The role of Interventional Radiology in primary and metastatic liver disease – a short review of primary methods and therapy approaches

Rola radiologii interwencyjnej w zmianach pierwotnych i wtórnych wątroby – krótki przegląd podstawowych metod i podejść terapeutycznych

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KEYWORDS:

- interventional radiology
- hepatocellular carcinoma (HCC)
- metastatic liver disease

ABSTRACT

Primary and metastatic liver tumors are an increasing global health burden. As of 2020 colorectal cancer (CRC), which often presents with hepatic metastasis in the course of the disease was a second leading cause of cancer-related mortality worldwide. This was followed by hepatic cell carcinoma (HCC). Besides systemic therapies and surgical methods, which are not always applicable, many locoregional approaches were developed and are being increasingly implemented in the field of interventional radiology (IR) – both as primary and bridging procedures.

The purpose of this article is to outline and briefly discuss these primary approaches used in IR in liver neoplastic disease.

SŁOWA KLUCZOWE:

- radiologia interwencyjna
- rak wątrobowokomórkowy (HCC)
- przerzuty do wątroby

STRESZCZENIE

Guzy pierwotne i przerzutowe wątroby stają się coraz większym, globalnym obciążeniem zdrowotnym. W roku 2020, rak jelita grubego (CRC), który w swoje historii naturalnej często prezentuje się wraz ze zmianami przerzutowymi do wątroby był epidemiologicznie drugą przyczyną śmiertelności związanej z chorobami nowotworowymi.

Zaraz za nim w kolejności znalazł się rak wątrobowokomórkowy (HCC). Oprócz terapii systemowych i resekcji chirurgicznych, które nie zawsze mogą być zastosowane, dziedzina radiologii interwencyjnej (IR) rozwinęła wiele metod małoinwazyjnych – zarówno jako metody podstawowe, jak i terapie pomostowe.

Celem tego artykułu jest zarysowanie i krótkie omówienie tych podstawowych metod stosowanych w zmianach nowotworowych w obrębie wątroby w IR.

Introduction

Primary liver malignancies and hepatic metastasis are an increasing global health burden. Colorectal cancer (CRC), which often presents with liver disseminated process throughout the course of the disease was a second leading cause of cancer-related mortality as of the year 2020. This was followed by primary hepatic malignancies mainly in the form of hepatocellular carcinoma (HCC) (1).

Surgical resections are still the main curative approach in liver neoplastic disease (2). Unfortunately, many patients present with nonresectable lesions or significant contradictions, which disqualify them from classic approach.

This created a need for other less invasive procedures. Throughout the years many locoregional techniques were advanced. Model examples being ablative, embolic and other intraarterial therapies. This significantly changed management algorithms in these patients – both as curative and palliative treatment.

Objectives

The purpose of this article is to review and briefly discuss the IR arsenal of methods in liver neoplastic disease.

Materials and methods

We searched Pubmed, Cochrane and Google Scholar databases. Keywords that we used were: interventional radiology, locoregional therapies for liver cancer, management of HCC,

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liver metastatic disease, intraarterial therapies, ablation, radioembolization, chemoembolization, CRC, percutaneous approach, minimally invasive. Relevant articles were narrowed down do publication dates between 2012-2021.

This not being a systematic review the quality, methodology and number of articles was not further assessed.

Percutaneous ablation

Several local ablative modalities are included in guidelines for the management of primary and metastatic liver disease both as primary and adjunct methods (2). Radiofrequency ablation (RFA) is the most commonly used and studied. This method utilizes local tissue hyperthermia, subsequent necrosis and possible immune-enhancing effect by the means of oscillating electrical currents of different probes placed under CT, US or MRI guidance (3). Apparent benefits of RFA compared to resection is its minimally invasive nature and lower rate of significant complications.

Lesion size is the main criteria of RFA suitability with complete ablation rates up to 90-95% with lesions less than <3 cm (4). Survival rates for low and intermediate stage patients with HCC (i.e., Child Pugh A and B cirrhosis score) were shown to be non-inferior to surgical resection with lesions of comparable size (4).

Other criteria depend on lesion location, e.g., hilar masses may entail a possible risk of major vascular or biliary compromise and large vessel proximity may minimize thermal effect due to the so called "heat-sink"phenomenon (4).

More recent microwave ablation (MVA) method may be an acceptable alternative to RFA. This method uses electromagnetic emitting antennas often with internal cooling agent which through friction of targeted tissues generate heat and resulting cell death.

Possible advantage of MVA is the ability to perform multiple ablations simultaneously, shorter procedure time, larger tumoral ablation volumes, lower molecular impedance with no tissue charring and lower "heat sink" effect comparing to RFA (5). In one meta-analysis it was concluded to be of a similar efficacy to RFA with larger lesions (6). Several studies also showed no significant difference between MVA and surgical resection in small, less then 3 cm lesions (7).

Cryoablation employs low temperatures (-20 to -60°C) applied to target tumors with subsequent tissue necrosis. Potential benefits consist of easier imaging monitoring and less injuries to neighboring structures e.g., gallbladder and diaphragm when applied to targets located peripherally. One randomized controlled trial showed reduced local recurrence after cryoablation comparing to RFA (8).

Irreversible electroporation (IRE) is one of the more recent and promising ablation methods. It operates through creation of nanopores in cell membranes by probes emitting high-voltage currents with no direct thermal effect. This makes it a viable technique when applied to lesions located in the proximity of vessels and other critical structures. Literature presents various response rates suggesting that it could be utilized in patients where other thermal-based techniques are contraindicated (4).

Chemical ablation using percutaneous ethanol injections is the first original method that was implemented. Absolute alcohol solution causes coagulative necrosis and death of tumor cells. This may be still feasible in lesions located close to vital structures that measure less than 2 cm (9).

Other ablative approaches consist of high-intensity focused ultrasound (HIFU) and laser ablation. The former employs ultrasound generated vibrations, while the latter uses light energy as the source of cell-destructing heat. Further research is needed in the role of these methods in liver neoplastic disease (10, 11).

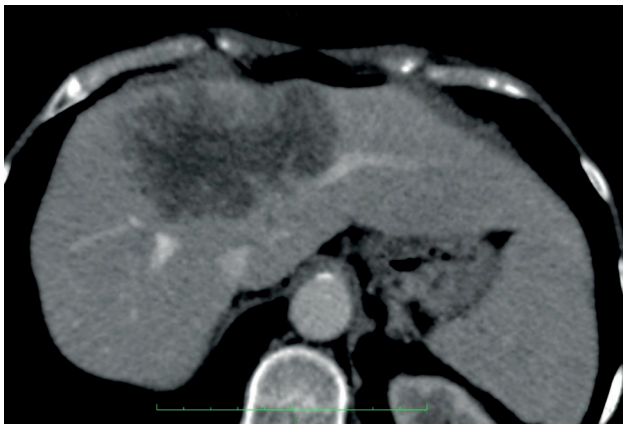
Finally, it is worth noticing that the use of different ablation techniques is often based on institutional preferences and capabilities rather than strictly on efficacy proven algorithms.

Arterial interventions – chemo- (TACE) and radioembolization

While healthy liver tissue is supplied both by portal and arterial circulation, most of the metastatic and primary lesions are preferentially perfused by arterial feeders. This allows for a selective intraarterial infusion of high doses of chemotherapeutics with simultaneous embolic effect that causes tissue ischemia and blocks potential drug washout. This concept is utilized in classic transcatheter chemoembolization technique (cTACE) where lipiodol is delivered with one of several cytotoxic agents (e.g., doxorubicin, cisplatin, mitomycin C or irinotecan) and with or without embolic agents.

Increasing local drug concentration while reducing the systemic dose is one of the main rationales of this approach. This is further complemented by using drug-eluting beads (DEB-TACE) which provide gradual dose release through a longer period of time which may lead to fewer postembolization adverse effects (12).

Transarterial radioembolization (TARE) or selective internal radiation therapy (SIRT) consists of injection of target



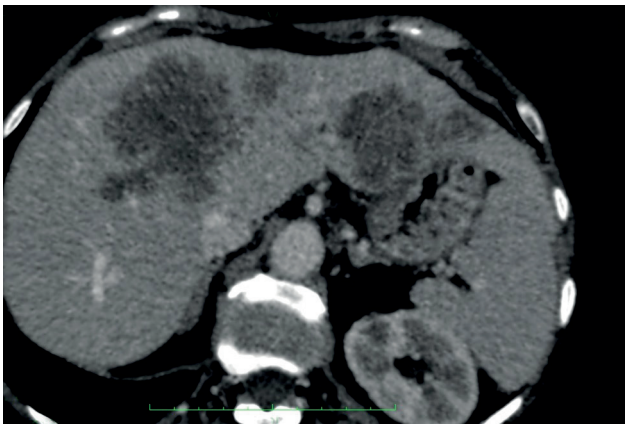
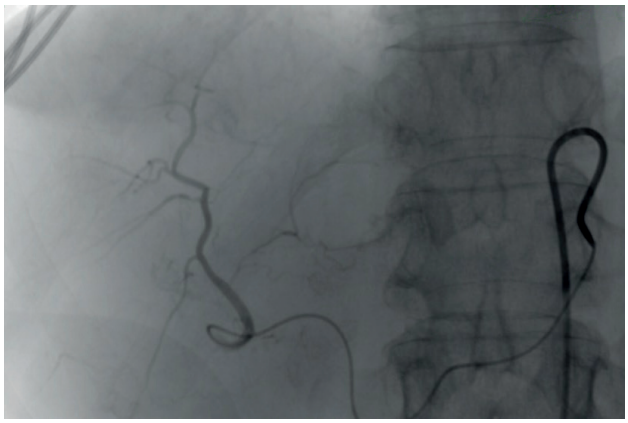


Figure 1, 2. Pre-intervention contrast-enhanced CT (CECT) of a 72 y.o. patient with mCRC and extensive bilobar metastasis nonresponsive to prior chemotherapy.



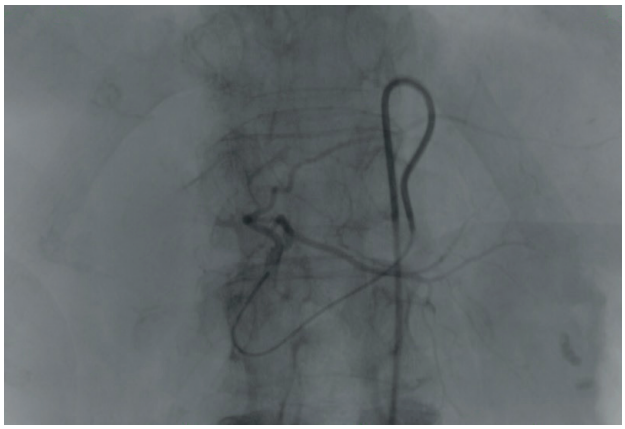
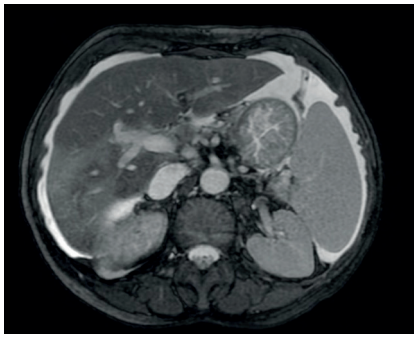
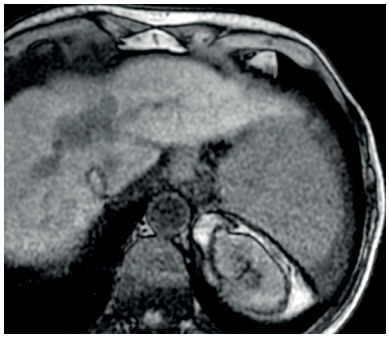


Figure 3, 4. TARE/SIRT procedure with selective right and left lobe Y-90 injection in the same patient.





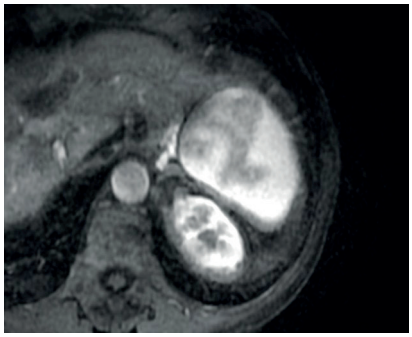


Figure 5, 6, 7. MRI (T2, GRE, T1 post-contrast) 3 months after TARE/SIRT in the same patient showing nearly complete resolution of metastatic lesions in both hepatic lobes (courtesy of Nowicki M. M.D. Ph.D. and Mruk B. M.D. Ph.D.).

lesions, segments or lobes with radioactively loaded microspheres (most often with yttrium-90). This allows for a higher dose of radiation to be delivered selectively to target lesions with a relatively low bystander effect to neighboring liver tissue. SIRT is being increasingly applied in patients with unresectable HCC, metastatic colorectal cancer, neuroendocrine tumors and metastatic melanomas (13). As it does not cause significant ischemia it can be performed in the context of portal vein thrombosis in patients with advanced disease (14). This method was proved to be non-inferior to systemic therapy in a recent meta-analysis in patients with advanced HCC (15).

Fusion therapies, bridging procedures and novel approaches

The main advantage of a vast arsenal of methods is the opportunity of combining them in synergy. For example, TACE may be used as a down-staging procedure prior to RFA by decreasing local perfusion and reducing heat loss (9). The concept of down-staging procedures may also make patients viable for orthotopic liver transplant, which is the main curative method (16). Radioembolization may also serve this purpose (17).

Combination of radioembolization and systemic therapy with sorafenib were also studied showing improvement in overall survival (18).

Even bland embolization plays its role as a bridging procedure. Portal vein embolization allows major hepatectomies by the means of compensatory hypertrophy that increases liver tissue reserve prior surgery (19).

Aforementioned drug delivery by drug eluting beads may be further expanded beyond traditional chemotherapeutics. Advantageous pharmacokinetics of selective infusions that limit the potential systemic adverse reactions are already being tested with modern drugs. Several tyrosine kinase inhibitors (TKIs) loaded beads are in preclinical studies with promising effect (20). Similar approach is being studied with antiproliferative agents such as bevacizumab (21).

Using specific chelating agents may also couple these modalities with local radiation therapy. This hybrid approach could unite the properties of all standard techniques (22).

Finally, many locoregional therapies can increase cancer immunogenicity through local inflammatory reaction and tissue destruction. This effect is usually of little importance however it may be further complemented when combined with other modalities e.g., immune checkpoint inhibitors or monoclonal antibodies (23). One study already utilized this concept showing promising effect and other are underway (24).

Conclusion

Minimally invasive procedures in the field of IR play an important role in the management of patients both with primary and metastatic liver neoplasms. This is likely to grow even more given the advancement in these techniques. In carefully selected patient populations, these methods were proven to offer extended survival rates often comparable or non-inferior to standard surgical approaches. This may be further emphasized by the benefits in the form of potential reduction in morbidity, quality of life improvement and

shortened hospitalization time. Often these approaches seem to be the more viable methods due to high level of patients' comorbidities and significant contraindications. Being less invasive it also allows for further repetitions if needed with possible lower periprocedural burden for the patients (25, 26).

Finally, it is worth emphasizing that availability and efficiency of such approaches is highly dependent on close multidisciplinary cooperation and local reimbursement policies.

Further improvement in these therapies and combining them in tandem, more complex and possibly synergistic procedures present high positive impact on the care of patients with hepatic neoplasms in the future of the IR field.

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