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Hans汉斯

# 肝细胞癌伴门静脉癌栓转化治疗进展

**周雍博，宋春雷，樊海宁***

青海大学附属医院肝胆胰外科，青海 西宁

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## 摘　要

**肝细胞癌伴门静脉癌栓发生率高，预后差，现有治疗方式仍存在较大争议。在最新版肝细胞癌合并门静脉癌栓诊疗指南中已明确推荐癌栓侵犯门静脉一级或二级的患者(程氏分型I/II型)，首选手术切除。然而临床中有相当一部分患者的病灶范围较广或癌栓侵及门静脉主干(程氏III型)无法根治性切除，需要经转化降期治疗后再手术切除。笔者结合国内外相关文献报道，发现通过肝动脉化疗栓塞术、肝动脉灌注化疗、放疗、免疫及靶向等治疗方法，部分患者可出现门静脉癌栓消退、肿瘤体积缩小，从而使病灶降期，转化成功并接受根治性手术从而延长了生存时间。同时，多学科之间的相互协作对进一步提高转化切除率也举足轻重。**

## 关键词

**肝细胞癌，门静脉癌栓，转化治疗，降期治疗，靶向治疗**

# Progress in Transformation Therapy of Hepatocellular Carcinoma with Portal Vein Cancer Thrombus

**Yongbo Zhou, Chunlei Song, Haining Fan***

Department of Hepatopancreatobiliary Surgery, Affiliated Hospital of Qinghai University, Xining Qinghai

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## Abstract

**Hepatocellular carcinoma with portal vein thrombectomy has a high incidence and poor prognosis, and the existing treatment methods are still controversial. In the latest edition of the guidelines**

*通讯作者。

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**for the diagnosis and treatment of hepatocellular carcinoma complicated with portal vein thrombectomy, it is clearly recommended that surgical resection be the first choice for patients with portal vein thrombectomy at Grade I or Grade II (Cheng's type I/II). However, in clinical practice, a considerable number of patients with a wide range of lesions or cancer embolism and main portal vein (Cheng's Type III) cannot be radically resected, and need to undergo transformation downphase treatment before surgical resection. Combined with relevant literature reports at home and abroad, the author found that through the treatment methods of hepatic artery chemoembolization, hepatic artery infusion chemotherapy, radiotherapy, immunization and targeting, some patients could have the regression of portal vein cancer thrombus and tumor volume reduction, thus making the lesion downphase, and successfully transforming and receiving radical surgery, thus extending the survival time. At the same time, multidisciplinary cooperation is also important to further improve the conversion reduction rate.**

## Keywords

**Hepatocellular Carcinoma, Portal Vein Cancer Thrombus, Conversion Therapy, Descending Treatment, Targeted Therapy**



## 1. 引言

原发性肝细胞癌(简称肝癌)在全球恶性肿瘤发病率中排名第 6 位，是 2020 年全世界癌症死亡的第 3 大原因[1]。根据中国癌症统计，我国有肿瘤登记的地区最新数据表明，肝癌的发病率在男性患者中排名第 4 位，死亡率在所有恶性肿瘤中排名第 3 位，是中国居民在 60 岁之前最常见的恶性肿瘤[2]。近年来，随着影像诊断技术不断发展，健康体检的不断普及，肝癌的检出能力有了一定的提高。但因肝癌早期的临床症状并不明显，多数患者就诊时已进入进展期。所以其目前整体预后仍不理想。由于肝癌细胞极易侵犯门静脉系统，形成门静脉癌栓(Portal vein tumor thrombus, PVTT)，据统计其发生率高达 44%~62.2% [3]。且无任何干预时进展迅速，肝功能明显恶化，中位生存期仅为 2.7 个月[3]。由于预后极差且缺乏有效的治疗手段，PVTT 是影响肝癌整体疗效提高的瓶颈。

欧美国家的肝癌指南以巴塞罗那肝癌分期(Barcelona Clinic Liver Cancer Staging, BCLC)为标准将肝癌合并 PVTT 归入进展期(BCLCC 期)，此期推荐分子靶向药物如索拉非尼和仑伐替尼等作为一线治疗[4]。然而，中国与西方国家在肝癌的病因学、生物学特性、对治疗的反应性方面存在差异。我国肝癌最常见的原因为 HBV 感染，临床数据显示 HBV 相关性肝癌对索拉非尼的反应性显著低于西方国家的 HCV 相关性肝癌[5]。由于肝癌起病隐匿，进展快，一大部分患者就诊时已失去手术指征。中国及日韩等国的许多研究认为先通过非手术治疗使病灶体积缩小，再进行根治性手术可取得较好的预后[6]。

## 2. 肝癌合并 PVTT 的临床分型和意义

PVTT 的发生部位、范围与病人临床症状及预后密切相关。常用 PVTT 分型主要有日本肝癌学会提出的 VP 分型[7]和我国程树群教授提出的程氏分型[8]。程氏分型根据癌栓侵犯范围分为 I 型：癌栓侵犯门静脉二级及以上分支；II 型：癌栓侵及门静脉一级分支；III 型：侵犯门静脉分叉部和主干；IV 型：侵犯肠系膜上静脉。程氏分型较日本 VP 分型更适用于我国肝癌合并 PVTT 病人的病情评估、治疗指导及

预后判断[9] [10]。

门静脉癌栓的临床分型对于治疗方案的选择非常重要。首次治疗尽量选择最大可能去除或控制肝癌原发灶以及 PVTT 的方法。Kokudo 等[11]对 6474 例肝癌合并 PVTT 患者进行倾向性匹配分析，其中 2093 名接受手术治疗的患者和 4381 名接受其他治疗的患者进行了比较。结果：I/II 型癌栓手术切除效果显著优于非手术治疗，手术没有为 III 型癌栓带来明显的生存获益。手术组的中位生存时间比非手术组长 1.77 年(2.87 年 vs. 1.10 年；$p < 0.001$)。根据多中心、大队列的研究表明：肝功能 Child-Pugh A、原发灶可切除、PVTTI/II 型癌栓首选治疗方案为手术[12] [13] [14] [15]。因此，若能通过一些治疗方法使癌栓范围缩小后再行手术治疗，可能会有更好的结果。

最新发布的《中国肝细胞癌合并门静脉癌栓诊疗指南(2021 年版)》将转化治疗推荐用于治疗原发肿瘤不可切除、分型较差的 PVTT 患者[12]。转化治疗是在降期治疗的基础上拓展，通过化疗、放疗、介入、免疫靶向等治疗方法将癌栓分型降低、范围缩小后再进行手术以期获得更好的临床疗效。

## 3. 肝癌合并 PVTT 的转化治疗

### 3.1. 放疗

由于肝组织对放疗的耐受性低，所以曾经放疗一般不用于肝癌的治疗。但随着放疗技术的发展，精确放射治疗技术使得放疗具有更高的精度和更好的适应性，而且不会增加正常组织发生并发症的几率，因此现在放射治疗已经越来越多的用于治疗肝癌[16]。

国内上海东方肝胆外科医院的一项随机、多中心对照研究[17]比较了新辅助三维适形放疗(3DCRT)后行肝切除术与单纯肝切除术的生存结果，结果发现术前放疗组中 20.7%的患者出现了癌栓的降期，并明显延长了患者术后生存时间。Hamaoka 等[18]的回顾性研究显示 3DCRT 联合肝动脉灌注化疗(HAIC)使 17.3%不能切除的患者转化为可切除的患者，并且接受手术的患者生存时间较非手术患者明显延长。韩国的一项回顾性研究[19]纳入 637 例 BCLCC 期初始不可切除肝癌，3/4 伴有门静脉的侵犯，在接受调强放疗(IMRT)联合 HAIC，41 例(16.9%)患者降期后接受手术，手术组与未手术组的中位总生存期为 103.8 和 11.4 个月($p < 0.001$)。

上述放疗方案均属于外放射治疗，在内放射治疗中，国内常见的方式为植入碘-125 ($I^{125}$)，实验表明[20] [21] [22]经门静脉植入 $I^{125}$ 粒子与肝动脉化疗栓塞(TACE)联用的中位生存期优于单独 TACE 或者 TACE 联用靶向药物。近年国外有应用钇-90 ($Y^{90}$)微球经肝动脉植入治疗肿瘤的报道，称为肝动脉放疗性栓塞(TARE)。Garin 等[23]报道了 41 例 PVTT 患者使用钇-90 微球治疗的病例，最终 30 名患者部分缓解，5 名完全缓解，剩余 6 名病情稳定，总缓解率为 85%。其中五名患者接受了根治性手术，总体的生存期显著高于其他没有接受手术的患者。Edeline 等[24]对比了钇-90 与索拉非尼对于 PVTT 的疗效，34 例接受钇-90 治疗的患者最终有 4 例转化成功并进行了根治性手术。接受钇-90 治疗的中位生存期为 18.8 个月，显著超过索拉非尼治疗的中位生存期 6.5 个月。另一项回顾性研究[25]比较了钇-90 与索拉非尼单药治疗的疗效，其结果显示钇-90 对于 PVTT 的转化成功后手术率为 24.4%，显著高于索拉非尼的 4.2%。即使未转化成功，钇-90 组的存活率也更高。近期国内刚完成首例钇-90 治疗肝癌后的的手术根治性切除，期待未来更大的发展空间。

### 3.2. 经导管动脉化疗栓塞术 Transcatheter Arterial Chemoembolization (TACE)

TACE 是一种常用于治疗不可切除肝癌合并 PVTT 的方法，但由于癌栓也会导致门静脉血流受阻，肝功能不全甚至肝衰竭，因此其是否适用于 PVTT III/IV 型患者尚存争议。不过越来越多的研究结果显示：因为 TACE 可以阻塞肝动脉，减少原发灶及癌栓的血供，从而使肿瘤及癌栓缺血坏死达到降期的目的。

所以对于肝功能良好，门静脉侧支循环建立的病人可以行 TACE，且对于肝功能良好但无法手术的病人，TACE 是首选姑息性治疗方法[26] [27]。Yoon 等[28]人的一项随机对照试验纳入了 90 例 PVTT 患者，其中 45 人接受 TACE + 体外放射治疗，另 45 人接受靶向药物治疗。先通过放疗控制癌栓的体积，为后续 TACE 提供更好的条件。最终 TACE 组的总生存期(55.0 vs. 43.0 周；$p = 0.04$)明显长于索拉非尼组，且 TACE 组中 5 例分期下降接受了根治性的手术。Fan 等[29]报道 360 例不可切除肝癌行肝动脉化疗栓塞术(TACE)后，成功转化的患者(转化率达 18.1%)再行手术切除后其 5 年生存率与早期肝癌切除术后生存率接近。

### 3.3. 肝动脉灌注化疗术(HAIC)

HAIC 是指插管进入肝动脉进行灌注化疗。有研究显示 HAIC 的中位总生存期(OS)和客观缓解率(ORR)均优于 TACE 并且不良反应更小，适用范围更广[30] [31]。最终转化成功并接受手术的患者显示出了更高的 5 年生存率[32]。Lyu 等[33]对比了 HAIC 与索拉非尼的疗效，结果显示：HAIC 中位生存期明显长于索拉非尼组(14.5 个月 vs. 7.0 个月，$p < 0.001$)，且 HAIC 组中有 47 例(26.1%)分期降低从而有机会接受局部治疗。而 HAIC 与索拉非尼联合使用可能也会有更好的效果，Nagai 等[34]的研究显示联合治疗较单独使用 HAIC 的总生存期(OS)延长 4 个月。Lee 等[35]报道了一项纳入 243 例 PVTT 患者的回顾性研究，接受 HAIC 和同步放化疗(CCRT)后剩余肝体积增加，提高了肿瘤的可切除性，其中 41 例(16.9%)接受了根治性切除。一项对于 98 例 PVTT 患者的回顾性研究[36]显示，纳入患者 5 周内接受总剂量为 45 Gy 的 3DCRT 治疗，同时在第 1 和第 5 周行 5-氟尿嘧啶(5-FU)的 HAIC，放疗结束后 1 个月开始每 4 周接受 1 次 5-Fu 联合顺铂的 HAIC。结果通过中位 3.5 个周期的 HAIC 后，转化成功接受手术患者有 26 人，转化率为 26.5%，其中 5 例病灶评估为完全缓解，13 例部分缓解。所以，HAIC 与放疗或靶向药物联合使用可能效果会更好。

### 3.4. 免疫及靶向治疗

近年来，靶向药物和免疫检查点抑制剂(ICIs)在实体肿瘤的治疗中发展迅速，但单一用药治疗的客观缓解率有限，据统计[37] [38] [39]索拉非尼、卡博替尼、瑞戈非尼、仑伐替尼治疗肝癌的客观缓解率分别为(3.3%、4.0%、6.5%、18.8%)。而以 ICIs 为代表的免疫治疗拥有更高的客观缓解率和更低的不良反应率[38]。与单一用药相比，联合用药可能将进一步提高转化治疗的客观缓解率[40]。Huang 等[41]的回顾性单臂研究结果显示仑伐替尼联合 PD-1 对于 PVTT 的客观缓解率为 54.4%。17 例达到客观缓解的患者中，6 例(18.1%)接受了手术，术后病理提示 66.7%的癌栓达到病理完全坏死。Tsai 等的一项研究纳入 28 例 PVTT 患者，PD-1 联合 TKI 的客观缓解率为 50%，其中两例完全缓解，一例接受了根治性切除。如上文提到索拉非尼与 HAIC 联合使用可能会有更好的效果，He 等[42]的研究比较了 HAIC 联合索拉非尼与索拉非尼单独治疗 PVTT 的疗效，结果显示联合治疗的中位总生存期(13.37 个月 vs. 7.13 个月，$p < 0.001$)显著优于单药治疗，并且联合治疗组 12.8%的患者转化成功接受了后续手术治疗。另一项回顾性研究[43]也显示了联合治疗的优势：仑伐替尼联合特瑞普利单抗以及 HAIC 治疗相比仑伐替尼单药治疗有更高的客观缓解率(59.2% vs. 9.3%, $p < 0.001$)和转化切除率(9 例 vs. 0 例，$p = 0.001$)。

## 4. 小结

近年来，对于肝癌合并 PVTT 的诊断与治疗取得了很大的进步，治疗方式的多样化与治疗积极性的提高使得越来越多的患者从中获益，但依然有大部分患者由于癌栓或者原发病灶范围广泛而无法获得令人满意的疗效。转化治疗作为一种新兴的治疗方式为 PVTT 患者带来了更多的机会，肝癌生物学上的异质性和病情的复杂性使单一治疗方式明显受到限制，通过多种不同的治疗方式相结合，一部分患者的肿

瘤体积缩小、癌栓降期，从而提高了手术切除率及延长了生存时间。

我国肝癌合并 PVTT 患者数量多，病情多变复杂，在治疗时可能需要同时面对原发肿瘤、癌栓以及肝功能不全等多方面的问题，因此单一学科治疗很容易出现偏向性，而这种误差很可能会错过了治疗的最佳时期导致病情出现进展。所以多学科综合治疗的重要性就凸显出来，例如对于转化治疗而言就涉及到肝胆外科、肿瘤内科、介入科、影像科、放疗科等。这样各取所长才能提高肝癌合并 PVTT 患者的转化切除率。笔者认为：肝癌合并 PVTT 的转化治疗现处于快速发展期，应结合国内病人的实际情况，从临床出发，积极开展多中心前瞻性或随机对照试验，筛选出不同治疗方案的最佳获益对象，判断转化手术的最佳时机，最大限度提高治疗效果，改善其生活质量。

## 参考文献


[1] Sung, H., Ferlay, J., Siegel, R.L., *et al*. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Chen, W., Zheng, R., Baade, P.D., *et al*. (2016) Cancer Statistics in China, 2015. *CA*: *A Cancer Journal for Clinicians*, **66**, 115-132. https://doi.org/10.3322/caac.21338

[3] Zhang, Z.M., Lai, E.C., Zhang, C., *et al*. (2015) The Strategies for Treating Primary Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *International Journal of Surgery*, **20**, 8-16. https://doi.org/10.1016/j.ijsu.2015.05.009

[4] European Association for the Study of the Liver (2018) EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma. *Journal of Hepatology*, **69**, 182-236.

[5] Ng, J. and Wu, J. (2012) Hepatitis B- and Hepatitis C-Related Hepatocellular Carcinomas in the United States: Similarities and Differences. *Hepatitis Monthly*, **12**, e7635. https://doi.org/10.5812/hepatmon.7635

[6] Lu, J., Zhang, X., Zhong, B., *et al*. (2019) Management of Patients with Hepatocellular Carcinoma and Portal Vein Tumour Thrombosis: Comparing East and West. *The Lancet Gastroenterology & Hepatology*, **4**, 721-730. https://doi.org/10.1016/S2468-1253(19)30178-5

[7] Ikai, I., Yamamoto, Y., Yamamoto, N., *et al*. (2003) Results of Hepatic Resection for Hepatocellular Carcinoma Invading Major Portal and/or Hepatic Veins. *Surgical Oncology Clinics of North America*, **12**, 65-75. https://doi.org/10.1016/S1055-3207(02)00082-0

[8] 程树群, 吴孟超, 陈汉, 等. 肝癌门静脉癌栓分型的影像学意义[J]. 中华普通外科杂志, 2004, 19(4): 200-201.

[9] Niu, Z.-J., Ma, Y.-L, Kang, P., *et al*. (2012) Transarterial Chemoembolization Compared with Conservative Treatment for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: Using a New Classification. *Medical Oncology*, **29**, 2992-2997. https://doi.org/10.1007/s12032-011-0145-0

[10] Shi, J., Lai, E.C., Li, N., *et al*. (2011) A New Classification for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Journal of Hepato-Biliary-Pancreatic Sciences*, **18**, 74-80. https://doi.org/10.1007/s00534-010-0314-0

[11] Kokudo, T., Hasegawa, K., Matsuyama, Y., *et al.* (2016) Survival Benefit of Liver Resection for Hepatocellular Carcinoma Associated with Portal Vein Invasion. *Journal of Hepatology*, **65**, 938-943. https://doi.org/10.1016/j.jhep.2016.05.044

[12] 中国医师协会肝癌专业委员会. 中国肝细胞癌合并门静脉癌栓诊疗指南(2021 年版) [J]. 中华医学杂志, 2022, 102(4): 243-254.

[13] Zhang, X.-P., Wang, K., Wei, X.-B., *et al*. (2019) An Eastern Hepatobiliary Surgery Hospital Microvascular Invasion Scoring System in Predicting Prognosis of Patients with Hepatocellular Carcinoma and Microvascular Invasion after R0 Liver Resection: A Large-Scale, Multicenter Study. *Oncologist*, **24**, e1476-e1488. https://doi.org/10.1634/theoncologist.2018-0868

[14] Zheng, N., Wei, X., Zhang, D., *et al*. (2016) Hepatic Resection or Transarterial Chemoembolization for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Medicine*, **95**, e3959. https://doi.org/10.1097/MD.0000000000003959

[15] Wang, K., Guo, W.X., Chen, M.S., *et al*. (2016) Multimodality Treatment for Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Large-Scale, Multicenter, Propensity Mathching Score Analysis. *Medicine*, **95**, e3015. https://doi.org/10.1097/MD.0000000000003015

[16] Yu, J.I. and Park, H.C. (2016) Radiotherapy as Valid Modality for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis. *World Journal of Gastroenterology*, **22**, 6851-6863. https://doi.org/10.3748/wjg.v22.i30.6851

[17] Wei, X., Jiang, Y., Zhang, X., *et al*. (2019) Neoadjuvant Three-Dimensional Conformal Radiotherapy for Resectable

Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Randomized, Open-Label, Multicenter Controlled Study. *Journal of Clinical Oncology*, **37**, 2141-2151. https://doi.org/10.1200/JCO.18.02184

[18] Hamaoka, M., Kobayashi, T., Kuroda, S., *et al*. (2017) Hepatectomy after Down-Staging of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus Using Chemoradiotherapy: A Retrospective Cohort Study. *International Journal of Surgery*, **44**, 223-228. https://doi.org/10.1016/j.ijsu.2017.06.082

[19] Byun, H.K., Kim, H.J., Im, Y.R., *et al*. (2019) Dose Escalation by Intensity Modulated Radiotherapy in Liver-Directed Concurrent Chemoradiotherapy for Locally Advanced BCLC Stage C Hepatocellular Carcinoma. *Radiotherapy and Oncology*, **133**, 1-8. https://doi.org/10.1016/j.radonc.2018.12.025

[20] Li, Y., Li, H., Hu, H., Yuan, H. and Zhao, Y. (2020) Efficacy and Safety of Transcatheter Arterial Chemoembolization Combined with either $^{125}$I Seed Implantation or Apatinib in Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Retrospective Comparative Study. *Journal of Cancer Research and Therapeutics*, **16**, 1691-1697.

[21] Zhang, Z.-H., Zhang, W., Gu, J.-Y., *et al*. (2018) Treatment of Hepatocellular Carcinoma with Tumor Thrombus with the Use of Iodine-125 Seed Strand Implantation and Transarterial Chemoembolization: A Propensity-Score Analysis. *Journal of Vascular and Interventional Radiology*, **29**, 1085-1093. https://doi.org/10.1016/j.jvir.2018.02.013

[22] Yang, M., Fang, Z., Yan, Z., *et al*. (2014) Transarterial Chemoembolisation (TACE) Combined with Endovascular Implantation of an Iodine-125 Seed Strand for the Treatment of Hepatocellular Carcinoma with Portal Vein Tumour Thrombosis versus TACE Alone: A Two-Arm, Randomised Clinical Trial. *Journal of Cancer Research and Clinical Oncology*, **140**, 211-219. https://doi.org/10.1007/s00432-013-1568-0

[23] Garin, E., Rolland, Y., Edeline, J., *et al*. (2015) Personalized Dosimetry with Intensification Using $^{90}$Y-Loaded Glass Microsphere Radioembolization Induces Prolonged Overall Survival in Hepatocellular Carcinoma Patients with Portal Vein Thrombosis. *Journal of Nuclear Medicine*, **56**, 339-346. https://doi.org/10.2967/jnumed.114.145177

[24] Edeline, J., Crouzet, L., Campillo-Gimenez, B., *et al*. (2016) Selective Internal Radiation Therapy Compared with Sorafenib for Hepatocellular Carcinoma with Portal Vein Thrombosis. *European Journal of Nuclear Medicine and Molecular Imaging*, **43**, 635-643. https://doi.org/10.1007/s00259-015-3210-7

[25] Martelletti, C., Ricotti, A., Gesualdo, M., *et al*. (2021) Radioembolization vs Sorafenib in Locally Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis: A Propensity Score and Bayesian Analysis. *Journal of Digestive Diseases*, **22**, 496-502. https://doi.org/10.1111/1751-2980.13030

[26] Wang, J.-C., Xia, A.-L., Xu, Y. and Lu, X.-J. (2019) Comprehensive Treatments for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis. *Journal of Cellular Physiology*, **234**, 1062-1070. https://doi.org/10.1002/jcp.27324

[27] Chung, G.E., Lee, J.-H., Kim, H.Y., *et al*. (2011) Transarterial Chemoembolization Can Be Safely Performed in Patients with Hepatocellular Carcinoma Invading the Main Portal Vein and May Improve the Overall Survival. *Radiology*, **258**, 627-634. https://doi.org/10.1148/radiol.10101058

[28] Yoon, S.M., Ryoo, B.-Y., Lee, S.J., *et al*. (2018) Efficacy and Safety of Transarterial Chemoembolization plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial. *JAMA Oncology*, **4**, 661-669. https://doi.org/10.1001/jamaoncol.2017.5847

[29] Fan, J., Tang, Z.-Y., Yu, Y.-Q., *et al*. (1998) Improved Survival with Resection after Transcatheter Arterial Chemoembolization (TACE) for Unresectable Hepatocellular Carcinoma. *Digestive Surgery*, **15**, 674-678. https://doi.org/10.1159/000018676

[30] He, M.-K., Le, Y., Li, Q.-J., *et al*. (2017) Hepatic Artery Infusion Chemotherapy Using mFOLFOX versus Transarterial Chemoembolization for Massive Unresectable Hepatocellular Carcinoma: A Prospective Non-Randomized Study. *Chinese Journal of Cancer*, **36**, 83. https://doi.org/10.1186/s40880-017-0251-2

[31] Hu, J., Bao, Q., Cao, G., *et al*. (2020) Hepatic Arterial Infusion Chemotherapy Using Oxaliplatin Plus 5-Fluorouracil Versus Transarterial Chemoembolization/Embolization for the Treatment of Advanced Hepatocellular Carcinoma with Major Portal Vein Tumor Thrombosis. *CardioVascular and Interventional Radiology*, **43**, 996-1005. https://doi.org/10.1007/s00270-019-02406-3

[32] Yoon, H.I., Song, K.J., Lee, I.J., *et al*. (2016) Clinical Benefit of Hepatic Arterial Infusion Concurrent Chemoradiotherapy in Locally Advanced Hepatocellular Carcinoma: A Propensity Score Matching Analysis. *Cancer Research and Treatment*, **48**, 190-197. https://doi.org/10.4143/crt.2014.276

[33] Lyu, N., Kong, Y., Mu, L., *et al*. (2018) Hepatic Arterial Infusion of Oxaliplatin plus Fluorouracil/Leucovorin vs. Sorafenib for Advanced Hepatocellular Carcinoma. *Journal of Hepatology*, **69**, 60-69. https://doi.org/10.1016/j.jhep.2018.02.008

[34] Nagai, H., Mukozu, T., Ogino, Y., *et al*. (2015) Sorafenib and Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Anticancer Research*, **35**, 2269-2277.

[35] Lee, H.S., Choi, G.H., Choi, J.S., *et al*. (2014) Surgical Resection after Down-Staging of Locally Advanced Hepatocellular Carcinoma by Localized Concurrent Chemoradiotherapy. *Annals of Surgical Oncology*, **21**, 3646-3653.

https://doi.org/10.1245/s10434-014-3652-3

[36] Chong, J.U., Choi, G.H., Han, D.H., *et al*. (2018) Downstaging with Localized Concurrent Chemoradiotherapy Can Identify Optimal Surgical Candidates in Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. *Annals of Surgical Oncology*, **25**, 3308-3315. https://doi.org/10.1245/s10434-018-6653-9

[37] Kudo, M., Finn, R.S., Qin, S., *et al*. (2018) Lenvatinib versus Sorafenib in First-Line Treatment of Patients with Unresectable hepatocellular Carcinoma: A Randomised Phase 3 Non-Inferiority Trial. *The Lancet*, **391**, 1163-1173. https://doi.org/10.1016/S0140-6736(18)30207-1

[38] Abou-Alfa, G.K., Meyer, T., Cheng, A.L., *et al*. (2018) Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *The New England Journal of Medicine*, **379**, 54-63. https://doi.org/10.1056/NEJMoa1717002

[39] Cheng, A.-L., Kang, Y.-K., Chen, Z., *et al*. (2009) Efficacy and Safety of Sorafenib in Patients in the Asia-Pacific Region with Advanced Hepatocellular Carcinoma: A Phase III Randomised, Double-Blind, Placebo-Controlled Trial. *The Lancet Oncology*, **10**, 25-34. https://doi.org/10.1016/S1470-2045(08)70285-7

[40] Mohr, R., Jost-Brinkmann, F., Ozdirik, B., *et al*. (2021) Lessons from Immune Checkpoint Inhibitor Trials in Hepatocellular Carcinoma. *Frontiers in Immunology*, **12**, Article 652172. https://doi.org/10.3389/fimmu.2021.652172

[41] Huang, C., Zhu, X.-D., Shen, Y.-H., *et al*. (2021) Organ Specific Responses to First-Line Lenvatinib plus Anti-PD-1 Antibodies in Patients with Unresectable Hepatocellular Carcinoma: A Retrospective Analysis. *Biomarker Research*, **9**, Article No. 19. https://doi.org/10.1186/s40364-021-00274-z

[42] He, M., Li, Q., Zou, R., *et al*. (2019) Sorafenib plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma with Portal Vein Invasion: A Randomized Clinical Trial. *JAMA Oncology*, **5**, 953-960. https://doi.org/10.1001/jamaoncol.2019.0250

[43] He, M.-K., Liang, R.-B., Zhao, Y., *et al*. (2021) Lenvatinib, Toripalimab, plus Hepatic Arterial Infusion chemotherapy *versus* Lenvatinib Alone for Advanced Hepatocellular Carcinoma. *Therapeutic Advances in Medical Oncology*, **13**, Article ID: 17588359211002720. https://doi.org/10.1177/17588359211002720