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Please cite this article: **EMBOLIZATIONS OF THE HEPATIC TUMORS - TWO-YEAR SINGLE CENTER EXPERIENCE**

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**UDC:**

**DOI:** https://doi.org/10.2298/VSP170721152J

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
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- TWO-YEAR SINGLE CENTER EXPERIENCE.

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Abstract:

Introduction: Transcatheter arterial chemoembolization (TACE) and portal vein embolizations (PVE) are established methods of treatment patients with hepatic tumors. The aim of the study was to present our experience in the treatment of liver tumors with embolization as a preliminary treatment for surgery or a part of palliative treatment.

Material and methods: The analysis included 29 patients who had undergone embolization. Results. TACE was performed in 26 cases with hemangiomas in unfavorable location or mass effect and inoperable malignant tumors both primary and metastatic. PVE was performed in 8 cases with primary liver tumors and colon liver metastases. All included patients presented with inoperable hepatic tumors. TACE was carried out in patients with hepatocellular carcinoma (n=1), cholangiocarcinoma (n=1), metastatic tumor (n=8), and hemangioma (n=16), while PVE in patients with cholangiocarcinoma (n=2), metastatic tumor (n=5), and neuroendocrine tumor (n=1). Embolization was followed by surgery in 5 PVE patients and 6 TACE patients. Postembolization was observed in 7 subjects. Death due to cancer progression occurred in 4 PVE patients and 7 TACE patients. One patient died during TACE due to hemorrhagic shock.

Conclusions:
Right PVE and selective TACE are efficient for preliminary preparation of patients with healthy hepatic parenchyma for major liver resections, but patients with liver cirrhosis require careful assessment. In patients with hemangioma, embolization allows to avoid surgical treatment by reducing the lesion mass, or to reduce the extent of hepatic resection. The preliminary results of arterial embolizations with bleomycin, leading to tumor reduction in cases of giant liver hemangiomas are promising.

Keywords: liver tumor; embolization; TACE; PVE
**Introduction**

Embolization is a method used in the treatment for liver tumors as an alternative to surgical treatment as well as for preparation to major liver resections.(1) In the 4th Military Clinical Hospital in Wroclaw, embolizations with the closure of both hepatic arteries and portal vein branches have been performed since July 2013. This procedure is reserved for patients who do not qualify for surgery due to a large tumor, hazardous (particularly parahilar) location, or poor overall health status while meeting conditions for embolization. By blocking the tumor's blood supply, arterial embolization selectively cuts off the supply of nutrients and oxygen to the tumor tissues.

Embolization procedure consists of introducing a fine catheter along the arteries into the close vicinity of the tumor and delivering a substance that causes the closure of the arterial vessel. In contrast to healthy liver parenchyma, tumor cells receive the nutrients from hepatic artery rather than from hepatic vein vessels; thus, transcatheter arterial chemoembolization (TACE) was introduced to administer a chemotherapeutic agent followed by vessel closure and radioembolization. The most frequent radiotherapeutic agent used in TACE is yttrium-90 which, delivered in microspheres, undergoes radioactive decay to release energy destroying tumor cells. (2, 3)

Portal vein embolization (PVE) is a procedure involving transcutaneous punctures of the branches of the right (less commonly the left) branch of the portal vein followed by introduction of the vessel-closing agent. This is aimed at blocking blood from being supplied via the portal vein into a hepatic lobe to induce secondary hypertrophy of the other hepatic lobe. This allows for major resection procedures being performed on initially inoperable liver tumors. Hepatic hypertrophy increases the efficacy of the part of hepatic parenchyma being left after the resection; thus, PVE is a procedure that prepares the patient for major resections and enables so that the remaining part of the liver might function properly. Optimum hepatic hypertrophy is achieved 2-4 weeks after the procedure in healthy hepatic parenchyma and 6-8 weeks after the procedure in liver cirrhosis of steatosis.
Objective

The aim of the study is to present the embolization as a method for treatment of inoperable liver tumors and a part of palliative treatment in large or numerous nodular liver lesions in patients disqualified from surgery, with lesions in parahilar location or as a preliminary treatment for surgery of large focal liver lesions within a single lobe.

Material and Methods

The study included 34 embolizations performed in 29 patients (14 male and 15 female patients) performed in the 4th Military Clinical Hospital in Wroclaw, Poland between July 2013 and December 2015. The mean age of all patients was 55.5 years. At the time of the procedure, the youngest patient was a 39-years-old male patient with an extensive hemangioma within the right hepatic lobe treated with arterial embolization procedure. The oldest patient was an 83-years-old male patient subjected to two arterial embolization procedures due to inoperable hepatic metastases of colon cancer.

Among analyzed embolizations, 26 procedures were TACE and 8 PVE. Indications for TACE included large benign liver tumors (hemangiomas, focal nodular hyperplasias) with unfavorable, i.e. parahilar location or presenting with mass effect, as well as large inoperable malignant tumors within the liver both primary and metastatic. TACE were also performed in patients who were disqualified from surgical treatment due to their overall health condition, numerous comorbidities or the presence of other contraindications for general anesthesia. Embolizations were not performed in patients with hepatic abscesses or cysts. TACE may be carried out periodically depending on the expected outcomes. Indications for PVE included large or numerous malignant tumors within a single hepatic lobe that, if resected without prior embolization, would lead to postoperative liver failure due to the insufficient amount of liver parenchyma being left after the surgery.
All procedures were followed in accordance with the ethical standards and with the Helsinki Declaration of 1964 and later versions. The informed consent was obtained from all the patients included in the study. Patients’ medical records were analyzed retrospectively. The data were presented as means and percentages.

**Results**

In the study, liver embolizations were performed in patients with inoperable hepatic tumors: 16 in benign and 18 in malignant. The benign lesions included hemangiomas, while the malignant lesions included hepatocellular carcinoma (HCC) - cases secondary to post-HCV, and post-HBV inflammation cirrhosis; cholangiocarcinoma (CC); neuroendocrine tumors, and colon cancer metastases. Three patients had to undergo repeated embolizations due to the extent of nodular lesions. Of these, one patient underwent TACE procedure four times as a staged treatment of extensive hemangiomas within both liver lobes. The patient was qualified for the surgery that involved the resection of liver segments 2, 3, 4, and 5.

Lipiodol, polyvinyl alcohol (PVA), and metal springs were most often used as embolization agents. In 13 cases, bleomycin was used. Cases qualified for PVE included 2 patients diagnosed with HCC, one patient with a neuroendocrine tumor, and 5 patients with hepatic metastases of colon cancer.

Right PVE was performed in 8 patients; 5 of these patients were subsequently subjected to surgical treatment (Figure 1, Figure 2 and Figure 3), while the remaining 3 underwent the embolization procedure as part of palliative treatment. Palliative TACE was performed in 6 cancer patients. In 10 patients with hemangiomas, TACE resulted in the reduction in lesion size allowing for the abandonment of surgical treatment. Surgical procedures were performed after TACE in 6 patients.

Liver failure symptoms developed after right-sided hemihepatectomy in 2 patients with post-inflammatory cirrhosis after HBV infection and type II diabetes (following right PVE). Deaths occurred in 12 patients: one was due to perioperative hemorrhagic shock and 11 were due to the progression of cancer several months after the embolization. Postembolization was observed in 7 subjects and manifested as transient abdominal pain with isolated episode of increase in body temperature up to 38°C observed during hospitalization. The symptoms resolved after...
administration of analgesic and antipyretic drugs. No abscesses or necrotic foci requiring surgical interventions were observed. Table 1 presents characteristics of the study group and results of treatment.

Table 1. The characteristics of the study group and the results of treatment

<table>
<thead>
<tr>
<th>Type of embolization</th>
<th>PVE (8 cases)</th>
<th>TACE (26 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of patients</td>
<td>63.3 years</td>
<td>47.7 years</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>2 HCC, 5 metastases of colon cancer, 1 neuroendocrine tumor.</td>
<td>1 HCC, 7 metastases of colon cancer, 1 neuroendocrine tumor metastasis, 16 hemangiomas, ICC.</td>
</tr>
<tr>
<td>Mean duration of hospitalization</td>
<td>5.5 days</td>
<td>4.5 days</td>
</tr>
<tr>
<td>Number of patients undergoing surgery</td>
<td>5 surgeries: - 3 hemihepatectomies - 1 laparotomy (biopsy) - 1 laparotomy (biopsy and RTA)</td>
<td>6 surgeries: - 4 cancer cases – laparotomy (biopsy) - 2 hemangioma cases – resection procedures</td>
</tr>
<tr>
<td>Deaths</td>
<td>-4 due to cancer progression</td>
<td>-1 perioperative -7 due to cancer progression</td>
</tr>
</tbody>
</table>

CC, cholangiocarcinoma; HCC, hepatocellular carcinoma; PVE, portal vein embolization; RTA, radio-frequency thermoablation; TACE, transcatheter arterial chemoembolization;

**Discussion**

In most countries, 5-year survival from liver cancer is low (below 20%) indicating that most patients are diagnosed when they are inoperable. (4) Additionally, primary liver and biliary cancers are very aggressive tumors which are the second leading cause of
cancer death worldwide. The incidence of those cancers decreases in Europe due to the decline of seroprevalence of hepatitis B virus as well as targeted screening and treatment of the hepatitis C virus. (5) In Poland, chronic hepatitis C virus affects about 200,000 individuals, but much less of them are aware of the infection, and even less are treated. (6) The present study included only inoperable liver tumors which were treated to enable surgery or as a part of palliative treatment. All 3 cases of HCC were associated with underlying hepatitis which is a risk factor for poor prognosis.

Surgical resection is a gold standard for hepatic malignancies, but majority of patients are diagnosed in inoperable state, thus embolization plays an important role in the treatment. Transarterial embolization is considered a palliative therapy for multifocal and large malignant tumors. The aim of this procedure is to deliver a chemotherapeutic drug and/or embolizing agent into the tumor, causing its necrosis. Data from the literature indicates that better results are obtained in smaller lesions. Miraglia et al. performed TACE in patients with HCC and obtained complete necrosis in 68% of patients with lesion between 4.1-5.0 cm, 50% of patients with lesion between 5.1-6.0 cm, and only 13% of patients with lesions over 6 cm. (7) In hemangioma, TACE may be used as alternative to surgery or with the aim to reduce the tumor size prior to surgery. Sun et al. reported a significant decrease in tumor size from 11.24 to 7.60 cm six months after embolization. (8) In the present study, surgery was performed in 6 (23.08%) patients who had undergone TACE. This type of embolization enabled surgery in 4 cancer patients, diminished extent of the resection by reducing the mass of hemangioma in 2 cases, and allowed to avoid surgical treatment in 14 hemangioma patients.

The aim of PVE is to induce regrowth of properly functioning liver parenchyma prior to a planned resection of a hepatic tumor. In case of malignant lesions, PVE may be combined with TACE. Disadvantage of this procedure is the delay of radical treatment increasing tumor growth and the possibility of the lack of liver hypertrophy. Patients with primarily unresectable tumors or require special approach because primary resectability of those tumors is limited mainly due to insufficient future liver remnant volume (FRLV). Risk factors such as chemotherapy, steatosis, diabetes mellitus, cholestasis and cirrhosis determine the development of the post-hepatectomy liver failure. Previous studies suggest that FRLV of above 20% is safe in healthy livers, above 30% in steatosis or during chemotherapy, and above 40% in cirrhosis. (9) Many researchers create strategies that help
to increase the FRLV pre-operatively to ensure proper liver function after surgery. Embolization is one the methods which decrease the rate of hepatic complications. It is recommended when estimated FRLV drops below 40% in the liver affected by a disease. (9-11) Volumetry of the liver is assessed directly before and 3-4 weeks after embolization. Obtained hypertrophy correlates with frequency of liver complications, hepatic failure, length of hospitalization, and mortality. (12) Extended hepatectomy may result in presentation with liver failure symptoms due to reduced mass of liver which is insufficient to maintain normal liver function. Clinical manifestation of liver insufficiency after extended hepatectomy is known as small for size syndrome (SFSS). Recent studies suggest that it is determined not only by FRLV but also by the hemodynamic parameters of the hepatic circulation. (13-15) In the present study, 2 out of 3 subjects with HCC, hepatic cirrhosis, and diabetes presented with liver failure symptoms after hemihepatectomy, despite meeting the 40% threshold of FRLV before surgery. This indicates that further research is required in the scope of the pathogenesis of SFSS which would allow surgeon for better patients’ qualification for liver surgery.

The presence of liver metastases in patients with colon cancer determines poor prognosis. Surgical resection improves survival, but may be impossible in cases with large lesions. Surgical removal of colorectal liver metastases improves survival in comparison with nonsurgical treatment (5-year overall survival rate 47% vs 6%). Repeated surgery has similar survival rate to surgical removal. (5) The present study included 5 cases of metastases of colon cancer subjected to PVE and 7 subjected to TACE. The majority of those embolizations were given to treat liver metastases for palliative effects.

Conclusions

Right portal vein branch or selective arterial embolization is an efficient method of preliminary preparation of patients with healthy hepatic parenchyma for major liver resections. No hepatic hypertrophy suitable for proper functioning of parenchyma preserved after the resection was obtained in patients with liver cirrhosis. In case of hemangiomas, embolization allows to avoid surgical treatment by reducing the lesion mass, or to reduce the extent of resection procedures. The preliminary results of arterial
embolizations with bleomycin, leading to tumor reduction in cases of giant liver hemangiomas are very promising.

Acknowledgments: This study was not funded by any grants.
Conflict of interest: The authors declare no conflict of interest in this work.

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Figure legend

**Figure 1.** The patient with HCC before PVE. CT scan shows a large hypodense and heterogenous tumor in the segments VII and VIII and partially in the segments V and VI of the right hepatic lobe, measuring 88x90x90mm, with necrosis in the central part.

**Figure 2.** CT scan shows the reduced size of the hepatic tumor of the same patient after the procedure of PVE.

**Figure 3.** The same patient after the right hemihepatectomy. CT scan shows the irregular and encysted fluid collection in the tumor bed, measuring 80x52x42mm, of 20 HU density, suggesting a postoperative inflammation.