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EMBOLIZATION IN HEPATIC CANCER THERAPY

EMBOLIZACJA W LECZENIU NOWOTWORÓW WĄTROBY

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Authors' contribution
Wkład autorów:
A. Study design/planning
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B. Data collection/entry
zebranie danych
C. Data analysis/statistics
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D. Data interpretation
interpretacja danych
E. Preparation of manuscript
przygotowanie artykułu
F. Literature analysis/search
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G. Funds collection
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Summary

Interventional radiology procedures have wide application in hepatic cancer therapy. They are preceded by imaging techniques like CT, MRI, ultrasound, and PET. Procedures used in case of hepatic cancer include: embolization, chemoembolization, radioembolization. The purpose of this article was to describe the use of interventional radiology procedures in the treatment of tumors and hepatic metastases. Interventional radiology treatments can function as palliative care as well as they prepare the patient for surgical treatment. The expected therapy effects are, for example, tumor mass shrinkage, pathological tissue necrosis, pain relief, and improvement in quality of life. The most common method of treating liver tumors is chemoembolization. After interventional radiology procedures, there is a risk of adverse events within the liver; nevertheless, the probability of those events is far lower than for surgical procedures.

Keywords: hepatic cancer, interventional radiology, embolization, chemoembolization, radioembolization

Streszczenie

Zabiegi z zakresu radiologii interwencyjnej mają szerokie zastosowanie w leczeniu nowotworów wątroby. Są one poprzedzone badaniami obrazowymi takimi jak TK, MR, USG, PET. Procedurami wykorzystywanymi w przypadku choroby nowotworowej tego narządu są: embolizacja, chemoembolizacja, radioembolizacja. Celem opracowania jest krótki opis zastosowania procedur radiologii zabiegowej w leczeniu guzów pierwotnych i przerzutów do wątroby. Zabiegi z zakresu radiologii interwencyjnej spełniają rolę leczenia paliatywnego oraz przygotowują pacjenta do leczenia chirurgicznego. Do spodziewanych efektów zabiegów należą między innymi: zmniejszenie masy guza, martwica tkanek patologicznych, ustąpienie dolegliwości bólowych, poprawa jakości życia pacjentów. Najczęściej wykorzystywana w leczeniu guzów nowotworowych wątroby jest chemoembolizacja. Po procedurach radiologii zabiegowej w obrębie wątroby mogą wystąpić powikłania jednakże prawdopodobieństwo ich wystąpienia jest o wiele niższe niż w przypadku zabiegów chirurgicznych.

Słowa kluczowe: nowotwory wątroby, radiologia zabiegowa, embolizacja, chemoembolizacja, radioembolizacja

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Figures: 1
References: 30
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Introduction

The liver is the biggest organ in the human body. It is located under the diaphragm in the epigastrium, in the right hypochondrium. The liver can be divided into eight segments. It is an organ that has multiple functions [1].

Cases of hepatic cancer constitute 7% of all incidents of cancer in the world. They occur approximately three times more often in men than women, usually over age sixty. In Poland, in 2010, the number of cases of malignant tumor of the liver was around 1400, and the number of fatal cases amounted to approximately 2000. In 2010 in Poland the death rate from liver cancer was lower than average death rate in the European Union [2,3].

Liver diseases may include both benign as well as malignant tumors. The following are considered malignant tumors: biliary duct epithelial cells cancer, angiogenic sarcoma, cystadenocarcinoma, hepatoma, lymphoma, and hepatocellular carcinoma - 80% of all liver cancers. The most frequent changes occurring in the liver structure are metastases. Liver metastases mostly originate from adenocarcinomas of the organs of the digestive system as well as neuroendocrine tumors: metastasis of colorectal cancer (most often) metastasis of pancreatic cancer, metastasis of thyroid cancer, metastasis of gastroenteropancreatic neuroendocrine tumors [4]. Hepatocellular carcinoma (HCC) is most frequently subjected to interventional radiology treatment [5]. There are many predisposing factors to liver tumors: male sex, age 40 or older, obesity, smoking, type II diabetes, anabolic steroids, hormonal contraceptives, cirrhosis, too much iron in the diet, alcohol abuse, HBV and HCV infection, and

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diseases of metabolic origin [2,6]. Diagnostic imaging is crucial in choosing a method of treatment for patients with hepatic cancer. Diagnostic methods of liver changes are computed tomography (CT), magnetic resonance imaging (MR), positron emission tomography (PET), and ultrasound [4].

Computed tomography with the use of iodine contrast agents is the "gold standard" in case of a suspected vascular invasion (Figure 1). The tests consist of: a no contrast phase (Figure A); an arterial phase (Figure B), where tumors supplied by arterial blood, e.g. HCC, neuroendocrine tumors, breast cancer metastases, are distinctly enhanced; and a hepatic phase (figure C).

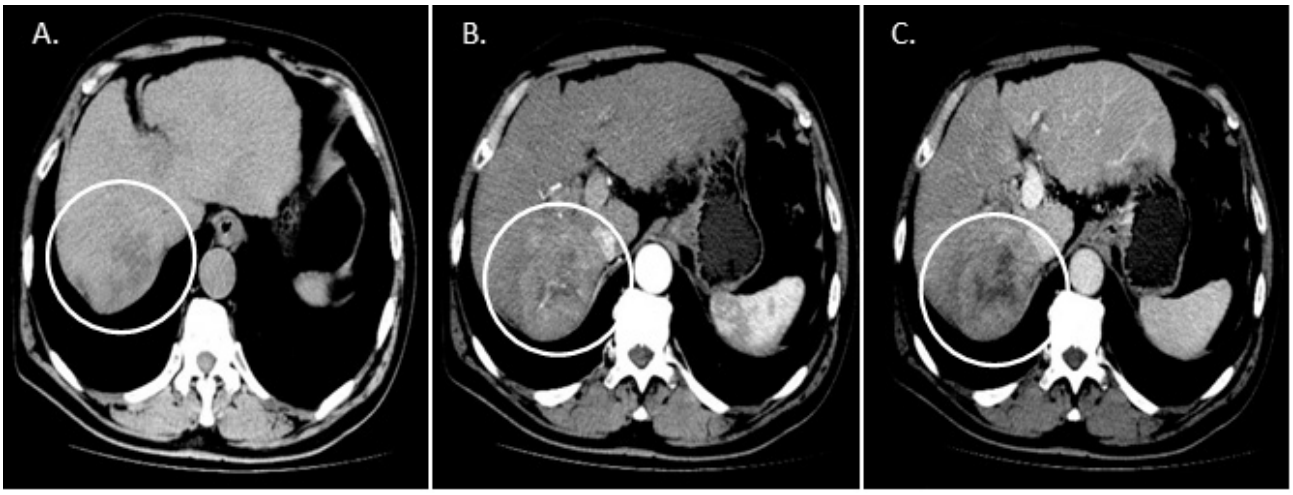

Figure 1. Hepatocellular carcinoma (HCC) in computed tomography. Patient at stage A with HCC (Barcelona Clinic Liver Cancer Classification). Figure A. HCC without a contrast agent. Figure B. HCC in arterial phase. Figure C. HCC in vascular phase [CT scans from TMS Diagnostyka in Bialystok]

Contrast agents used in MR are gadolinium-based. This test allows differentiating the character of the changes. The most sensitive in the detection and differentiation of solid tumors is T2-dependent sequences. Positron emission tomography plays a crucial role in: the assessment of the malignant tumor, the search for metastases of HCC. The most important ultrasound in the diagnosis of cancer is ultrasound with the administration of a contrast agent. The examination allows differentiating well-vascularized changes – HCC, focal nodular hyperplasia – and poorly vascularized changes – metastases of large intestinal cancer [4].

The first percutaneous vascular occlusion procedures were performed on patients with vascular malformations of the nervous system. The person considered to be the pioneer in this field is Dr. Doppman, who in 1966 performed a spinal hemangioma embolization. Chemoembolization of hepatic cancer was first performed by Yamada in 1977. The idea of using embolization techniques in the treatment of hepatic tumors is associated with the anatomical vascularization of this organ. Primary and secondary hepatic tumors draw blood from the hepatic artery. The flow of nutrients from the hepatic artery to a tumor is two times greater than from the portal vein. The principle of embolization is based on the closing branch of the hepatic artery which vascularized tumor. This action inhibits its growth. In addition, local delivery of cytostatics allows to maintain its high concentration [7,8].

Embolization of liver tumors is a procedure from the field of interventional radiology in oncology. It should be noted that performing these procedures is connected with radiation emission, its objective being the visualization of an area of clinical interest. Therefore, it is extremely important to optimize, i.e. ensure good image quality and low dosage absorbed by the patient. It is possible, as long as certain rules of radiological protection are followed, e.g. choosing the appropriate exposition parameter, and supervision of the X-ray camera ensured, e.g. periodically-performed quality control tests [9].

Aim of the work

The objective of this paper was the characterization and application of interventional radiology treatments based on embolization in hepatic cancer therapy. The method used in this paper is analysis of the literature. The literature overview was based on data contained in PubMed and Google Scholar. Content available online and in book publications was also used.

Brief description of the status of knowledge

Embolization is a procedure in the field of interventional radiology with the purpose of vessel occlusion under the control of X-rays. It is performed under local anesthesia. In oncologic diseases, the vessels supplying blood to the pathological cancer mass are closed. The result of this procedure is affected tissue necrosis due to lack of oxygen and nutrients [10].

Embolization is preceded by arteriography. It requires vascular access and the application of a contrast agent. Access is achieved using the Sven-Ivar Seldinger method. Vascular sheaths are used, enabling safe replacement of guidewires, catheters, and preventing the outflow of blood from vessels. The radiologist, using disposable instruments, reaches the artery or vein which is to be closed. The main purpose of embolization is to close the vessel's lumen by introducing a sterile embolization material, e.g. polyvinyl alcohol microspheres, tissue adhesive, vascular spirals [10].

Isolated occlusion of vessels does not produce the desired therapeutic effects – cancer tissue necrosis – due to rapidly developing collateral circulation. This procedure is usually performed as a preparatory treatment for surgical procedures. It is executed before liver surgeries to minimize blood loss and in the case of portal vein embolization so that healthy liver tissue (which is not resected) increases its mass. Apart from its preparatory function, embolization is used as a palliative treatment of well-vascularized tumors. It allows reduction of bleeding from the tumor, reduces cancer tissue volume, provides relief from pain, and improves patients' quality of life [2,11,12]. After the procedure, post-embolization syndrome may occur, accompanied by symptoms such as: abdominal pain, nausea, elevated body temperature, and vomiting. Syndromes subside after a relatively short period of time, usually approx. 2 days after the procedure [13].

Chemoembolization (TACE Transarterial chemoembolization) is a variation of embolization. The distinguishing element of TACE is providing cytotoxic drugs directly into the vessels supplying the cancer tissues, and not only closing their lumen. The most commonly used are doxorubicin and cisplatin [14]. During the procedures, cytotoxic drugs and embolization materials are used. TACE is used on well-vascularized primary and secondary changes in the liver. Nowadays, this method is a standard procedure in the treatment of HCC [10].

The first stages of TACE are performed similarly to embolization. Afterward, the radiologist administers through a catheter the embolization material combined with drugs. This method of drug administration ensures its upkeep over a long period of time (up to 7 days) in a high concentration in the area of the tumor, and in low concentration in other tissues [4,15].

After performing a single embolization, there is no complete necrosis of the tumor tissue. To bring the expected results, the procedure must be repeated several times (approx. 3 times). Nevertheless, the treatment does not lead to a complete cure as resection does [13]. Table 1 presents the indications, contraindications, and complications after the TACE procedure.

Table 1. Indications, contraindications, and complications after the RE and TACE

Indications [5,10,12,13,]	**Contraindications [15,16,17]**	**Adverse events [13,15,18,19]**
RE and TACE: • tumors ineligible for surgery; multifocal tumors (more than three), primary cancer changes: HCC, intrahepatic biliary duct cancer changes: large intestine metastases, breast cancer, melanoma; • inoperable stages of cancer, where systemic treatment is not effective. Only RE: • patient at stage A with intermediate HCC (Barcelona Clinic Liver Cancer Classification), ineligible for liver transplantation; • contradictions for TACE e.g. portal vein thrombosis. Only TACE: • patient at stage B with intermediate HCC (Barcelona Clinic Liver Cancer Classification).	RE and TACE: • lack of patient's consent; • advanced cancer – metastases to other organs; • vessels are cancerously changed; • lack of vascular access. • unstable condition of the patient; • serum bilirubin level >3.0 mg/dL; • serum creatinine level >2.0 mg/dL. Only RE: • the possibility of exceeding the dose of 30 Gy to the liver; • digestive system fistulas. Only TACE: • thrombosis of portal vein.	RE and TACE: • embolization syndrome; • bleeding from the puncture site; • sepsis. Only RE: • low white blood cell count; • lung and liver radiation damage. • ulceration of the stomach and the intestines; • biliary stricture; • cholangitis. Only TACE: • abdominal pain, nausea, vomiting; • peritonitis; • cirrhosis of the liver with fibrosis; • portal hypertension.

Radioembolization (RE), or selective internal radiation therapy (SIRT), is another treatment based on embolization. The embolization material (microspheres of resin or glass) with a radioisotope is introduced into the vessels which provide blood to the tumor. The objective of RE is to irradiate and destroy only the tumor tissue, sparing the surrounding structures. Generally, RE is less burdensome for the body than teleradiotherapy. However, selective internal radiation therapy is not a radical treatment. It leads to a reduction of tumor size (which may allow resection) and improvement in the quality of the patient's life. Table 1 presents the indications, contraindications, and complications after the RE procedure. Radioisotopes which are used in RE: Yttrium-90, lipidol labeled with Iodine-130, Rhenium-188 combined with microparticles of organic resisns. The most commonly used radioisotope is yttrium-90. This radioisotope emits high-energy beta radiation with soft tissue penetration of 2.5 mm, and its half-life is about 64 hours. Thus, irradiation of the tumor tissue lasts about two weeks, but the greatest portion of energy is transmitted into the tumor during the first four days. The rule is that during one treatment the radioisotope should be delivered to all tumors. If changes occur in the whole liver, the procedure can be performed by treating the first and then the second lobe. In sequential therapy, the interval of 30-45 days is assumed to ensure the launch of corrective mechanisms in the liver [10,18].

In the Hogeberg and associates examination, it was proven that the radiation dosage in hepatic cancer radioembolization has a large variability (5-1240 Gy). This is connected with the size of the vascular bed and the diameter of the pathological vessels. In addition, it should be considered that the dosage of 30-35 Gy is recognized as tolerable during irradiation from an external source. Thus, there is far greater probability of adverse events occurring after irradiation in the case of applying a higher dosage to the organ tissue [20]. The guidelines for the hepatic tumor radioembolization procedure, proposed by Kennedy's team, suggests planning the maximum dosage taking into account which other organs, such as lungs, digestive tract, are exposed, and which can be the consequence of unwanted migration of microspheres outside of the liver. That kind of personalized approach to treatment is a condition of radiation dosage optimization affecting the patient during the procedure [18]. Modern imaging methods - positron emission tomography/computed tomography (PET/CT) and single-photon emission computed tomography/computed tomography (SPECT/CT) – may use calculation absorbed dose in tumor and radiation risk nearby tissue [21].

The effectiveness of the described techniques can be evaluated by CT. With this method it is possible to recognize non-tumor/non-hepatic contrast delivery. MRI with the use of contrast agents shows a decrease of tumor volume and allows the assessment of necrosis in the tumor. MRI is typically performed 4 weeks after therapy, the usual follow-up period, to decide if an additional cycle is necessary. However, the optimum timing of imaging to detect tumor necrosis has not been identified. Compared with morphologic imaging modalities such as CT and MRI, PET with the glucose analog 18F-FDG returned superior results in monitoring therapy response and predicting survival in patients with various tumors [10,19,22,23,24,25,26].

In the field of embolization of liver tumors ongoing research on effective treatment patient at stage A and B with intermediate HCC. There have been reports regarding the use of the herb Bletilla striata as an embolic material in transarterial chemoembolization. Bletilla striata is a species of orchid native to Japan, Korea and China. The embolized herb disintegrates platelets, agglutinates erythrocytes and forms a thrombus, leading to longer therapeutic effect and inhibition of collateralization and metastasis [27]. There are trials of joining therapy stem cell therapy and TACE. Bone marrow stem cells injected into the liver before transarterial chemoembolization may help increase liver volume and consequently increase hepatic reserve [28]. They trials of joining TACE or RE with sorafenib. Here is theoretical reason - tumor hypoxia after chemo- or radioembolization can induce upregulation of circulating vascular endothelial growth factor (VEGF). This factor is essential for HCC growth, invasion, and metastasis. Shim et al reported a significant association between VEGF upregulation after TACE and poor prognosis [29]. Sorafenib is an oral multitargeted receptor tyrosine kinase inhibitor. There have been reports input to improve the therapeutic effect embolization [30].

The least effective method in the interventional radiology field is embolization. In turn, radioembolization and chemoembolization are performed more frequently, and have higher effectiveness. In the case of the unresectable hepatic tumors, the most famous, the most frequently performed, and generating the best results of all the described procedures is chemoembolization [2,15]. It is possible that new materials and techniques make the effectiveness of the described methods will be even higher.

Conclusions

1. For determining eligibility for a procedure, diagnostic imaging is crucial, including computed tomography, magnetic resonance imaging, ultrasound, and an examination in the field of nuclear medicine.
2. Chemoembolization is the most frequently used method for liver tumors.

3. Interventional radiology procedures fulfil the role of palliative care and ensuring relatively good quality of live, as well as preparation for surgery in some patients.

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