WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.63
Volume 15, Issue 6, 429-438. Review Article ISSN 2277–7105

ROLE OF EXTERNAL BEAM RADIOTHERAPY IN HEPATOCELLULAR CARCINOMA WITH PORTAL VEIN TUMOR THROMBOSIS

C. Sugavanam*[1], M. Ranjith[2], K. Rithika[2], S. Priyadharshini[1], V. Anushree[1]

[1]Students, SS Institute of Pharmacy, Sankari.

[2]Assistant Professor, SS Institute of Pharmacy, Sankari.

Article Received on 15 Feb. 2026,
Article Revised on 05 March 2026,
Article Published on 16 March 2026,

https://doi.org/10.5281/zenodo.19044508

***Corresponding Author**

C. Sugavanam

Students, SS Institute of Pharmacy, Sankari.

How to cite this Article: C. Sugavanam*[1], M. Ranjith[2], K. Rithika[2], S. Priyadharshini[1], V. Anushree[1]. (2026). Role of External Beam Radiotherapy In Hepatocellular Carcinoma With Portal Vein Tumor Thrombosis. World Journal of Pharmaceutical Research, 15(6), 429–438.

ABSTRACT

Hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) marks an advanced stage of the disease. This stage comes with few treatment options and a poor outlook. The presence of PVTT often prevents effective treatments like surgery and liver transplants. Locoregional therapies, such as transarterial chemoembolization, also carry a high risk of liver failure. Recently, improvements in external beam radiotherapy (EBRT) techniques have sparked renewed interest in its use for HCC patients with PVTT. Modern radiotherapy can precisely target the tumor in the portal vein while reducing exposure to healthy liver tissue. This review summarizes the reasons for using EBRT in HCC with PVTT. It outlines commonly used radiotherapy techniques, discusses how to select patients, and safety profiles reported in the literature. Available evidence shows that EBRT can significantly shrink the portal vein tumor thrombus, improve local tumor control, relieve symptoms, and provide modest survival benefits in carefully chosen patients. Additionally, EBRT can be safety combined with systemic therapies in a team-based treatment approach. Though most data come from retrospective studies and have their limitations, the consistent clinical benefits observed support the use of EBRT as a valuable treatment for unresectable HCC with PVTT. Future prospective studies are needed to better define the best treatment strategies and patient selection.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common types of liver cancer worldwide and is a leading cause of death due to cancer. Even with improvements in screening and treatment, many patients are diagnosed at an advanced stage. At this point, options like surgical removal or liver transplant are often not possible. Portal vein tumor thrombosis (PVTT) is a common and serious problem in advanced HCC.[1] It happens when cancer cells invade the portal vein, causing a blockage of blood flow, worsening liver function, and quick disease progression. Having PVTT is widely seen as bad sign, leading to significantly lower survival rates. Treating HCC with PVTT is still tough. Standard treatments, like surgical removal and transarterial chemoembolization (TACE), are often not suitable or come with a high risk of liver failure for these patients. Because of this, treatment choices are few, and there is no widely accepted standard approach for this group. Recently, advancements in external beam radiotherapy (EBRT) have sparked new interest in its use for HCC with PVTT.[2] Modern radiotherapy can accurately and the thrombosis in the portal vein while preserving healthy liver tissue. Several clinical studies have indicated that EBRT may offer good local control, relieve symptoms, and improve survival for certain patients with manageable side effects. Still, the exact role of EBRT in treating HCC with PVTT is not fully clear, and the available evidence varies widely. Thus, a thorough review of existing literature is necessary to understand its benefits, safety, and patient outcomes. This review seeks to summarize how external beam radiotherapy plays a role in patients with hepatocellular carcinoma and portal vein tumor thrombosis, focusing on the reasons for treatment, clinical outcomes, and safety issues.[3]

PORTAL VEIN TUMOR THROMBOSIS

Portal vein tumor thrombosis (PVTT) is a common and clinically significant complication of advanced hepatocellular carcinoma (HCC) and represents an aggressive manifestation of tumor progression. It is defined by the presence of viable malignant tumor tissue within the portal venous system, arising from the strong propensity of HCC for vascular invasion. Unlike bland portal vein thrombosis, which consists of fibrin and blood components, PVTT is composed of proliferating cancer cells that originate from the primary hepatic tumor. The development of PVTT occurs through direct extension of the hepatic tumor into adjacent portal vein branches or through microscopic invasion of the venous endothelium. As hepatocellular carcinoma progresses, malignant cells infiltrate segmental or lobar portal branches and subsequently proliferate within the vessel lumen, leading to intravascular tumor

growth and formation of a tumor thrombus. In advanced cases, this tumor thrombus may extend proximally into the main portal vein, reflecting extensive vascular involvement and advanced disease stage. The presence of tumor thrombosis within the portal vein results in partial or complete obstruction of portal venous blood flow to the liver. This obstruction leads to reduced hepatic perfusion and elevation of portal venous pressure, thereby causing significant hemodynamic disturbances. Impaired portal circulation contributes to the development of portal hypertension and its associated complications, including ascites, splenomegaly, and gastroesophagal variceal bleeding. Furthermore, diminished portal blood supply exacerbates underlying hepatic dysfunction, particularly in patients with cirrhosis, which is commonly associated with HCC. Clinically, PVTT is associated with rapid tumor progression, limited therapeutic options, and markedly reduced survival outcomes. The presence of PVTT often precludes curative surgical resection and renders transarterial therapies hazardous due to the risk of hepatic ischemia and liver failure. Consequently, PVTT is widely recognized as a major adverse prognostic factor in hepatocellular carcinoma and represents a critical challenge in disease management, necessitating alternative therapeutic approaches.[4]

WHY PVTT IS A TREATMENT CHALLENGE

Portal vein tumor thrombosis (PVTT) is a major treatment challenge in patients with hepatocellular carcinoma (HCC). PVTT happens when tumor cells invade the portal venous system. This invasion leads to obstruction of portal blood flow, which is crucial for normal liver function. As a result, liver blood flow is compromised, causing a decline in liver function and increasing portal pressure. Patients with PVTT often experience complications like fluid buildup, bleeding from varices, and reduced liver function. These issues significantly limit the safety and effectiveness of treatment options. PVTT is also linked to more aggressive tumor behavior and a worse prognosis. Survival rates are much lower for patients with PVTT compared to those with HCC without vascular invasion. Curative treatments, such as surgery and liver transplantation, are usually not possible due to technical challenges, advanced disease, and a high risk of recurrence. Moreover, locoregional therapies like trasarterial chemoembolization are often not suitable or need careful patient selection. This is because further reducing blood flow can lead to liver injury and decompensation. Systemic therapies are the standard treatment for advanced HCC, but their benefits for patients with PVTT are limited. In general, the combination of advanced tumor stage, poor liver function, high risk of bleeding, and limited options for curative or locoregional therapies

makes PVTT one of the most difficult conditions to manage in hepatocellular carcinoma.[5]

RATIONALE FOR USING EBRT IN PVTT

Portal vein tumor thrombosis (PVTT) indicates an advanced stage of hepatocellular carcinoma (HCC) and is linked to a poor prognosis because of reduced portal blood flow, rapid tumor growth, and limited treatment options. Surgical removal and liver transplantation are usually not suitable for most patients due to the advanced disease stage and poor liver function. Likewise, locoregional treatments like transarterial chemoemboization (TACE) pose a high risk of liver ischemia and failure when PVTTT is present, especially if the main portal vein is affected. External beam radiotherapy (EBRT) has become an important treatment option for unresectable HCC with PVTT. It can deliver precise, high doses of radiation to the tumor thrombosis while sparing the surrounding healthy liver tissue. New radiotheraphy methods, such as three-dimensional conformal radiotheraphy (3D-CRT), intensity-modulated radiotheraphy (IMRT), and stereotactic body radiotheraphy (SBRT), have greatly improved targeting accuracy and decreased radiation-related liver damage. EBRT is crucial for controlling local tumors by directly targeting the portal vein tumor thrombosis. This can lead to tumor shrinkage, reopening of the portal vein, and restoring portal blood flow. Improved blood flow can enhance liver function and make patients eligible for more systemic or locoregional treatments. Additionally, EBRT can safety be combined with systemic treatments like sorafenib, lenvatinib, or immunotherapy. This combination results in better overall survival and longer progression-free survival. For patients with PVTT not eligible for curative treatment, EBRT effectively reduces the tumor burden, manages disease progression, and enhances quality of life. Thus, EBRT is a sensible and effective treatment choice for patients with unresectable HCC and PVTT, especially for those with decent liver function when other treatment options are limited or unsuitable.[6]

TYPES OF EXTERNAL BEAM RADIOTHERAPY USED IN PVTT

Advances in external beam radiotheraphy (EBRT) techniques have made it possible to treat hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) safety and effectively. Modern EBRT methods provide precise targeting of the portal vein tumor thrombosis while reducing radiation exposure to nearby healthy liver tissue and other organs. The main types of EBRT used for PVTT, based on techniques highlighted in clinical studies, include three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT). Three-dimensional

conformal radiotherapy (3D-CRT) is often used to manage HCC with PVTT. This technique involves using multiple radiation beams that match the three-dimensional shape of the tumor and portal vein thrombosis. By optimizing the dose distribution, 3D-CRT effectively targets the tumor thrombus while limiting radiation to healthy liver tissue. This approach reduces the risk of radiation-induced liver disease. Clinical studies show that 3D-CRT provides good local control and symptom relief for patients with unresectable PVTT. Intensity-modulated radiotherapy (IMRT) is a more sophisticated EBRT technique that adjusts the intensity of radiation within each beam. IMRT allows for better dose targeting and protects normal liver tissue more effectively than 3D-CRT. This technique is especially useful for patients with weakened liver function or significant portal vein involvement, where precise dose delivery to the tumor thrombus is needed without compromising liver safety. IMRT has shown to improve local control and lower treatment-related side effects in certain PVTT patients. Stereotactic body radiotherapy (SBRT) administers high doses of radiation in fewer sessions with great accuracy. SBRT is typically used for carefully chosen patients with localized disease and relatively healthy liver function. Although the experience with SBRT in PVTT is still limited compared to traditional EBRT methods, growing evidence indicates that SBRT can provide promising local tumor control with acceptable side effects in selected cases. Overall, having multiple EBRT techniques available EBRT techniques available allows for personalized treatment planning for patients with HCC and PVTT, balancing effective control of the tumor thrombus with the preservation of liver function.[7]

PATIENT SELECTION CRITERIA

Choosing the right patient is key to getting the best results with external beam radiotherapy (EBRT) for hepatocellular carcinoma (HCC) patients who have portal vein tumor thrombosis (PVTT). EBRT is generally recommended for patients with unresectable disease who cannot undergo curative surgery. A careful evaluation of liver function, tumorsize, and overall health is vital for ensuring the treatment is safe and effective. Patients with unresectable HCC and confirmed PVTT are suitable for EBRT, especially when surgical removal or transarterial therapies are not options. Having sufficient liver function, often classified as Child-Pugh class A or select class B patients. Those with severe liver failure usually do not qualify due to a higher risk of radiation-induced liver disease. Factors related to the tumor also significantly influence patient selection. EBRT works best for patients with localized disease that is limited to the liver and without extensive spread to other organs. If the portal vein is involved, such as segmental, lober, or main portal vein thrombosis, treatment with EBRT

may proceed if enough unaffected liver tissue can be preserved during planning. Additionally, patients should have a good performance status, usually indicated by eastern Cooperative 0ncology Group (ECOG) performance status, which shows they have the ability to handle radiotherapy. It is also essential to have acceptable blood counts and no uncontrolled ascities or active gastrointestinal bleeding. In summary, EBRT is most appropriate for carefully chosen patients who have unresectable HCC and PVTT, along with preserved liver function, limited disease spread, and good performance status. This approach allows for effective control of the tumor while reducing the risk of treatment-related side effects.[8]

CLINICAL OUTCOMES

Clinical outcomes following external beam radiotherapy (EBRT) in hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT) have been evaluated in multiple restrospective and prospective studies. EBRT has demonstrated meaningful clinical benefits in terms of portal vein tumor thrombus response, local tumor control, survival outcomes, and symptom improvement. Several studies have reported significant regression of portal vein tumor thrombus following EBRT. Reduction in thrombus size and partial or complete recanlization of the portal vein have been observed, leading to improved portal blood flow and stabilization of liver function. This response of the tumor thrombus is a critical determinant of treatment success in PVTT patients. In terms of local tumor control, EBRT has been shown to effectively control both the primary hepatic tumor and the associated portal vein tumor thrombus. Improved local control contributes to delayed disease progression and reduces the risk of further vascular invasion. Advanced radiotherapy techniques such as IMRT and SBRT have further enhanced local control rates while minimizing radiation exposure to normal liver tissue. Survival outcomes have also been favorably influenced by EBRT in selected patients with PVTT. Although overall prognosis remains poor in advanced HCC, studies have demonstrated improved overall survival and progression-free survival in patients receiving EBRT compared with best supportive care or historical controls. Notably, patients who achieve EBRT in combination with systemic therapies tend to experience better survival outcomes. In addition to oncological outcomes, EBRT provides important palliative benefits. Symptom relief, including reduction in abdominal pain, improvement in liver-related symptoms, and enhanced quality of life, has been consistently reported. By improving portal vein patency and controlling tumor burden, EBRT contributes to clinical stabilization and allows some patients to receive subsequent

systemic or locoregional treatments. Overall, available evidence suggests that EBRT offers meaningful clinical benefits in carefully selected HCC patients with PVTT, particularly in terms of thrombus control, local disease management, and survival prolongation, with acceptable safety profiles.[9]

TOXICITY AND SAFETY

The safety profile of external beam radiotherapy (EBRT) in hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) has improved a lot with advancements in radiotherapy techniques. In the past, using radiotheraphy for liver tumors was limited due to worries about radiation-induced liver disease (RILD). However, modern EBRT methods allow for safer dose delivery while keeping healthy liver tissue intact. The main toxicity linked to EBRT in PVTT is radiation-induced liver disease, which shows up as liver dysfunction after treatment. Careful patient selection, sticking to dose limits, and keeping enough functional liver volume have cut down the cases of serious RILD. Patients with good baseline liver function handle EBRT better, while those with severe liver damage face a higher risk. Gastrointestinal issues, like nausea, vomiting, and radiation-related gastritis or duodenitis, can happen because the liver is close to other organs. These side effects are usually mild to moderate and can be managed with supportive car. Severe gastrointestinal problems are rare when modern planning methods are used. Other side effects include temporary fatigue and blood count suppression, which usually get better on their own. The use of techniques like IMRT and SBRT allows for precise dose distribution, which reduces exposure to healthy liver tissue, stomach, and intestines. Consequently, EBRT is generally well tolerated and has acceptable toxicity profiles in carefully selected patients. Overall, current evidence shows that EBRT is a safe treatment choice for HCC patients with PVTT when using modern radiotherapy techniques and suitable selection criteria. This approach balances effective tumor control with maintaining liver function.[10]

EBRT COMPARED WITH OTHER TREATMENTS

Treatment for hepatocellular carcinoma (HCC) complicated by portal vein tumor thrombosis (PVTT) faces challenges due to the advanced stage of the disease, poor liver function, and higher risks of treatment-related side effects. External beam radiotheraphy (EBRT) has become an important treatment choice. It works differently from other therapies and has specific clinical uses.

EBRT versus Surgical Resection

Surgical resection can lead to long-term survival for select patients with limited PVTT and good liver function. Still, most patients cannot undergo surgery because of extensive vascular invasion and cirrhosis. EBRT offers a non-invasive alternative, providing a safe way to treat cases that can't be surgically removed. While EBRT does not cure the cancer, it is important for stabilizing the disease and managing symptoms.[11]

EBRT versus Transarterial Chemoembolization (TACE)

TACE is often used for patients with intermediate-stage HCC but carries significant risks for those with PVTT due to reduced blood flow in the portal vein. Blocking this blood flow can lead to liver ischemia and failure. On the other hand, EBRT does not disrupt blood flow and can specifically target the portal vein tumor thrombus. Thus, EBRT is seen as a safer local treatment, especially for patients with main portal vein involvement, where TACE is not advised.[12]

EBRT versus Systemic Therapy

Systemic therapies, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, are the standard for advanced HCC. These treatments aim to address tiny spread-out cancer sites but struggle to control PVTT locally. EBRT supports systemic therapy by effectively controlling the local tumor thrombus, lowering tumor burden, and stabilizing liver function. New studies indicate that combining EBRT with systemic therapy may lead to better survival rates than using either treatment alone.[13]

EBRT in Multimodal Treatment Strategies

Unlike single-treatment approaches, EBRT can it into a broader treatment plan. It can be used as a main local therapy, as a bridge to systemic treatment, or alongside other locoregional therapies. This flexibility highlights the special role of EBRT in managing HCC with PVTT.[14]

LIMITATION OF CURRENT EVIDENCE

Despite growing evidence supporting the role of external beam radiotheraphy (EBRT) in hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT), several limitation must be noted when looking at current data. Must be noted when looking at current data. Most studies are retrospective, which introduces selection bias and limits our ability to establish cause-and-effect relationships. There is also a significant gap in the literature due to

the lack of large-scale randomized controlled trials comparing EBRT with other treatments. Another key limitation is the diversity of patient populations across studies. Variations in liver function, extent of portal vein involvement, tumor burden, and previous treatments make it difficult to generalize outcomes and identify the best patient groups. Additionally, differences in radiotherapy techniques, dose schedules, and definitions of target volumes complicate comparisons between studies. Survival outcomes reported in the literature are further affected by other therapies, including systemic treatments, which may obscure the independent impact of EBRT. Long-term toxicity data are limited, especially with newer radiotherapy techniques, and follow-up periods are often too short to fully evaluate late side effects. Finally, most evidence comes from single-centre experience or studies with selected patient groups, which may affect external validity. These limitations emphasize the need for well-designed prospective trials and standardized treatment protocols to better clarity the role of EBRT in HCC patients with PVTT.[15]

CONCLUSION

Hepatocellular carcinoma with portal vein tumor thrombosis represents a later stage of the disease, offering few treatment options and a poor outlook**.** External beam radiotherapy has become an important treatment in this difficult situation. It allows for direct targeting of the portal vein tumor thrombus while protecting healthy liver tissue. Improvements in radiotherapy methods have increased precision and safety, enabling EBRT to achieve significant local disease control with manageable side effects in carefully chosen patients. Research shows that EBRT can lead to a reduction in portal vein tumor thrombus, stabilization of liver function, relief of symptoms, and a slight survival advantage, especially when used as part of a broader treatment plan. Though most current information comes from retrospective studies, the consistent benefits seen across various studies support EBRT's role as a key part of multidisciplinary care for unresectable HCC with PVTT. More prospective studies are needed to optimize patient selection, treatment methods, and combinations to enhance clinical results.

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