Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignant liver cancer.[1] Hepatocellular carcinoma is the fifth most common cancer in men and eighth in women worldwide.[2] The development of this cancer occurs most often in patients with chronic liver disease, typically in cirrhosis of various etiology (alcohol abuse, chronic hepatitis B and hepatitis C). Hepatocellular carcinoma is the third most common cause of death worldwide.[3] In the Czech Republic, it is rather rare with **5–7/100,000 people**.[2] Surgical intervention is the only potential option for cure (resection or transplantation).

Epidemiology

The highest incidence rate of hepatocellular carcinoma occurs in **East Asian countries** (incidence = 35/100 000 people[3]), followed by African countries. Frequent occurrence in these areas are associated with high prevalence and perinatal transmission of *HBV* and *HCV*. In the Czech Republic, it is one of the most common cancers, particularly affecting older males.

Symptomatology

The clinical manifestation of the hepatocellular carcinoma at the time of diagnosis can vary. It is ideal if the lesion is caught during preventive examination, while patients have no symptoms. In patients with liver cirrhosis, the clinical manifestation varies based on the severity of cirrhosis. HCC is often the cause of **sudden deterioration of liver function**. It is also possible that the tumor mass embolizes the *portal vein*. Non-specific symptoms include, pain in the right lower jaw, discomfort, fatigue, fever, weight loss, anorexia, and jaundice.[4] Furthermore, the **signs of worsening of cirrhosis** may be observed (jaundice, ascites, hepatic encephalopathy, gastrointestinal bleeding from varicose veins).[2] On physical examination, hepatomegaly, splenomegaly, spider nevi, ascites palmar erythema, and gynecomastia (in men) can be found.

Etiology

Risk factors of HCC vary between regions. In developed countries, the most common cause is liver cirrhosis. [5] In developing countries, it is mainly caused by chronic hepatitis B, often without cirrhotic changes in liver. Another etiological factor is the presence of aflatoxin in the diet. General risk factors include chemical carcinogens (hydrazine, trichlorethylene, vinyl chloride), some medications (steroid hormones, phenobarbital). Patients with hemochromatosis, Wilson's disease, and porphyria cutanea tarda are also at risk.[6]

Diagnostics

The basic methods of diagnosis of liver lesion are imaging methods –ultrasound, CT and MRI. We can confirm HCC by non-invasive methods only in patients with cirrhosis. In these cases, **four-phase CT scans** (native, arterial, venous and late phase) or dynamic contrast MRI can be utilized. Confirmatory findings of HCC diagnosis are saturation of suspected lesion (at least 1 cm in size) in the arterial phase and elution of the contrast agent in the venous or late phase. In case when these signs in imaging techniques are absent or the patient is without liver cirrhosis, it is necessary to perform a biopsy and subsequent histological evaluation.[2] In laboratory tests, increase of alpha-fetoprotein level can be found which is not a specific sign for HCC, but it can be used to assess the prognosis of the cancer after the diagnosis.[1][7]

Pathology

Microscopically, HCC is formed by hepatocytes with atypia of nuclei and mitoses. Macroscopically, **multinodular HCC** (deposits in both lobes), **massive HCC** (large bearing with satellite deposits), and **diffuse HCC** (small deposits in the entire liver parenchyma) should be distinguished from each other.[1] The tumor grows into the hepatic veins and portal vein, followed by tumor thrombosis, and intrahepatic metastases. HCC metastasizes to the **lymph nodes and lungs**, and less often to the bones.

Staging

Systems used to classify HCC are:

- TNM classification
- MELD (Model For End-Stage Liver Disease) score (used to evaluate the priority of receiving liver transplant).
- classification according to the Barcelona Group,
- CLIP score (*Cancer of the Liver Italian Program*, which includes Child-Pugh classification, morphology of tumor, AFP levels, presence or absence of portal vein thrombosis, liver function and tumor characteristics),
- CUPI classification (*Chinese University Prognostic Index*, which better suits the Asian population), etc.[8]

Staging helps to determine the patient's prognosis and to select the suitable therapeutic approach.

In addition to the characteristics of tumor itself, the progression of chronic liver disease (e.g., *Child-Pugh score*) and the overall condition of the patient must be included in the prognosis of patients with HCC. **Barcelona Classification** (*BCLC - Barcelona Clinic Liver Cancer staging system*) is a frequently used classification. Its advantage is that the evaluated prognosis includes the factors of the tumor itself, the progression of liver cirrhosis, and *performance status*. Specific treatment methods are chosen based on the BCLC classification.[2]

Barcelona HCC classification[9]

stage	denotation	Child-Pugh score	tumor characteristics
very early	**BCLC 0**	Child-Pugh A	one lesion < 2 cm
early	**BCLC A**	Child-Pugh A, B	1–3 lesion upto 3 cm
intermediate	**BCLC B**	Child-Pugh A, B	multiple lesions
advanced	**BCLC C**	Child-Pugh A, B	invasion of portal vein
terminal	**BCLC D**	Child-Pugh C	

Therapy

The only curative treatment for HCC is by means of **surgery** - resection or liver transplantation-. However, only a limited number of patients are indicated for the surgical intervention due to the progression of HCC to an advanced stage already at the time of diagnosis. Other treatment options are trans-arterial chemoembolization, ablation techniques (radiofrequency ablation, alcohol application, cryotherapy, laser ablation), external beam radiotherapy, and systemic treatment, but these are only palliative methods. Biological therapy for cancer is one of the latest possible treatment option. Radiofrequency ablation, chemoembolization, or alcohol application are utilized as neoadjuvant treatment for HCC. Some studies suggest that the adjuvant treatment may improve the outcome of the surgery. [6]

Surgical Treatment

Methods of surgical treatment are resection and liver transplantation. Unfortunately, only a few patients are indicated for the surgical treatments.

Surgical resection

Liver resection is suitable for patients who do not have liver cirrhosis and have a single tumor lesion. Resection is only indicated for cirrhotic patients if the patient has preserved liver function and does not have portal hypertension. The deciding factor for this treatment is the functional level of liver. Perioperative mortality is 2-3%, five-year survival chance after the surgery approaches 60-80%. Up to 70% of patients after the operation develop the tumor again. [2]

Liver transplantation

According to the *Milan criteria*, transplantation is the method of choice for patients with a single lesion up to 5 cm, or 1-3 lesions up to 3 cm in size, without vascular invasion nor lymph node involvement. The five-year survival chance after transplantation is 70% for patients with HCC, which is almost the same percentage as the five-year survival chance after liver transplantation without cancer. Liver transplantation also treats the liver cirrhosis in patients with the condition. The major limiting factor for this treatment is a lack of donor.[6]

Non-surgical treatment

Patients who are not indicated for liver resection nor do not meet the criteria for transplantation are treated with non-surgical methods. Those non-surgical treatments are only palliative. Five-year survival chance is 40-50% in patients who are treated non-surgically. The disadvantage of these methods are the frequent local recurrences and need for repetitive individual procedures.[6]

Embolization and Chemoembolization

Hepatocytes are largely supplied with blood from the portal vein, while tumor cells are supplied mainly with arterial blood (hepatic artery). This is a key difference for the embolization and chemoembolization (*TACE - transcatheter arterial chemoembolization*).

Spongostan or lipidol are used for embolization. Mitomycin C, adriamycin and cisplatin, or doxorubicin bound to microspheres in hydrogels are used in chemoembolization. The method is indicated for patients with inoperable HCC, Child-Purgh A or B without portal thrombosis, AV shunts, extrahepatic impairment, or renal insufficiency.

Chemoembolization improves the overall survival chance of patients with inoperable HCC.[6]

Alcohol exposure of HCC lesions

Another method of local intervention is alcohol exposure (*PEI – percutaneous ethanol injection)*.

96% ethanol is introduced percutaneously to the lesion. Protein denaturation, tumor cell necrosis and ischemic necrosis occur locally. The end result of this procedure is coagulative necrosis of tumor. The method is indicated for patients with a maximum of 3 tumor foci up to 3 cm in size or Child-Pugh A or B.[6]

Radioablation

Radiofrequency ablation (*RFA*) is a method for the intervention of multiple (3-5) 3-5 cm tumor foci. The procedure is performed under CT or perioperively. A radiofrequency probe is inserted into the tumor foci, causing cell necrosis by local application of heat. The applied temperature is higher than 50 ° C. The method can be combined with *TECA* or *PEI*. For foci smaller than 3 cm, the entire tumor can undergo necrosis by one RAF in 88-98% of cases. The chance of a successful procedure for foci with a size of 3-5 cm is 80-90%. [6]

Other local methods

Cryotherapy (for tumors smaller than 3 cm) and **laser therapy for local intervention of foci** are also available as non-surgical treatment. **In Japan, transcutaneous microwave coagulation therapy** (PMCT) is often used. External radiotherapy has been less commonly utilized in recent years due to the high sensitivity of healthy liver tissue. Currently, it is used for the advanced stages of HCC.[6]

Pharmacological treatment

Another option for HCC therapy is systemic treatment, eventhough hepatocellular carcinoma is primarily **chemoresistant**. Therefore, the pharmacological treatment has no significant effects compared to surgical and ablation methods. Doxorubicin is known to achieve the best result.

With the development of molecular therapy, new potential methods are developed for pharmacological therapy of HCC. Administration of anticancer drugs brings out a good outcome in patients with an inoperable and advanced stage HCC. *Sorafenib* has been proven to have the best effect so far. Treatment outcome of HCC with chronic hepatitis C tends to be better than with chronic hepatitis B. The disadvantage of this biological therapy is that it is expensive.[6][10]

Prognosis

Patients in the terminal stage are indicated only for symptomatic palliative care. The possibility to cure the HCC is limited, thus the **prevention of tumor formation** is crucial. Preventions include the prevention and treatment of viral hepatitis B and C, the prevention and treatment of alcoholism, and the early diagnosis and treatment of metabolic liver diseases. Although there is a wide variety of treatment options available for HCC, patients with HCC very often have a poor prognosis. The tumor is often diagnosed when it is already at an advanced stage. Pre-existing liver cirrhosis in a great number of patients also plays a negative role.[6]The care for patients with HCC must be multidisciplinary.

References

Related articles

- Tumors of the liver

External Links

- Doporučený postup pro léčbu a diagnostiku HCC, 2011 (http://www.ces-hep.cz/file/321/doporuceny-postup-chs-hcc-2011.pdf)

Citations

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Recommended Literature

- POVÝŠIL, Ctibor – ŠTEINER, Ivo – DUŠEK, Pavel, et al. *Speciální patologie : interakce škodlivých látek s živými organismy, jejich mechanismy, projevy a důsledky.* 2. edition. Praha : Galén, 2007. 430 pp. pp. 209-210. ISBN 978-807262-494-2.
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