

Percutaneous Radiofrequency Ablation in Liver Tumor

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ABSTRACT

Treatment modalities for hepatocellular carcinoma (HCC) include curative therapy and palliative therapy. Potentially curative therapies are resection, liver transplantation and ablation. Tumor ablation is a minimally invasive approach commonly used in the treatment of liver tumors. Over the last two decades, percutaneous radiofrequency ablation (RFA) has been widely used for primary tumors and small metastases, especially in the liver. Effective treatment of RFA can be accomplished by complete ablation of the tumor accompanied by a margin resection of at least 0.5 cm. Many studies have confirmed that percutaneous RFA is a low-risk procedure with low morbidity and mortality. Bleeding, liver injury, extrahepatic organ injury, tumor development, skin burns due to poor contact between electrode pads and skin are complications that can occur.

Keywords: *tumor ablation, radiofrequency ablation, liver tumor*

ABSTRAK

Modalitas pengobatan untuk karsinoma hepatoseluler (HCC) termasuk terapi kuratif dan terapi paliatif. Terapi yang berpotensi kuratif adalah reseksi, transplantasi hati, dan ablasi. Ablasi tumor adalah pendekatan invasif minimal yang biasa digunakan dalam pengobatan tumor hati. Selama dua dekade terakhir, ablasi frekuensi radio perkutaneus (RFA) telah banyak digunakan untuk tumor primer dan metastasis kecil, terutama di hati. Pengobatan RFA yang efektif dapat dicapai dengan ablasi tumor lengkap disertai dengan reseksi margin minimal 0,5 cm. Banyak penelitian telah mengkonfirmasi bahwa RFA perkutan adalah prosedur berisiko rendah dengan morbiditas dan mortalitas yang rendah. Pendarahan, cedera hati, cedera organ ekstrahepatik, perkembangan tumor, kulit terbakar karena kontak yang buruk antara bantalan elektroda dan kulit adalah komplikasi yang dapat terjadi.

Kata kunci: *ablasi tumor, ablasi radio frekuensi, tumor hepar*

INTRODUCTION

Liver tumors usually present common clinical features, especially with the increasing use of various imaging modalities in the diagnosis of abdomen and other symptoms. Accurate and reliable determination of liver mass is very important to identify individuals with lesions and also to ensure that malignant lesions can be diagnosed correctly. Correct diagnosis is important to avoid the adverse consequences of missed diagnosis and the necessary treatment of malignancy or treatment of non-tameable lesions.¹

With careful history taken, physical examination, laboratory and imaging studies, most liver tumors can be characterized noninvasively. When noninvasive characterization cannot be determined, a biopsy may be required for a definite diagnosis. Standard histological examination is usually complemented by immunohistochemical analysis of protein biomarkers. Accurate diagnosis allows appropriate selection of optimal management. Imaging diagnosis of liver tumors is a clinical challenge in itself. Among them, the most common primary malignant tumors are hepatocellular carcinoma (HCC) and cholangiocarcinoma. Metastases are also another common lesion. For malignant lesions or malignant transformation, treatment is based on tumor stage, functional status of the uninvolved patient, and surgical technical considerations.^{1,2}

Tumor ablation is a minimally invasive approach commonly used in the treatment of liver tumors. Ablation therapy is considered a potential first-line treatment in many patients with small hepatocellular carcinoma or an alternative for people who cannot undergo surgical resection or chemotherapy failure. In addition, tumor ablation can also be useful as an adjunct therapy or may provide an alternative strategy to surgery.³ Over the last two decades, percutaneous radiofrequency ablation (RFA) has been widely used for primary tumors and small metastases, especially in the liver. Overall and survival rates of RFA were found to be more effective than those observed with surgical resection.³ In this literature, we will discuss percutaneous radiofrequency ablation in liver tumors.

HEPATOCELLULAR CARCINOMA

Definition

Hepatocellular carcinoma (HCC) is a primary liver tumor. More than 90% of the incidence is a primary liver tumor. Hepatocellular carcinoma occurs in approximately 85% of patients diagnosed with

cirrhosis. HCC is the fifth most common cause of cancer worldwide. The second leading cause of cancer death after lung cancer in men is HCC. Significant risk factors for hepatocellular carcinoma include viral hepatitis (hepatitis B and hepatitis C), alcoholic liver disease, and non-alcoholic liver steatohepatitis/non-alcoholic fatty liver disease. Hepatocellular carcinoma occurs in 80-90% of patients with cirrhosis. The annual incidence of HCC in patients with cirrhosis is 2-4%.⁵

PATHOGENESIS

Cirrhosis is the underlying condition in viral carcinogenesis for hepatocellular carcinoma. The integration of the hepatitis B virus genome into the host genome is the main pathogenesis of oncogenesis in HBV. The insertion of the viral genome at the telomerase reverse transcriptase (TERT) promoter site of the human genome results in mutations, accounting for 60% of cases. Other genetic changes include mutations in TP53 (affecting the cell cycle), beta-1 catenin (CTNNB1), axis inhibitor-1 (AXINI), a protein containing the AT 1A-rich interaction domain (ARID1A), and ARID2 (chromatin proliferation). The chronic inflammation of chronic hepatitis C virus infection with fibrosis, necrosis, and regeneration contributes to the development of liver cancer. Molecular biomarkers noted in hepatic carcinogenesis include structural and non-structural viral proteins (NS3, NS4A, NS4B, NS5A, and NS5B). HCV-associated HCC occurs mostly in patients with advanced cirrhosis or fibrosis. A risk factor that contributes to the development of HCC is the consumption of alcohol, NASH, and NAFL, exposure to alpha-toxin, diabetes mellitus, smoking, and genetic disorder such as antitripsin-alpha-1 deficiency, hemochromatosis, porphiria, and wilson's disease. Figure 1 summary risk factors of hepatocellular carcinoma.^{5,6}

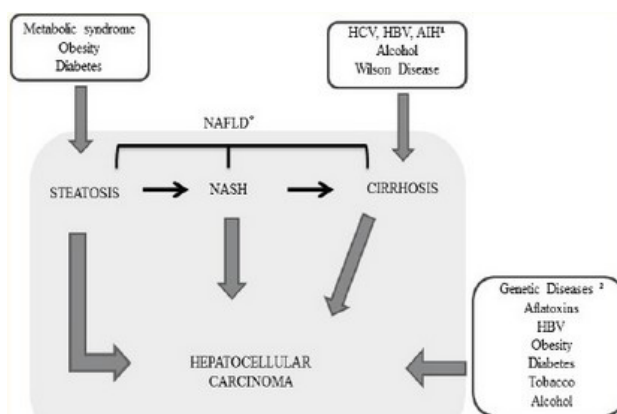


Figure 1. Hepatocellular carcinoma (HCC) risk factors

DIAGNOSIS

Patients with HCC may be asymptomatic or symptomatic, depending on whether the cirrhosis is clinically compensated or decompensated. In compensated cirrhosis, the patient is usually asymptomatic, and disease is detected incidentally by laboratory, physical examination, or imaging. One common finding is a mild to moderate increase in gamma-glutamyl aminotransferase or transpeptidase with enlargement of the liver or spleen on physical examination. On the other hand, patients with decompensated cirrhosis usually present with a variety of signs and symptoms arising from the combination of hepatic dysfunction and portal hypertension.⁷ HCC usually develops from dysplastic nodules and is characterized by increased arterial vascularity and progressive loss of the portal venous blood supply that supplies the regenerative nodules. These features produce a characteristic pattern of arterial phase enhancement followed by portal vein or delayed clearance phase on multiphase CT or contrast MRI. In lesions larger than 1 cm, this pattern is diagnostic for liver cancer and is considered a "radiological feature of HCC" (Figure 2).⁸

Hepatocellular Carcinoma Treatment Algorithm

Treatment modalities for hepatocellular carcinoma (HCC) include curative therapy and palliative therapy. Potentially curative therapies are resection, liver transplantation and ablation. Palliative therapies include transarterial chemoembolization (TACE), stereotactic body radiation therapy (SBRT), external beam radiation therapy (EBRT), selective internal radiation therapy (SIRT) and systemic therapy. In determining HCC therapy, there are several stages that can be seen in Figure 3. The choice of modality for HCC therapy is determined based on the degree of liver function, performance status and tumor burden including extrahepatic spread, vascular invasion, number of nodules and nodule size. Management of HCC should be discussed in a multidisciplinary team in order to obtain a comprehensive picture of the patient's condition and treatment options can be adjusted based on the patient's condition. The multidisciplinary team generally consists of hepatologists, hepatobiliary and/or transplant surgeons, oncologists, interventional radiologists, radiotherapists, pathologists and nurses.⁹

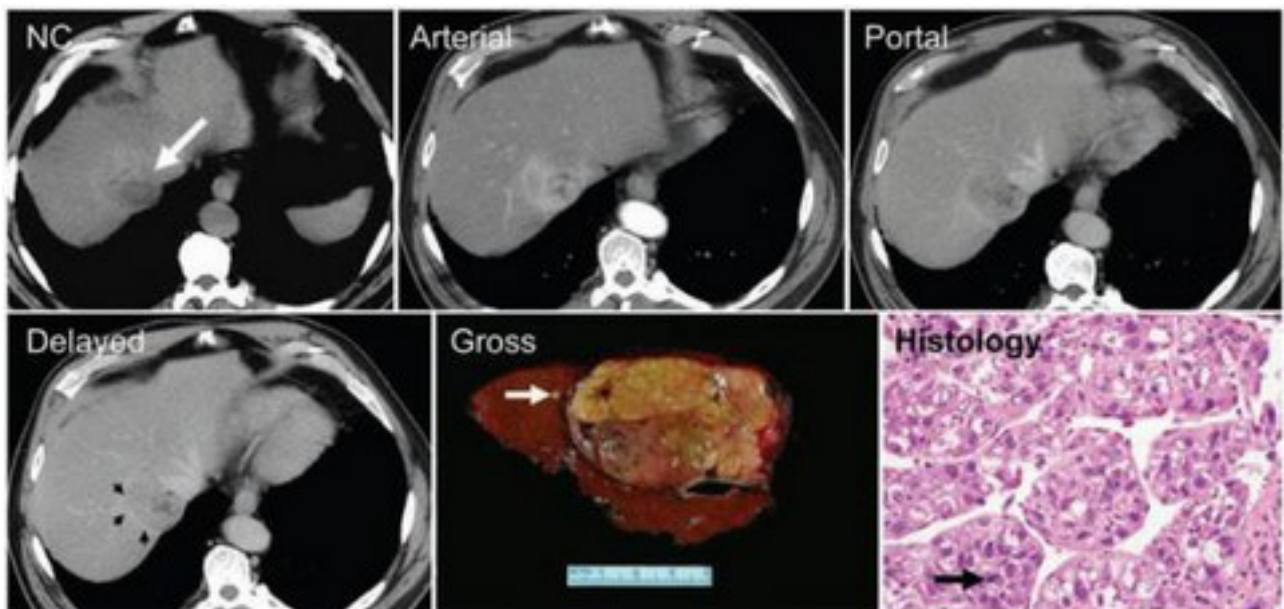


Figure 2. Hepatocellular carcinoma of the liver. The mass appeared heterogeneous due to the presence of intra-tumoral fat which was confirmed on histology. The mass shows arterial phase enhancement with portal vein and delayed phase washout with a thin pseudocapsule (black arrow). A rough outline shows a large mass in the right lobe. Separate small satellite lesions are also visible (white arrows). Microscopic sections (hematoxylin and eosin $\times 400$ staining) show hepatocellular carcinoma showing rare trabecular and mitotic architecture (black arrows).⁸

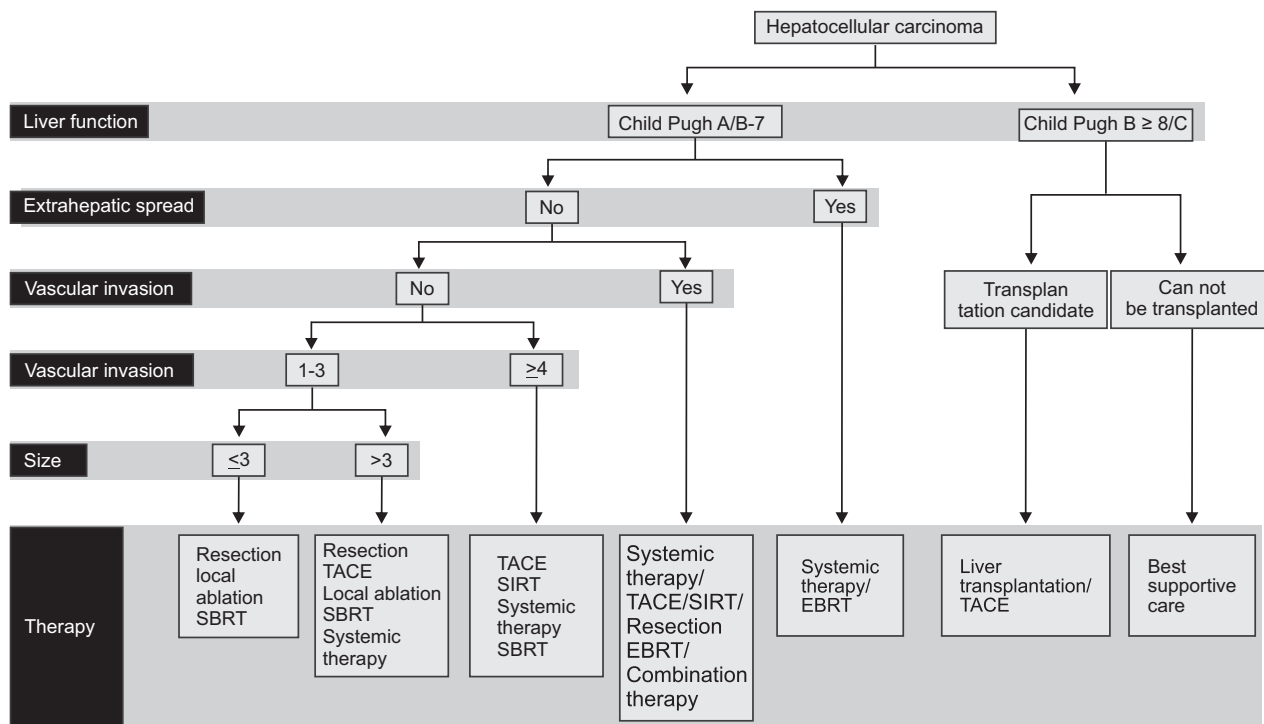


Figure 3. Hepatocellular carcinoma (HCC) treatment algorithm⁹

PERCUTANEOUS RADIOFREQUENCY ABLATION (RFA)

Over the past two decades, radiofrequency ablation (RFA) has been widely used for primary tumors and small metastases. The overall and disease-free survival rate of RFA was found to be more effective than surgical resection. In addition, RFA has been shown to be more effective than percutaneous ethanol injection for local tumor control and has lower side effects compared to other ablative procedures. Effective treatment of RFA can be accomplished by complete ablation of the tumor accompanied by a margin resection of at least 0.5 cm. The success rate of RFA is highly dependent on the precision of tumor targeting, which is influenced by two main factors, such as electrode tip placement and angulation for electrode placement. Various previous studies have shown the failure of RFA to completely ablate tumors due to the inability to determine optimal electrode location and angulation.⁴ Liver tumor radioablation has developed as a minimally invasive treatment with curative potential, and is integrated into international treatment protocols. This method is increasingly being used because it has been shown to be effective compared to the group of patients treated with resection alone. The combination of highly effective treatment and low complication rate makes this method commonly used. This method is suitable for the management of patients with liver tumors,

such as hepatocellular carcinoma (HCC), intrahepatic cholangiocellular carcinoma (ICC), or metastatic disease.

Radiofrequency Ablation (RFA) Indication

In the treatment of liver tumors, the indications for percutaneous RFA are wider than surgery and intra-arterial therapy, these include HCC in the early stages, primary treatment for small tumors, inoperable primary liver tumors, treatment of patients who cannot undergo general anesthesia or not a candidate for surgery because of comorbidities or advanced age, hepatic metastases, most often colorectal, especially if the patient have breast, thyroid, and neuroendocrine metastases, treatment of patients who have a hepatoma or multiple small and moderate lesions pending liver transplantation, recurrent and progressive lesions and RFA can also be used in HCC 3 cm or smaller in size in Child-Pugh grade A or B cirrhosis. Percutaneous RFA are first-line treatment in HCC 2 cm or smaller in Child-Pugh grade A or B.^{11,12}

Contraindication of Radiofrequency Ablation (RFA)

In general, percutaneous RFA is considered for peripheral lesions less than 5cm or up to three lesions smaller than 3cm in diameter in Child-Pough A or B patients, without surgical treatment of choice, or in patients who are poor candidates for surgical procedures

because of comorbidities. Contraindications include absolute and relative contraindications.¹³

Absolute contraindications are the presence of an operable tumor and/or awaiting transplant (if the tumor is considered operable and/or the patient is a good candidate for transplant), vascular invasion by the tumor, tumor location < 1 cm from the main bile duct, at a distance of 1 cm from the main bile duct. In this way, the bile ducts are at risk of injury if not protected. Abscess formation, biliary stenosis, and biliary obstruction occur more frequently when the bile duct is within the area of thermally induced necrosis, intrahepatic biliary duct dilatation, exophytic tumor site and irreversible coagulopathy.¹⁴

For relative contraindications, i.e. extrahepatic metastases (treatment of liver tumors may be performed if successful treatment of extrahepatic metastases is deemed achievable), bilioenteric anastomosis (possibility of causing infection; antibiotic prophylaxis may help with prevention), superficial/subcapsular lesions, especially those adjacent to the any of the gastrointestinal tract or gallbladder (risk of thermal injury to the gastric/intestinal wall or iatrogenic cholecystitis; open approach is preferred), decompensated cirrhosis, tumor difficult to reach with electrodes or when electrode placement is impaired (in this case, open approach is preferred), single tumor greater than 5 cm in diameter or multiple lesions greater than 3 cm in diameter each (RFA may be used in larger liver tumors for the purpose of wound healing before chemotherapy or for pain relief), more than 3 tumors and tumors directly adjacent to hepatic blood vessels (flowing blood usually protects the vessel wall from thermal injury but reduces the effectiveness of the procedure due to heat loss by convection).¹⁴

Principles of Radiofrequency Ablation (RFA)

Radiofrequency percutaneous ablation causes cell death due to thermocoagulation necrosis. Heat is generated by ionic excitation and is related to the strength of the applied energy. Currently, two types of RFA devices are used clinically. Monopolar (MP) RFA uses a single antenna, while bipolar (BP) RFA uses dual antennas, or two electrodes on the same antenna facing each other. Monopolar RFA is commonly used for liver cancer ablation. According to the size and shape of the probe, a spherical ablation area is produced in about 10–30 minutes, generally with a diameter of 2 to 5 cm. With RFA, the heating zone of the active tissue is limited to a few millimeters surrounding the active electrode, with the remainder of the ablation zone being

heated by thermal conduction. With an increase in the size of the target area, the effectiveness of the treatment decreases, since the maximum yield is obtained for a volume of less than 3.5 cm.^{3,15}

In addition, several tissue properties, such as electrical conductivity, thermal conductivity, dielectric permittivity, heat capacity, and blood perfusion rate, greatly affect the growth of the ablation zone. RFA induces thermal breakdown by utilizing high-frequency currents (375–500 kHz), which cause ionic oscillations, frictional heating, and coagulation necrosis as the end result. Temperature at 50°C for 4–6 minutes causes toxicity, while irreversible protein coagulation occurs between 60–100°C. In addition, during ablation, the tissue can become dehydrated, which can increase the impedance of the tissue to the flow of electric current. RFA is limited by increased impedance and excessive temperature. Several technical devices exist to avoid this effect, such as monitoring temperature or impedance during the procedure or simultaneously implanting saline solution into the tissue surrounding the RF area.^{3,15}

Equipment in Radiofrequency Ablation (RFA)

Radiofrequency ablation is an ablation technique that cause necrosis by applying heat to the tumor tissue. To create an ablation zone, an electric current is applied to the tumor through electrodes. To create a closed electrical circuit, the electrode operates as the cathode, while several pads attached to the skin act as the anode. Ions near the electrodes reverberate rapidly as they try to align with the current. This causes an increase in temperature inside the tumor (direct heating), as well as the surrounding tissue (indirect heating), a combination of these effects, forming an ablation zone. RFA requires 3 main pieces of equipment, consisting of, probe, power generator (Figures 4 and 5) as well as some ground bearings. The RF generator is connected to the electrodes via an insulated cable as well as several grounding pads that are placed on the skin of the patient's thigh. The electric generator creates a current of about 300-500kHz.^{14,16}



Figure 4. The AMICA radiofrequency ablation system¹⁶



Figure 5. The STAR Tumor Ablation System consists of the MetaSTAR generator and the SpineSTAR ablation instrument (Courtesy of DFINE, Inc)¹⁶

Procedure for Radiofrequency Ablation (RFA)

Radiofrequency percutaneous ablation was performed by an interventional radiologist in the radiology room, after anesthesia/sedation. Before the needle is inserted into the lesion, pre-procedural imaging is performed to determine the point of entry, safe passage, and position of the needle tip. Once access is established, the probe is inserted into the tumor percutaneously, usually under ultrasound or computed tomographic (CT) guidance. If needed, local anesthesia can be given. Next, the electrode is passed through the anesthetized pathway and into the mass. For lesions equal to or less than 2 cm in diameter, a needle electrode is placed in the center of the tumor. The electrodes are extended to produce a current of 50-200 watts. After the temperature reaches 90° C, ablation is carried out for approximately 8-25 minutes. The duration of ablation depends on the type of probe used. The tumor and a margin of about 1 cm of normal tissue were ablated. An air temperature of 60°C, approximately 30 seconds after the end of ablation, is required to confirm tumor necrosis.¹⁴

Large tumors require multiple areas of ablation. Instead of placing the probe in the center of the lesion as is done with smaller lesions, the electrodes are placed along the distal edge of the tumor. Multiple ablations were performed sequentially, moving proximally until the entire lesion and a 1 cm margin of normal tissue adequately ablated. A successful RFA requires continuous progressive heat. This ensures that the temperature required to cause coagulative necrosis is reached without creating "burning" (carbonization), which could block the flow of electricity. For tumors located near blood vessels, heat can be removed by the flow of blood through an effect known as a "heat sink".¹⁴

To reach the effective temperature, the tynes must be turned or pulled slightly. Postoperatively, patients may undergo immediate re-imaging (usually with contrast-enhanced CT) to evaluate ablation and to

look for potential complications. RFA is usually carried out in specialized centres. This allows for evaluation of the post-RFA image of the tumor. Post-RFA assessment often involves CT, ultrasound, MRI, and/or PET imaging. Examination is usually done 4-6 weeks after ablation. Subsequent imaging studies may be performed on a variable schedule and aim to detect local tumor recurrence, development of new lesions, or the appearance of extrahepatic disease.¹⁴

Radiofrequency Ablation (RFA) Complication

Studies have confirmed that percutaneous RFA is a low-risk procedure with low morbidity and mortality. Many factors are thought to be associated with the cause of the major complications, including tumor size, number of ablation sessions, type of electrode (single or cluster) and operator experience.¹²

The study conducted by Maeda et al, explained that among 11,298 procedures performed, 330 complications (2.92%) were identified. Six patients (6/9,411 patients; 0.064%) died of RFA-related complications (from intraperitoneal hemorrhage, refractory ascites, bowel perforation, bile duct injury, diaphragmatic injury, and refractory pleural effusion, respectively). Bleeding, liver injury, extrahepatic organ injury, tumor development, skin burns due to poor contact between electrode pads and skin are complications that can occur. The most frequent complication was liver injury (1.95%) followed by bleeding (0.47%).¹⁷

CONCLUSION

The classification of liver tumors is broadly divided into 3 such as benign liver tumors that do not require treatment, benign liver tumors that require treatment, and malignant liver tumors that require treatment. One of the malignant liver tumors is hepatocarcinoma which is closely related to cirrhosis. Hepatocellular carcinoma occurs in approximately 85% of patients diagnosed with cirrhosis. The disease is now the fifth most common cause of cancer worldwide.

Management of liver tumors other than surgery and chemotherapy is radioablation. One of the commonly used methods is percutaneous radiofrequency ablation. The overall and disease-free survival rate of RFA was found to be more effective than that observed with surgical resection. The success rate of RFA is highly dependent on the precision of tumor targeting, which is governed by two main factors, such as electrode tip placement and angulation for electrode placement.

Many studies have confirmed that percutaneous RFA is a low-risk procedure with low morbidity and mortality. Bleeding, liver injury, extrahepatic organ injury, tumor development, skin burns due to poor contact between electrode pads and skin are complications that can occur.

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