细胞自发性破裂的临床表现及诊断

虽然 rHCC 可以表现出很多种临床症状, 但超过 66%的患者都会出现急性腹痛的症状[32]。失血性休克是 rHCC 的第二大常见并发症, 发生率在 33%到 90%之间[8] [10] [18] [33], 同时有 12%到 42%的患者会并发肝脏功能衰竭[14]。在 Zhu 等[25]的研究报告中, 自发性 rHCC 的患者可以是无特殊症状或出现腹胀和贫血的症状, 这表明 rHCC 的表现也是因人而异的, 甚至有一些 HCC 破裂后不会出血或仅表现为血胸[34]。rHCC 患者在临床上多表现为急性腹痛, 利用影像学 and 实验室分析结果, 再结合患者病史, 通常确诊较为容易。超声及 CT 扫描可快速确定肿瘤的破裂位置以及血肿的密度变化, 通过 CT 扫描确诊 rHCC 的最直接证据即在腹腔内发现积血[35], 但也并不是所有的 rHCC 都能在 CT 上观察到腹腔积血。此外, 腹腔的血肿、CT 增强时造影剂外漏、肿瘤轮廓突出肝脏表面、肝脏包膜不连续等也是 rHCC 在 CT 图像上常见的征象[36]。

在怀疑 HCC 患者并发了 rHCC 时, 诊断性腹腔穿刺也可做为一种快速的诊断方法[37]。如果在腹腔穿刺过程中用注射器抽出不凝血, 说明腹腔内有内脏出血, 这也是诊断腹腔内脏出血最有效、最常规的

检查方法[38]。

4. 经导管血管栓塞术/肝动脉灌注化疗栓塞术治疗肝细胞癌破裂

虽然 rHCC 患者的预后并不理想,但已有过介入手术或外科切除术治疗 rHCC 并使患者获益的报道。已有几项研究报道了肝切除术比 TAE/TACE 实现了更好的治疗和止血效果,住院总生存率为 76.5%,1 月生存率为 71% [39] [40] [41], 然而 TAE/TACE 是实现止血和稳定患者病情最常用的选择。一项包括了 974 名 rHCC 患者涉及 21 项研究的荟萃分析(485 名患者接受 TAE/TACE 治疗, 489 名患者接受急诊手术治疗)报道了 TAE/TACE 在术后并发症(OR = 0.36, 95%CI: 0.22~0.57)和住院死亡率(OR = 0.52, 95%CI: 0.29~0.94)方面明显优于急诊手术[6]。

TAE/TACE 治疗 rHCC 的主要优势有: ① 手术在局麻下进行, 避免了全身麻醉对患者生命体征的影响, 患者耐受性更好, 可以为一些同时患有凝血功能异常、肝功能储备差、血流动力学不稳定等危险因素无法耐受急诊手术的 rHCC 患者提供手术止血的机会; ② 止血成功率在 53%~100%, 效果立竿见影且可以重复操作, 更容易发现异位的肿瘤供血动脉并予以治疗。选择性血管栓塞在有效止血的同时, 也最大限度地保护了正常肝组织的功能, 实现了精准治疗; ③ HCC 的血供约 95%由动脉提供, TAE/TACE 可有效阻断肿瘤的大部分血供, 控制出血的同时抑制肿瘤的生长, 为后续手术治疗提供便利; ④ 如病人情况允许, 还可在术中灌注化疗药物治疗原发病; ⑤ 可清楚了解肿瘤的血供、肿瘤与周围血管关系, 以及是否存在动静脉瘘、门静脉血栓等, 为后续治疗提供参考[40] [42]-[48]。

TAE/TACE 还可作为那些等待分期肝切除术患者的临时治疗, 并且也有研究表明 TAE/TACE 术后联合外科分期肝切除术的效果优于单纯的 TAE/TACE、化疗和保守治疗。因此, 建议 rHCC 患者在行介入止血后, 在肝功能储备和贫血状况改善后争取尽快行外科手术切除以改善长期预后。根据 Lee 等[49]和 Hsueh 等[50]的报道, 在行 TAE/TACE 术后行分期肝切除术的患者的总生存率明显高于单纯行 TAE/TACE 的患者。研究发现, 部分 HCC 还存在肝外动脉供血, 包括胃十二指肠动脉、肠系膜上动脉、肾上腺动脉、膈动脉等, 发生率约为 17%~27% [51] [52] [53]。如果这些肝外供血动脉发生破裂, 可能直接导致栓塞不完全和术后反复出血, 所以术中我们更应逐个探查常见的 HCC 肝外供血动脉, 以预防漏栓, 确保止血的效果。临床上常用的栓塞剂有聚乙烯醇颗粒(PVA)、明胶海绵颗粒、碘化油、正丁基-2-氰丙烯酸酯(NBCA)、Onyx 胶、弹簧圈等[54]。在目前的临床实践中, 介入科医生通常会根据肿瘤的位置、出血程度和个人经验使用多种栓塞剂联合止血, 没有证据表明最常用的明胶海绵和 PVA 哪种栓塞剂的止血效果更好。

在我们看来, 治疗 rHCC 的首要的目的还是预防低血容量休克和稳定患者的病情, 次之才是在可行的范围内尽可能地栓塞肿瘤组织[55]。

5. 总结

总之, 对于 rHCC 患者的治疗及临床管理仍是一个不小的挑战, 肝细胞癌自发性破裂出血的治疗应该兼顾快速有效止血以及肿瘤的治疗, 这篇综述通过搜集和总结部分现已发表的临床试验结果, 阐明了介入治疗对于大多数 rHCC 患者来说是实现紧急止血以及分期肝切除术的必要方法。

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