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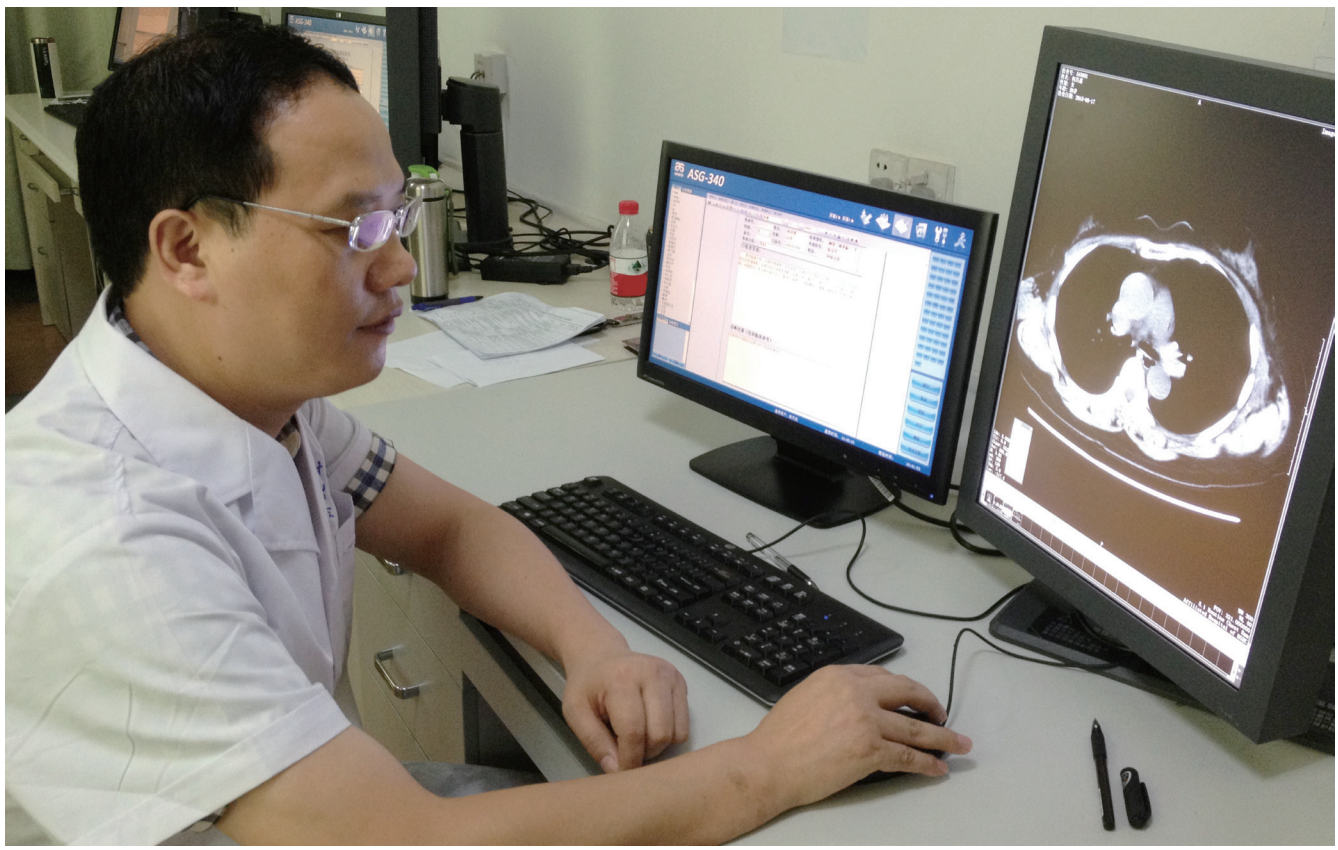

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述评 EDITORIAL

肝硬化患者肝外肿瘤的发病风险及治疗措施

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Risk and treatment of non-hepatic cancers in patients with cirrhosis

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Abstract

Patients with cirrhosis are at a high risk for hepatocellular carcinoma. However, it remains controversial about whether or not there is a high risk for non-hepatic cancers in patients with liver cirrhosis. Additionally, the management of non-hepatic cancers in cirrhotic patients is a clinical challenge, because the use of surgery and anticancer drugs is often compromised by the presence of liver dysfunction. This editorial aims to briefly summarize the findings on the risk and management of non-hepatic cancers in patients with cirrhosis.

Key Words: Liver cirrhosis; Non-hepatic cancer; Alcoholic cirrhosis; Surgery; Chemotherapy

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摘要

肝硬化患者是肝癌的高危人群, 然而, 肝硬化患者是否也存在更高的肝外肿瘤风险仍存争议. 此外, 肝硬化患者肝功能不全常常限制了肝外肿瘤的外科手术和抗癌药物治疗的应用, 这使得肝硬化患者肝外肿瘤的治疗也面临着巨大挑战. 这篇述评旨在简要回顾肝硬化患者肝外肿瘤的发病风险及治疗策略.

关键词: 肝硬化; 肝外肿瘤; 酒精性肝硬化; 手术; 化疗

核心提要: 肝外肿瘤使肝硬化患者生存期更短、生存质量更差, 探索肝硬化患者更易罹患何种肝外肿瘤将有助于明确此类患者是否需要进行更积极的恶性肿瘤筛查. 此外, 探索Child-Pugh B/C级肝硬化合并肝外肿瘤患者手术及化疗药物的疗效和安全性也有着非常重要的临床价值.

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0 引言

肝硬化和恶性肿瘤的发病率均较高[1], 这也增加了同时罹患这两种疾病的概率. 肝硬化是慢性肝病的终末阶段[2], 也是肝细胞癌(hepatocellular carcinoma, HCC)发生发展的主要危险因素[3-5]. 然而, 肝硬化是否增加了肝外肿瘤(non-hepatic cancers, NHC)的发病风险尚存争议. 一些研究发现, 肝硬化与NHC的发病风险无关; 虽然肝硬化患者HCC发病风险升高导致总体癌症发病风险小幅上升, 但NHC的发病风险并未增加[6-9]. 相反, 另一些研究发现, 肝硬化患者某些部位NHC的发病风险增加. 例如, 原发性胆汁性肝硬化(primary biliary cirrhosis, PBC)患者乳腺癌[标准化发病率比值(standardized incidence ratios, SIR): 1.8; 95%CI: 1.08-2.81]的发病风险可能增加[10]; 酒精性肝硬化患者口腔癌(SIR: 8.62; 95%CI: 3.14-18.9)及结肠癌(SIR: 2.81; 95%CI: 1.40-5.04)的发病风险可能增加[11]. 因此, 探索肝硬化患者更易罹患何种NHC将有助于明确此类患者是否需要进行更积极的恶性肿瘤筛查.

合并失代偿期肝硬化的NHC患者预后往往取决于肝硬化并发症, 而非恶性肿瘤本身[12]. 这些患者在进行外科干预或化疗前需考虑肝硬化分期. 若存在严重肝功能不全, 他们将无法耐受外科手术[1,2,13]. 此外, 化疗药物常存在肝细胞毒性, 可能会诱发致命的肝衰竭, 故化疗前需谨慎评估肝功能. 实际上, 癌症治疗的临床试验多排除合并肝硬化的肿瘤患者, 因此, 积极评估化疗药物对不同程度肝功能不全患者的疗效和副作用也是非常重要的.

本文将对肝硬化合并NHC的发病风险以及治疗的研究进展作一综述.

1 肝硬化患者肝外肿瘤的发病风险

1.1 PBC患者乳腺癌发病风险的争议 PBC是一种病因不明的自身免疫性肝病[9], 免疫监视缺陷、肝脏灭活雌激素作用减弱、炎症反应和脂溶性维生素缺乏可能是PBC患者乳腺癌发病率增高的原因[14,15]. 20世纪80年代, 美国和欧洲的研究就已报道了PBC和乳腺癌之间的相关性, Goudie等[15]、Wolke等[16]和Mills等[17]发现PBC患者乳腺癌的发病率增加, 这一结论也被1998年丹麦的全国性队列研究[18] (SIR: 1.3, 95%CI: 1.0-1.6)和2014年Boonstra等[10]的研究所证实(SIR: 1.8; 95%CI: 1.08-2.81). 然而, 2012年, 一项纳入16篇文献的荟萃分析[9]显示PBC与乳腺癌发病风险之间无相关性(SIR: 0.9), 但PBC患者乳腺癌发病风险增加的研究都是在1990年之前进行的, 这可能与1990年以前广泛使用免疫抑制剂有关. 实际上, 2015年, Floreani等[19]分别在意大利帕多瓦(361例患者)和西班牙巴塞罗那(397例患者)进行了两项随访研究, 发现PBC与乳腺癌的发病风险无关(SIR: 0.7, 95%CI: 0.4-1.3), 但国家地区、NHC危险因素和熊去氧胆酸(Ursodeoxycholic acid, UDCA)疗效可能影响研究结论. 未来需要更多大样本前瞻性研究明确PBC与乳腺癌之间的关系.

1.2 酒精性肝硬化患者NHC的发病风险增加 酒精性肝硬化患者可能由于功能性肝细胞减少、酒精脱氢酶活性降低和酒精的直接作用使胃癌、结直肠癌以及胰腺癌的发病率增高[4,11,18,20]. 一项基于27项研究的荟萃分析[21]显示, 每天饮用两种酒精饮料, 结直肠癌的相对风险(relative risk, RR)为1.1 (95%CI: 1.05-1.14). 1998年, 一项丹麦的全国性队列研究[18]随访了11605例存活至少一年的肝硬化患者, 发现酒精性肝硬化患者的口腔癌和咽癌(SIR: 11.6, 95%CI:9.6-14.0）、食道癌(SIR: 9.0, 95%CI: 6.4-12.3)、胃癌(SIR: 1.4, 95%CI:0.8-2.2)、结肠癌(SIR: 1.5, 95%CI: 1.1-2.2)、胰腺癌(SIR: 1.6, 95%CI: 0.9-2.6)发病率均增加. 2008年, Goldacre等[11]也发现酒精性肝硬化患者的口腔癌及唇癌(SIR: 10.1, 95%CI: 5.94-16.2)、咽癌(SIR: 5.01, 95%CI: 1.99-10.5)、食道癌(SIR: 4.05, 95%CI: 2.15-6.96)、胃癌(SIR: 2.01, 95%CI: 0.81-4.16)、结肠癌(SIR: 2.04, 95%CI: 1.19-3.27)、直肠癌(SIR: 2.47, 95%CI: 1.31-4.24)、胰腺癌(SIR: 4.43, 95%CI: 2.28-7.77)的发病风险均增加. 2011年, Kalaitzakis等[4]对1019例肝硬化患者(48%为酒精性肝病)进行分析, 发现酒精性肝硬化患者的食道癌(SIR: 8.3, 95%CI: 1.7-24.2)、结肠癌(SIR: 3.6, 95%CI: 2.0-6.0)、胰腺癌(SIR: 5.1, 95%CI: 1.4-13.2)的发病风险增加. 另外, 酒精性肝硬化患者常伴有吸烟等其他致癌危险因素, 故也可能增加与吸烟相关的肺癌、胆囊癌、肾癌的发病风险[18]. 综上, 酒精性肝硬化患者应适当加强相关恶性肿瘤的监测.

1.3 病毒性肝炎肝硬化患者NHC的发病风险增加 病毒性肝炎是全身性疾病. 肝炎病毒易诱发自身免疫系统紊乱以及肾脏、皮肤、血液、风湿病等肝外疾病. 病毒蛋白对原癌基因、抑癌基因和信号转导途径的影响以及慢性炎症可增加NHC的发病风险[22-24]. 有研究发现, 抗病毒治疗根除丙肝病毒后, 不仅病毒性肝炎得到了缓解, 淋巴瘤也出现了消退, 这证实了病毒性肝炎可能与淋巴瘤存在一定的相关性[25,26]. 也有研究发现, 病毒性肝炎肝硬化可增加口腔癌、肺癌、乳腺癌、食管癌、胰腺癌、前列腺癌、结直肠癌、肾癌及非霍奇金淋巴瘤等NHC的发病风险[24,27-32]. 此外, 病毒性肝炎肝硬化患者多有吸烟史、饮酒史和糖尿病史等, 这些危险因素的

共同作用可能会影响肝脏的免疫功能, 诱发慢性炎症和DNA损伤, 进而增加肝硬化患者的NHC发病风险[24,30]. 2020年, Nyberg等[24]也发现吸烟和糖尿病等危险因素增加了肝硬化患者发生NHC的发病风险. 因此, 对病毒性肝炎肝硬化患者也应适当监测恶性肿瘤.

2 肝硬化患者肝外肿瘤的治疗措施

2.1 *肝硬化合并NHC患者的手术治疗* 手术是肿瘤的治愈方法之一[33,34]. 然而, 若手术应激超出受损肝功能范围, 则可出现腹水、肝功能衰竭和肝性脑病[35-37]. 肝功能不全的严重程度是评估术后死亡率的主要危险因素[38,39]. Child-Pugh A、B、C级患者术后的死亡率分别为10%、30%-31%、76%-82%[2]. 终末期肝病模型(model for end-stage liver disease, MELD)评分≤7、8-11、12-15、16-20、21-25和≥26的术后30天死亡率分别为5.7%、10.3%、25.4%、44.0%、53.8%和90.0%[40]. 也有研究发现, MELD评分5-20分之间每增加1分, 死亡率就增加约1%; MELD评分在20分以上每增加1分, 死亡率就增加约2%[41].

内镜黏膜下剥离术(endoscopic submucosal dissection, ESD)在肝硬化合并早期胃癌患者是可行的, 但其在Child-Pugh B/C级患者的角色尚存争议[42-45]. 2008年, Ogura等[42]纳入了18例行ESD治疗的胃癌患者, 其中, 15例伴有肝硬化(均为Child-Pugh A/B级); 研究表明ESD可安全地用于肝硬化合并胃癌的患者, 整体切除率高. 2015年, Kato等[43]比较了行ESD的肝硬化患者和无肝硬化患者之间的短期结局; 虽然两组间的短期结局无显著差异, 但是肝硬化患者的长期预后明显差于无肝硬化患者(5年总生存率分别为60%和91%). 胃癌根治术加扩大淋巴结清扫术对Child-Pugh A级的胃癌患者来说是可行的, 但Child-Pugh B/C级患者应慎重[46-48]. 合并肝硬化的结直肠癌患者总生存(overall survival, OS)率更低[49-51]、术后并发症发生率更高(P = 0.005)[50]; MELD评分>8分(P<0.001)和Child-Pugh B/C级患者不建议手术治疗[49,52-54]. Child-Pugh B/C级肝硬化合并非小细胞肺癌患者也需慎重行肺癌手术[35,37,55,56]. 综上, 为了尽量减少肝硬化患者术后并发症及死亡率, 应积极评估并改善患者肝功能. Child-Pugh A级或MELD评分≤7分的肝硬化患者手术耐受性良好; Child-Pugh B级需在术前及时纠正肝功能; Child-Pugh C级患者不建议手术.

2.2 *肝硬化合并NHC患者的化疗* 化疗是癌症的另一种主要治疗手段, 但其可引起从轻度转氨酶升高到严重肝衰竭等不同程度的肝毒性[57-59]. 对于肝硬化合并NHC患者来说, 若预计生存期超过3 mo、Child-Pugh评分≤7分且无腹水, 则可考虑化疗[2]. 研究发现Child-Pugh A级患者接受腹腔化疗不仅安全, 而且可以延长远期生存[60,61]; 有病例报道提示, Child-Pugh B级肝硬化合并急性早幼粒白血病患者的化疗效果非常好[62]; Child-Pugh B级肝硬化合并非小细胞肺癌患者口服吉非替尼未见疾病进展, 且无任何肝毒性[63]. 总的来说, 肝硬化患者需依据化疗药的肝毒性及肝功能评分来衡量是否需要适当减少化疗药物剂量. 由于目前的研究多为小样本回顾性研究或Ⅰ期临床试验, 属于低质量证据[2], 因此未来的临床试验需进一步探索针对肝硬化患者的个体化和规范化的化疗治疗策略.

3 结论

基于当前研究证据, 肝硬化是否增加NHC的发病风险仍不确定. 由于肝硬化患者NHC的发病率较低, 未来的研究需要纳入更多的研究人群, 且需注意排除导致肿瘤的其他病因、尽可能避免选择偏倚. 此外, Child-Pugh B/C级肝硬化合并NHC的患者中, 综合性治疗的角色尚不确定. 目前, 仅少数研究评估了肝硬化合并NHC患者手术及化疗的疗效及安全性; 分子靶向治疗和免疫治疗的研究证据也非常欠缺. 期待未来更多临床试验结果为此类患者诊疗的个体化和最优化提供科学依据.

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