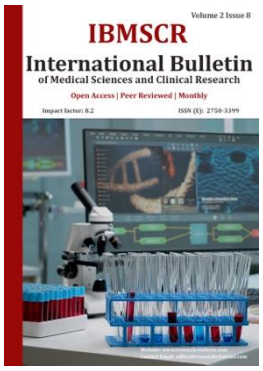

MODERN METHODS OF ABLATION FOR MALIGNANT LIVER TUMORS (LITERATURE REVIEW)

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Abstract

The purpose of this review is to demonstrate the possibility of performing various methods of thermal and non-thermal ablation in patients with primary and metastatic liver tumors on the basis of data available in the world medical literature.

As conservative variants of local action in patients with non-resectable primary and secondary liver tumors and inoperable patients, various ablative techniques have been developed and used to achieve local control over the disease and increase the life expectancy of this group of patients. These include: radiofrequency ablation, microwave ablation, HIFU therapy, laser ablation, cryotherapy, chemical destruction of the tumor, irreversible electroporation, stereotactic radiation therapy.

The effectiveness of these ablation methods depends on the size and localization of the tumor focus, and for thermal techniques — also on its location relative to large vessels. Ablative techniques have the maximum efficiency (in some cases, similar to surgical intervention) when exposed to early forms of primary cancer or secondary tumor formation of the liver in the presence of a solitary node with a maximum size up to 5 cm or 3 and less foci size up to 3 cm. The effectiveness of local destruction of tumor formations of the liver of larger diameter is increased by carrying out ablation by the second stage after performing chemoembolization of the hepatic artery or by combining various techniques of local action.

The use of various modern methods of ablation of solid primary and secondary liver tumors in medical practice can expand the possibilities of antitumor treatment of this category of patients.

Keywords: primary liver cancer, hepatocellular carcinoma, hepatic metastases, radiofrequency ablation, microwave ablation, high-intensity focused ultrasound therapy, laser ablation, cryoablation, percutaneous ethanol injection, irreversible electroporation, stereotactic body radiation therapy.

Introduction

Despite significant advances in modern oncology, in Uzbekistan, as well as worldwide, metastatic

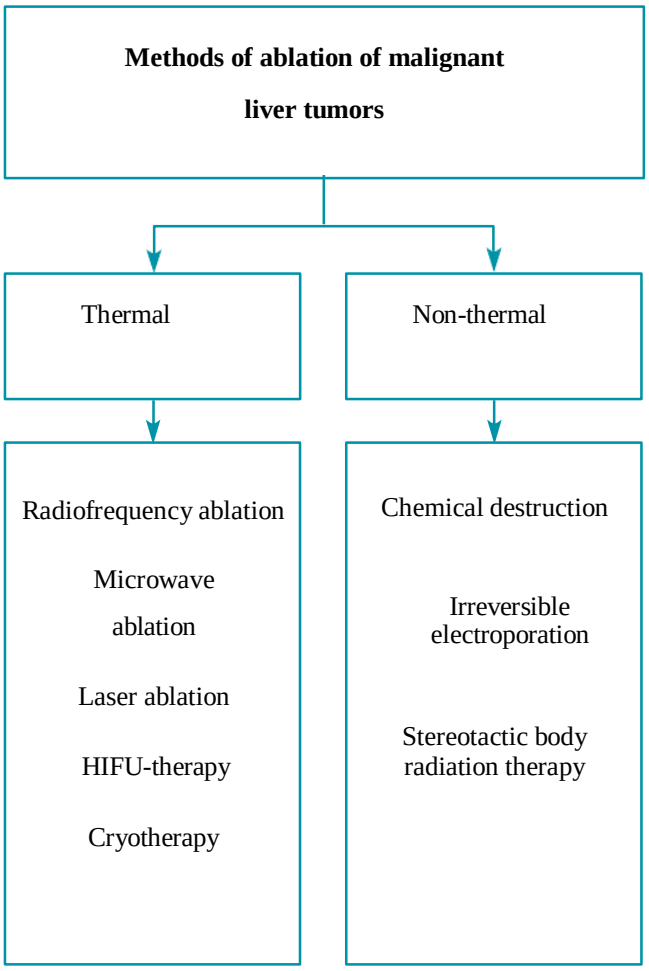
liver involvement is diagnosed in every third oncology patient regardless of the location of the primary tumor. This is associated with the anatomical and functional characteristics of the liver [1].

The most common secondary (metastatic) liver lesions are observed in malignant tumors of the gastrointestinal tract, pancreas, gallbladder, breast and lungs [2].

The "gold standard" in the treatment of liver metastases of colorectal cancer is resection of the affected hepatic segment, where the average overall survival reaches 35–40 months, and the 5-year survival rate is 30–60% [3]. However, due to the extent of the disease or the general condition of the patient, this method can be applied in only 10–25% of cases [4, 5].

In addition to metastatic malignancies, primary liver cancer is also of great importance. This disease develops against the background of severe cirrhotic changes in the liver tissue, significantly limiting the functional reserve of the organ. More than 6,000 new cases of primary liver cancer are diagnosed annually [2]. The most common form of the disease is hepatocellular carcinoma (80–85% of epithelial liver tumors) [6]. The 5-year cumulative incidence of hepatocellular carcinoma against virus-related cirrhosis is approximately 10–30%. In 25% of patients, cancer may develop in the presence of hepatitis B even without cirrhotic manifestations [7].

Among patients with primary liver cancer, 69.7% die within the first year after diagnosis [2].



The main treatment methods for primary liver cancer are liver transplantation and resection. However, these approaches are applicable in only 10–25% of cases. Ablation techniques, local chemotherapy and targeted therapy are also of current relevance. For example, in unresectable primary liver cancer, administration of Sorafenib extends median overall survival to 7.9–10.7 months and time-to-disease progression to 2.8–5.5 months [8].

In cases where liver resection or transplantation cannot be performed for primary or metastatic cancer, local and regional treatment modalities may be used: various ablation, radiotherapeutic and interventional techniques, which prolong patient survival [9].

In world practice, various ablation methods are widely used against liver tumors because they offer high effectiveness, relatively good patient tolerance, low complication rates when properly performed, and the possibility of combination with other systemic or local treatment modalities [10].

These methods are based on the impact of different physical and chemical factors, causing non-specific damage to the tumor—disrupting cellular structure dynamics. They may be

performed percutaneously (through the skin), via laparoscopic or laparotomic access and, in some cases, even remotely (see figure above).

Radiofrequency ablation (rfa)

Radiofrequency ablation (RFA) is a method of local thermal destruction of tissues, based on delivering high-frequency alternating current (400–500 kHz) through the cells via electrodes (under ultrasound, CT, or MRI guidance), resulting in heating of tissues to 50–100°C. Heating causes protein denaturation, and both local and systemic immune-stimulating effects have also been observed [11, 12].

RFA may be performed intraoperatively (open method), as well as percutaneously or laparoscopically under ultrasound, CT, or MRI guidance. The advantages of open RFA include the ability to examine the entire abdominal cavity, more favorable electrode positioning, and the possibility of combining ablation with other surgical interventions. However, open surgery is associated with greater trauma, relatively higher complication rates (9.6–32%) and mortality (up to 2.3%), and may be contraindicated in patients with severe somatic conditions [13].

Minimally invasive RFA techniques are more common due to lower complication rates (percutaneous 0–4.7%, laparoscopic 3.1–4.4%), lower mortality (percutaneous 0%, laparoscopic 0.3%), and shorter rehabilitation periods [14].

Complications of RFA include liver abscess, cholecystitis and cholangitis, skin burns in the contact zone, thermal injury to adjacent structures (perforation of hollow organs, biliary strictures), gastrointestinal or intra-abdominal bleeding, portal vein thrombosis, and the risk of implantation metastases [15].

Local tumor recurrence rates after RFA vary depending on tumor size, ranging from 6.6–66.7% within 12–49 months of follow-up [16–18]. If the lesion is well visualized and favorable in location, successful treatment can be achieved for tumors up to 5 cm in diameter. Recurrence rates are 3–5.6% for lesions up to 3 cm and 4–19.5% for lesions 3–5 cm in size [17, 18]. For tumors larger than 5 cm, recurrence rates increase to 27–45%.

Studies show that the maximum efficacy of RFA is observed in a single lesion (up to 5 cm) or up to three lesions (up to 3 cm each). In patients with HCC and Child-Pugh class A cirrhosis, 3- and 5-year overall survival reaches 60–78% and 50–64%, respectively [19].

According to T. Ruers et al., in colorectal liver metastases (up to 6 cm, not exceeding six lesions), RFA provides 3- and 5-year survival rates of 28–46% and 25–46%, respectively [20]. Adding RFA to systemic chemotherapy significantly increases 5-year survival from 30.3% to 43.1% (p=0.01) [21].

In 2013, Y.S. Kim et al. reported results of a study involving 1,305 HCC patients treated with RFA, with solitary tumors up to 5 cm or no more than three tumors up to 3 cm. The mean tumor size was 2.2 cm. During follow-up ranging from 0.4 to 146.6 months (mean 33.4), recurrence occurred in 60.9% of patients (1–17 episodes). The median overall survival was 75 months, and 10-year survival reached 32.3% [22]. Some authors consider RFA to be an effective bridging therapy for patients awaiting liver transplantation [23, 24].

Microwave Ablation (MWA)

Microwave ablation is a local ablation technique similar to RFA, with the main difference related only to the electromagnetic wave frequency (915 MHz or 2450 MHz). During MWA, the temperature in the target tissue rises to 60–110 °C, resulting in protein denaturation, vaporization of fluid, and tissue carbonization [25].

According to many researchers, MWA has several advantages over RFA: higher achievable tissue temperatures, more uniform heat distribution, the possibility of using multiple electrodes simultaneously and coagulating larger volumes of tissue, less dependence on tissue conductivity, reduced heat-sink effect from blood vessels, less pain due to shorter high-power exposure time, and the absence of neutral grounding pads eliminates the risk of skin burns at distant sites [26].

This technique is technically simple (technical success rate of 88–98%) and is associated with fewer complications even for lesions located in the subdiaphragmatic area or close to the gallbladder wall [27, 28].

MWA can be performed using laparotomic, laparoscopic, or percutaneous approaches. Specific complications of MWA (abdominal pain, nausea, fever, increased liver enzymes, liver abscess, ascites, reactive pleural effusion, thermal injury, internal bleeding, implantation metastasis) are observed in 4–23.4% of cases, while 30-day mortality does not exceed 0.5% [29].

The main indication for MWA is solitary but unresectable tumors, as well as liver lesions up to six nodules (up to 6 cm in diameter) or lesions located less than 1 cm from major blood vessels. According to the literature, in such cases (primary or secondary liver cancer), the 3- and 5-year survival rates reach 46–51% and 17–32%, respectively [27, 30–32].

In a randomized trial comparing the effectiveness of MWA and liver resection in colorectal cancer metastases (30 patients), median survival was 27 months in the MWA group and 25 months in the resection group ($p = 0.83$), indicating no significant difference [30].

Post-MWA local recurrence rates range from 2.7% to 45.7%, with mean overall survival of 36.3 months for colorectal cancer metastases and 38.3 months for hepatocellular carcinoma [33, 34]. In hepatocellular carcinoma, 3-year overall and recurrence-free survival are 60% and 27%, respectively. Ablation combined with transarterial chemoembolization extends survival up to 42.6 months [35].

High-Intensity Focused Ultrasound (HIFU)

HIFU is a non-invasive ablation method that works on the principle of directing high-frequency ultrasound waves (>20 kHz) in a focused manner to the tumor, inducing thermal injury, acoustic cavitation, direct damage to small vessels, and immune response due to cell disruption [36].

HIFU can be applied under ultrasound or MRI guidance, either alone or in combination with other treatment modalities [37].

Ultrasound waves reflect and attenuate at interfaces between media with different acoustic impedance and conductivity, causing energy weakening at the focal point. Bone tissues, such as the ribs, strongly absorb ultrasound, producing a “border surface” effect and indirect skin heating, which explains the high incidence of skin burns during HIFU [38].

Specific complications of HIFU for liver tumors include moderate to severe pain, paresthesia, grade 1–3 skin burns, subcutaneous fat swelling, elevated liver enzymes (27–84%), and occasionally subcutaneous tissue fibrosis, liver abscesses, acute cholecystitis, bile duct obstruction, mechanical jaundice, reactive pleuritis or pericarditis, spinal injury, fever, arrhythmias, and others (1–14%) [39].

According to some authors, in patients with liver lesions 0.9–14 cm in diameter, HIFU can improve pain control (84.8%), complete ablation of the tumor (69.2–88.8%), and 5-year

survival (up to 31.8%) [40, 41]. The best results are observed in lesions up to 3 cm: instrumental studies show complete ablation in 93.3% of patients, 1- and 3-year survival of 97.4% and 81.2%, and recurrence-free survival of 63.6% and 25.9% [42].

For tumors larger than 4 cm, pre-treatment with transarterial chemoembolization (TACE) can increase effectiveness, as reduced tumor blood supply prevents heat dissipation. In a randomized study (F. Wu et al.) of 50 patients with IVA-stage hepatocellular carcinoma (4–14 cm), HIFU combined with TACE reduced tumor volume by 28.6–50% at 1, 3, 6, and 12 months, compared to only 4.8–10% in the TACE-only group ($p < 0.01$). Median survival was 11.3 months in the combined group versus 4.0 months in the TACE-only group ($p = 0.004$). One-year overall survival was 42.9% versus 0% ($p < 0.01$) [43].

Laser Ablation

Laser ablation (interstitial laser-induced thermotherapy) is a method of thermal destruction of tumor tissue by delivering high-energy laser light (optical fiber laser) directly into the tissue. Since infrared light has the best tissue penetration, low-power Nd:YAG laser (1064 nm wavelength) or diode lasers (800–980 nm) are used for ablation. The light energy converts into heat, raising the tissue temperature above 120 °C and causing coagulative necrosis [44].

This technique can be performed percutaneously, via open surgery, or laparoscopically. During the procedure, laser beams are delivered to the target area through optical fibers under ultrasound guidance. Advantages of laser ablation include cost-effectiveness, ease of application, suitability for patients with pacemakers, and independence from tissue impedance. Treatment time ranges from 6 to 24 minutes, depending on lesion size and the number of fibers used. Thin needles (17–21 G) help prevent many complications [45, 46].

The main limitation of this technology is the small penetration depth of the laser beam into tissue. Ablation zones created with a single fiber usually do not exceed 1–2 cm in diameter. However, modern devices with specialized cooling fluid–cooled catheters allow power to be increased up to 50 W, preventing tissue charring and enabling safe ablation of lesions up to 8 cm [47].

According to the literature, the technical success of laser ablation is achieved in 99% of cases, mortality does not exceed 0.8%, and 6-month local recurrence rates range from 5.2–10% [48]. Excellent outcomes, similar to other thermal ablation methods, are observed for lesions up to 5 cm in diameter: complete ablation in a single lesion ≤5 cm is achieved in 81.1–97% of cases [49].

In cases of colorectal cancer metastases, median survival reaches up to 54 months, with 5-year survival ranging from 10–37% [50]. In patients with hepatocellular carcinoma or cirrhosis, 1-, 3-, and 5-year survival rates are 94%, 80%, and 41%, respectively, with a median overall survival of 3.5 years [51].

Cryoablation

Cryoablation is a thermal ablation technique that involves rapid freezing of tissue using liquid nitrogen or argon, followed by thawing with passive or helium-assisted warming. During freezing, intracellular water crystallizes, mechanically damaging cell membranes.

Cryoablation can be performed percutaneously, via laparotomy, or laparoscopically, using ultrasound (US), CT, MRI, or PET guidance for navigation. Similar to other local destruction

methods, it can also be combined with hepatic resection or a simulated operation on the primary lesion.

Reported complication rates after cryoablation range from 5.8–66%, including bile duct fistulas, liver abscesses, intra-abdominal bleeding, reactive pleural effusion, hemothorax, myoglobinuria, disseminated intravascular coagulation (DIC), coagulopathy, thrombocytopenia, pulmonary artery thromboembolism, acute kidney injury, and others [52].

According to D.I. Glazer et al., adverse events occur in 31.3% of patients with liver tumors smaller than 4 cm and 19.5% in lesions ≥4 cm (p=0.04). MRI-guided cryoablation shows lower complication rates (22%) compared with CT (42.9%) or PET-CT (40%) (p=0.004). Mortality ranges from 0.4–1.5%, with causes including "cryo-shock" (sudden release of cellular components, inflammatory mediators, and DIC) [53, 54].

Technical success rates for cryoablation range from 51–100%; complete ablation is achieved in 93.4% of lesions <4 cm, and up to 60% in larger tumors (p<0.0001) [53].

B. Wu et al. demonstrated the safety and efficacy of MRI-guided percutaneous cryoablation in 32 patients with hepatocellular carcinoma (tumor size 2.5–10 cm). The procedure involved two freeze-thaw cycles, and no serious complications were observed during 6–12 month follow-up. Overall survival at 6 months was 96.8% and 90.6% at 1 year. MRI at 3 months showed 100% necrosis in 31.3% of cases, 80% necrosis in 56.3%, 50–79% necrosis in 9.4%, and disease progression in 3.1% [55].

Local recurrence rates were 63.3% for lesions >4 cm and 18.0% for lesions <4 cm (p<0.0001) [56]. In metastatic liver cancer, particularly colorectal metastases, 29-month follow-up revealed recurrence in 23–24.6% of cases, with median time to recurrence 7.9–9.5 months, and 5-year overall survival ranging from 5–44% [57–59]. Similar statistics were observed in primary liver cancer: 24.5% recurrence at 29 months, 5-year survival 13–60.3%, median survival 77.9 months [55, 56].

Xu Ke-Cheng et al. reported that combining cryoablation with TACE reduced recurrence to 11%, compared with 23% for cryoablation alone (p=0.001), with 5-year survival rates of 39% and 23%, respectively (p=0.001) [60].

Chemical Ablation

For unresectable liver tumors, chemical ablation using 96% ethanol (percutaneous ethanol injection, PEI) can be employed. Sterile ethanol is injected into the tumor under US or X-ray guidance until the tissue appears homogeneously "porous." Ethanol induces cell dehydration, protein denaturation, microvascular thrombosis, ischemia, and necrosis [61–64].

Advantages of chemical ablation include relative safety, simplicity, and low cost [65]. It is mainly indicated when thermal ablation is contraindicated, such as tumors near major vessels, bile ducts, stomach or intestinal walls, kidneys, or subcapsular/extracorporeal lesions [63, 66]. Limitations include restricted ethanol diffusion in large or fibrous lesions and the need for 12 or more sessions [67].

Possible complications include elevated liver enzymes and bilirubin, infarction and suppurative necrosis, liver abscess, bleeding, thrombosis, pancreatitis, cholecystitis, cholangitis, pulmonary artery thromboembolism, and occasionally implantation metastases (up to 2%) [68, 69].

Chemical ablation may be less effective for colorectal metastases due to dense tumor capsule, while hepatocellular carcinoma in a cirrhotic liver shows better outcomes [70]. In

hepatocellular carcinoma ≤3 cm, chemical ablation achieved 80–100% non-enhancing lesions on MRI, local recurrence 11–45% at 2 years, and 1-, 3-, 5-year survival rates of 98%, 81.6%, and 60.3%, respectively [71].

Combining RFA with ethanol injection improves outcomes, particularly for larger tumors by reducing heat loss through blood vessels. For example, Y.J. Zhang reported 5-year survival of 49.3% for RFA+ethanol versus 35.9% for RFA alone (p=0.04) in hepatocellular carcinoma 3.1–5.0 cm, with local recurrence 6.7% vs. 20.9% (p=0.012) [72]. Chemical ablation is also suitable for patients awaiting liver transplantation [73].

Irreversible Electroporation (IRE)

Irreversible electroporation is a non-thermal technique in which strong electrical pulses (1000–3000 V/cm, 20–100 ms duration) create nanopores in the lipid bilayer, causing osmotic shock and triggering apoptosis [74]. These disruptions primarily affect lipid membranes, sparing collagen and elastin-rich tissues, resulting in controlled ablation with minimal risk to vessels and bile ducts [75]. IRE uses a specialized generator, monopolar probes (2–6), and cardiac synchronization. The procedure is performed under general anesthesia and deep muscle relaxation. It is contraindicated in patients with pacemakers, arrhythmias, or metallic implants [76].

IRE has been safely applied near major hepatic vessels, nerves, and bile ducts. Complication rates include vascular stenosis or thrombosis (3–9.9%), bile duct stenosis or dilation (up to 14.5%), liver injury, bleeding into the pleural cavity, pleuritis, ascites, arrhythmias, pulmonary thromboembolism, infarction, or stent complications (8–29%) [74, 68].

Technical success ranges from 83–100%; MRI shows 72–100% non-enhancing lesion, histopathologic confirmation 83%, 6-month local recurrence 13.6–25%. Median survival is 19.9 months for metastatic liver cancer and 26.8 months for hepatocellular carcinoma. One-year recurrence-free survival is 59.5–74.8%, with no procedure-related mortality [71–73].

Stereotactic Radiation Therapy (SRT)

Stereotactic radiation therapy (SRT) is a form of external beam radiotherapy in which high doses of radiation are delivered to the tumor in small fractions. Ionizing radiation disrupts chemical processes in tumor cells, leading to cell death.

SRT can be used for primary or secondary liver cancer that is unresectable or unsuitable for ablation (tumor ≤6 cm, ≤5 lesions), including patients who cannot tolerate other treatment modalities. Total doses of 22–75 Gy can be delivered in 1–6 fractions [74].

Complications include general radiation reactions (fatigue, headache, dizziness, loss of appetite, decreased or increased salivation, nausea, diarrhea) and local radiation effects (abdominal pain, elevated liver enzymes, increased bilirubin, hypoalbuminemia, hepatic encephalopathy, ascites, gastrointestinal bleeding, dermatitis, dilation of intrahepatic bile ducts, radiation pneumonitis, radiation-induced liver disease). According to the Child-Pugh classification, grade 3 or higher complications are more frequent in class B patients compared with class A (p=0.0127) [75–77].

In primary liver cancer, 3-year overall survival with SRT ranges from 53–74.4%, and 3-year local control rates reach 58–92% [78]. Tae Hyun Kim et al. reported that in hepatocellular carcinoma, complete tumor disappearance was observed in 93% of patients by imaging. Three-

year overall survival was 81.1%, recurrence-free survival 28.3%, and local progression-free survival 95.5% (0% in patients whose tumor was not completely ablated) [76].

In metastatic liver cancer, 3-year local control ranges from 66–81%, median overall survival is 27–43 months, and 3-year survival is 48–65% [70]. Mahadevan et al. analyzed 427 patients with 568 liver metastases treated with SRT, reporting median survival of 22 months overall. For colorectal, breast, and gynecologic metastases, median survival was 27, 21, and 25 months, respectively, whereas lung (10 months) and pancreatic (6 months) metastases had lower survival ($p<0.0001$). One-year survival rates were 76.4%, 66.4%, 81.3%, 50%, and 18%, respectively. Tumors <40 cm^3 had median survival of 25 months; larger tumors, 15 months ($p=0.0014$). Local control duration was significantly longer for smaller tumors (52 vs. 39 months; $p<0.0001$) [71].

Conclusion

Currently, 75–90% of patients with high-risk liver tumors are inoperable for various reasons, and systemic or symptomatic therapy alone often provides insufficient results. In such cases, various ablation techniques can significantly prolong survival.

Analysis of global literature shows that the effectiveness of all local treatments is highly dependent on tumor size and location. Ablation is especially effective for a single lesion ≤5 cm or up to three lesions ≤3 cm each, with outcomes comparable to surgery in some patients. Larger tumors achieve better ablation results when combined with hepatic artery chemoembolization or other local techniques.

Modern sources report complication rates after liver ablation of 4–35% and 30-day mortality of 0–2.3%.

In both primary and secondary liver cancer, the use of modern ablation methods expands therapeutic options and improves long-term outcomes

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