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Yttrium-90 Selective Internal Radiation Therapy for Liver Tumors

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Abstract

The aim of this chapter to evaluate the effects of yttrium-90 (Y-90) radioembolization on primary and metastatic liver tumors with delivering implantable radioactive microspheres into branches of hepatic arteries that feed liver tumors to provide a high dose of targeted radiation to tumor tissue. Yttrium-90 (Y-90), a high-energetic beta emitter, is the most preferred radionuclide, which is used to label microspheres. The principle of this therapeutic option depends on the different blood sources of healthy and malign cells in liver. In liver primary or metastatic tumor cells, most of the blood is supplied via the hepatic artery. Arterial supply of malignant liver tumors in contrast with mostly portal venous supply of normal hepatocytes as well as excess amount of arterial neovascularization in the tumor bed. Therefore, intra-arterial radionuclide therapy can provide very high radiation exposure to tumor tissue, which is impossible to reach with external radiation therapy due to serious side effects. Y-90 microsphere therapy is an efficient and safe locoregional therapeutic option for unresectable primary and metastatic liver tumors.

Keywords: yttrium-90, internal radiation therapy, liver tumor

1. Introduction

Yttrium-90 (Y-90) microsphere therapy of liver tumors is an internal radiotherapy method by administering Y-90 radiopharmaceutical loaded microspheres that emit therapeutic beta-radiation from the relevant branch feeding the hepatic arterial tumor through femoral artery. The theoretical basis of treatment based on the fact of the different blood sources of healthy and malign cells in liver.

Most of the blood of healthy hepatocytes is supplied from the portal venous system, but a very small part is fed from the hepatic artery. In liver primary or metastatic tumor cells, most

of the blood is supplied via the hepatic artery. Based on this different nutritional pathway between benign and malignant cells in the liver, when microspheres that contain high dose radiation applied from hepatic artery intra-arterially, a very large portion of the applied radiation is targeted directly to the tumor cells; and healthy cells are protected as long as they are protected from radiation damage.

Since the intra-arterial delivery route is a local application, the radiomicrospheres cannot reach the extrahepatic tissues if there is no vessel shunt and as a result of this side effects based on treatments are seen very rare compared to other oncologic treatments [1, 2].

Y-90 used as a radiation source for intra-arterial Y-90 microsphere treatment is a pure beta-emitter radionuclide with a physical half-life of 64.2 hours. Tissue permeability of Y-90 microspheres is very low (mean 2.5 mm and maximum 10 mm), and therefore, if targeted correctly, is unlikely to cause harmful side effects to the surrounding tissues. The mean beta-particle energy given to tumor cells in Y-90 microsphere treatment is quite high and is around 2.28 MeV. Accordingly, high dose radiation therapy is provided in targeted tumor cells [1–4].

Two types of radiomicrospheres are used in the treatment of intra-arterial Y90-microspheres: resin-based (Y90-resin microspheres SIRSphere®, Sirtex Medical Europe, Bonn, Germany) and glass-based (Y90-glass microspheres Therasphere®, MDS Nordion, Toronto, Canada). Despite having similar biological behaviors, the physical properties of resin and glass radiomicrospheres are different, and the methods of treatment selection and application differ accordingly [3, 4] (**Table 1**).

	Resin radiomicrosphere	Glass radiomicrosphere
Diameter	22 ± 10 µm	32 ± 10 µm
Density	1.6 g/dL	3.6 g/dL
Average microsphere number (for the same treatment dose)	60 million/3 GBq	1.2 million/3 GBq
Average activity amount per microsphere	50 GBq	2500 GBq

Table 1. Some physical properties of commercial microspheres used in intra-arterial Y-90 microsphere treatment.

2. Patient evaluation

Intra-arterial Y-90 microspheres in liver tumors are an effective and safe treatment modality for primary and metastatic tumors that cannot be treated surgically, but each patient is not eligible for this treatment. For the efficiency and safety of the treatment, it is necessary to apply the patient selection steps very carefully. The evaluation and application of Y-90 microsphere therapy require a multidisciplinary approach. As a discipline applying nuclear medicine and interventional radiology to this approach, the relevant clinical branch patients, especially medical oncology, gastroenterology, and general surgery, should take an active role in evaluating the patient's treatment adequacy as the disciplines that direct this treatment.

Pretreatment assessment is mainly carried out in two stages. During the initial evaluation stage, the patient's general condition, physical examination, laboratory, and imaging findings are examined in detail. Hepatic angiography and hepatic artery perfusion scintigraphy are used for second-stage evaluation.

In order to receive intra-arterial Y-90 microspheres, the liver functional reserve must be such that the patient's life can be survived after treatment. In this context, the first preferred biochemical criteria for evaluating the suitability of treatment is being the normal upper limits of total bilirubin <2 g/L, albumin >3 g/dL, Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) 5 times lower. In addition to this for some assessments such as invasion level of tumor to the liver, vascularization of tumor, whether vascular structures invaded by tumor or not, neighborhood of tumor to main vascular structures and large bile ducts computerized tomography (CT) or magnetic resonance imaging (MRI) are examined in detail.

If appropriate indications are available for assessment of disease prevalence and phase, F-18 fluorodeoxyglucose positron emission tomography (FDG PET/CT) imaging is used for whole body. In general, in patients with widespread extrahepatic disease and in those patients whose life expectancy is less than 3 months, treatment is not preferred except in very special cases.

In addition to these assessments, the interventional radiology department evaluates the advantages and disadvantages of Y-90 microsphere treatment according to whether alternative vascular access is possible or not in the first stage and other alternative interventional treatments. Clinical disciplines that refer the patient to this treatment should also consider in detail whether there is a surgical chance of the patient's tumor in the first stage and evaluation of treatment prioritization in patients who require systemic treatment in addition to the local treatment approach [1, 4].

In the pretreatment evaluation, if it is decided as a result of the above-mentioned multidisciplinary studies, the evaluation is passed to the second stage. This stage includes hepatic angiography in the interventional radiology department and intra-arterial hepatic artery perfusion scintigraphy performed on the same day in the nuclear medicine department. This stage includes hepatic angiography in the interventional radiology department and intra-arterial hepatic artery perfusion scintigraphy performed on the same day in the nuclear medicine department.

Hepatic angiography: Arterial vascularization of the liver occurs directly from the celiac truncus in 55–65% of cases. Mostly celiac truncus are divided into three branches such as splenic artery, left gastric artery, and arteria hepatis communis. Up to 90% of cases, gastroduodenal artery arises from the arteria hepatis communis and after this branching it is named as arteria hepatica propria. Depending on some developmental anomalies that may occur in the embryonic period, arterial vascularization of the entire liver or related segment of the liver may be obtained from a different source except the arteria hepatis propria in some cases and this is called "replaced hepatic artery." At the same time, even though a portion of the liver may be fed from the same lob or from arteria hepatis propria it may also be fed from an aberrant artery and this artery called as "accessory artery."

If the radiomicrospheres are directed to the lobe where the tumor is or selectively to the segment in the liver, there is a high likelihood of escape to the gastrointestinal tract due to feeding from the accessory arteries. For this reason, it is very important to evaluate liver vascularization in detail during hepatic angiography and to perform arterial mapping studies.

Angiography begins with the entering to femoral arteria and the evaluation of all abdominal vessels that are likely to feed the liver. Thus, arterial vascularization of the liver is revealed in detail. Then, it is planned where the treatment is to be performed by entering the arteries feeding the lobe, segment, or subsegmentary part.

At this stage, embolization with coil of gastroduodenal, right gastric artery, and some accessory arteries is preferred in order to prevent some treatment-related complications such as radiomicrosphere leakage and gastroduodenal ulcer. After each procedure, contrast is given to test the success of the coil embolization and make sure that whether there is contrast transmission to the gastrointestinal tract or lungs or not.

Hepatic artery perfusion scintigraphy: After the detection of artery feeding the lobe, segment or the area constituted by the segments where the treatment wanted to applied and coil-embolization to accessory vessels to prevent possible leakage to the gastrointestinal area during hepatic angiography 5 cc volume of Tc99m-macrogrege albumin (MAA) are intra-arterially injected. After this procedure, it is necessary to monitor the patient in the nuclear medicine department within 1 hour.

Hepatic artery perfusion scintigraphy is performed both to predict the distribution of Y-90 microspheres, which will be applied in the same way for the same treatment, and to detect possible radioactivity escape to the gastrointestinal tract and lung by imaging the distribution of radioactivity in the liver. As the imaging technique, thoracic or abdominal planar imaging and abdominal spot planar imaging with thoracic and abdominal computed tomography and additionally single photon emission tomography (SPECT) or SPECT/CT hybrid cross-sectional imaging methods are preferred (**Figure 1**).

The received images are evaluated visually, and the gastrointestinal system is checked for radioactivity leakage. Regardless of the amount and location in the presence of a leakage to the gastrointestinal system, the patient is considered as contraindicated to the treatment. In this case, the patient is subjected to another hepatic angiography again, and an accessory vein

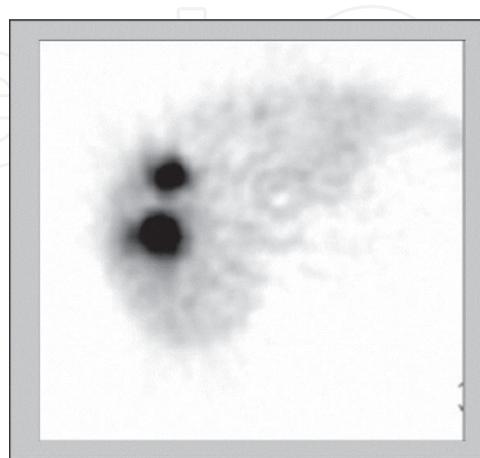


Figure 1. Abdominal spot planar imaging is performed to predict the distribution of Y-90 microspheres, which will be applied in the same way for the treatment and to detect possible radioactivity escape to the gastrointestinal tract in this patient.

which has caused the erosion and has not undergone coiling-embolization in the previous study is investigated and coil embolization applied to prevent leakage. Y-90 microsphere treatment is discontinued if it is determined by the interventional radiologist that coiling-embolization of all possible accessory arteries in the patient has been made and that there is no other artery to cause erosion.

Semiquantitative assessment is also performed with visual evaluation in hepatic artery perfusion scintigraphy. The aim of semiquantitative assessment is to quantitatively determine the possible radioactivity shunt ratio (hepatopulmonary shunt) from the liver to bilateral lungs. For this, region of interest (ROI) is drawn on images taken from the anterior and posterior projections of the liver and bilateral lungs in torso or half-body imaging. Pulmonary shunt ratio is calculated using the below formula [3, 4]:

$$\text{Pulmonary shunt ratio (\%)} = \frac{\text{Geometric mean of lung counts (anterior and posterior)} \times 100}{\text{Geometric mean of lung + liver counts (anterior and posterior)}} \quad (1)$$

When the rate of lung shunt is 20% or more in resinous Y-90 microsphere therapy is a contraindication to treatment. If shunt ratio is between 10 and 20%, it is recommended to reduce the dose as shown below, whereas the shunt ratio is less than 10%, indicating that the calculated dose can be given to the patient. If the shunt ratio is less than 10%, it is suggested that all of the calculated dose can be given to the patient. If the shunt rate is between 10 and 20%, it is recommended to reduce the dose as shown below for the treatment [3] (**Table 2**).

SPECT/CT imaging is more successful than SPECT/CT hybrid planar imaging and only SPECT imaging in determining gastrointestinal arteriovenous shunts in hepatic artery perfusion scintigraphy. It is possible to perform a full anatomic localization of nonhepatic involvement in the gastrointestinal tract with the CT component of SPECT/CT hybrid imaging. Another benefit of SPECT/CT hybrid imaging is the ability to anatomically assessment of intrahepatic Y-90 microsphere distribution. For this reason, it is advisable to add SPECT/CT hybrid imaging if possible in hepatic artery perfusion scintigraphy.

Lung shunt ratio	Suggested treatment dose decrement percentage
<10%	It does not need to be done
10–15%	20
15–20%	40

Table 2. Suggested treatment dose decrement dose percentages depend on lung shunt ratio in resin Y-90 microsphere treatment.

3. Determination of treatment dose

When the patient considered appropriate to the treatment in intra-arterial Y-90 microsphere treatment, transited to the determination of appropriate treatment dose. There are different methods which differ according to the type of radiomicrosphere used for treatment.

For Y-90 glass microspheres: Basically, it is assumed that the glass microspheres are homogeneously distributed in the liver, and therefore a dose calculation formula that takes into account liver volume is recommended. Although the target dose for the tumor is not known in this calculation method, it is aimed to calculate the activity to give 100–120 Gy radiation to the tumor to reduce the risk of hepatic fibrosis least.

For the Y-90 glass microspheres, the recommended formula for determining the desire for treatment is as follows:

$$\text{Activity (GBq)} = \frac{\text{Dose (Gy)} \times \text{liver mass (kg)}}{50} \quad (2)$$

A practical method based on liver lobe volume and hepatopulmonary shunt ratio and simple internal dosimetric approach is widely used in routine practices for the determination of the dose of treatment in Y-90 glass microspheres. By using software developed to facilitate the calculation of treatment dose, treatment dose practically can be calculated by using the hepatopulmonary shunt ratio obtained from liver lobe volume and hepatic artery perfusion scintigraphy and the radiation dose to be given to the tissue is estimated to be 120 Gy [4].

For Y-90 resin microspheres: Since it is assumed that the resinous radiomicrospheres are heterogeneously distributed in the liver, the determination of the treatment dose to the patient is performed by a series of calculations based on “body surface area” and “partition model” methods.

Calculation based on the body surface area is a relatively simple and fast method of calculation compared to other methods and is based on the body surface area calculated from the patient’s height and body weight and the tumor’s volume invasion rate (tumor/liver ratio):

$$\text{Activity (GBq)} = \frac{[\text{Body surface area (m}^2\text{)} - 0.2] + \text{tumor volume}}{\text{Tumor volume} + \text{liver volume}} \quad (3)$$

The liver and tumor volumes included in this formula are calculated from CT, MRI, or SPECT/CT images of the patient who have been assessed for eligibility for treatment.

In the Y-90 resin microsphere treatment calculation method based on the body surface area, it is suggested to reduce the calculated dose by 10–20% in patients with borderline liver function [1].

In addition, it is recommended to perform the necessary dose reductions according to the hepatopulmonary shunt rate [3].

The goal of the treatment with the partition model is to give the lowest possible dose to the remaining liver parenchyma while the tumor is being dosed at the maximum intensity of the tumor.

This method is based on the “medical internal radiation dose” (MIRD) theoretical bases and accounts for the tumor and nontumoral liver tissue separately. In the partition model, the Y-90 microsphere treatment dose is calculated as follows:

1. Tumor and nontumor liver volumes are calculated by any of the CT, MRI, or SPECT/CT methods.
2. The activity ratio that tumor and nontumor liver tissue will get is calculated using the Tc 99m-MAA hepatic artery perfusion scintigraphy SPECT or SPECT/BT images:

$$T/N = \frac{(\text{Tumor activity/tumor mass})}{(\text{Liver activity/liver mass})} \quad (4)$$

3. The lung (hepatopulmonary) shunt rate is calculated using planar Tc 99m-MAA hepatic artery perfusion scintigraphy.

When these parameters are calculated, treatment dose is calculated according to the partition model for Y-90 resin microspheres using the following formula:

$$A (\text{GBq}) = \frac{D_{\text{liver}} ((T/N \times \text{tumor mass}) + \text{liver mass})}{49,670 (1 - \text{lung shunt \%}/100)} \quad (5)$$

where D liver is the nominal dose in Gy for the liver.

When partition model is used, D value should not exceed 80 Gy in nontumor parenchyma in patients with adequate liver reserve and 70 Gy in nontumor liver in cirrhotic patients. The calculated dose is also recommended to be reduced by 40%. The radiation dose to the lungs should not exceed 25 Gy. There is no upper limit for the dose to be given.

The calculated dose is also recommended to be reduced by 40% [2]. The radiation dose to the lungs should not exceed 25 Gy. There is no upper limit for the dose that will be given.

3.1. Treatment administration

A suitably designed “dose applying set” is required based on the type of microsphere in treatment for both resin and glass Y-90 microspheres. Dosage application set varies according to the type of microsphere and includes methacrylate armor, dose vial, catheter connection set, and suitable needles.

For the Y-90 microsphere treatment, the patient-specific prescribed treatment dose emptied to the treatment vial with 5 ml volume injectors that settled into the application set. While glass microspheres are compatible with saline, resin microspheres are compatible with sterile injectable water. Once the dose preparation and vial settlement procedure is complete, the radiation dose is measured and recorded by the radiation physicist in the nuclear medicine department with a dose counter at a distance from the four sides of the methacrylate armor. This record is a practical method of indirectly understanding whether the treatment dose is complete after treatment infusion of the dose is over or not.

In the interventional radiology department, when the patient is interfered with via the femoral artery and the Tc99m-MAA is confirmed by contrast angiography where the catheter is placed, the connection set of the dose vials placed in the treatment set appropriately is connected

to the outer end of the angiographic catheter. During Y-90 resin microsphere treatment, slow infusion activity is sent. In order to provide to direct the microspheres to the liver without blockage in the set contrast media and injectable water infusions are performed. For Y-90 glass microsphere application, 20 cc is taken from the saline solution placed in the application set and the microspheres are directed to the catheter liver for about 2 min with slow infusion. After the procedure is finished, the infusion is terminated by washing 2 times with 20 cc saline.

It is of utmost importance that the direction of the entire dose calculated for the efficacy of the treatment is appropriately to the liver. It can be easily understood whether the whole dose is given or not in Y-90 glass microsphere treatment with dose counter which is a component of the application set. On the other hand, it can be determined that whether the whole treatment dose is given or not in Y-90 microsphere applications by measuring the radiation dose at the same distance from four sides of methacrylate treatment set after the treatment. In any case where the infusion should be discontinued during treatment, the activity can be indirectly calculated by radiation physician by measuring the radiation dose with radiation counter and proportioning this with the pretreatment dose. After the procedure, it is recommended that the treatment vial be counted directly in the dose calibrator to determine the actual amount of activity sent to the patient. Since Y-90 is a pure beta emitter radionuclide, very careful study of internal contamination is required especially during application. For this reason, it is recommended that radiopharmacists and/or radiochemists, especially those who provide dose withdrawal and set connection, work with double gloves, not to touch the vial directly with hands, and make the habit of working with control list method not to skip any step in the procedure.

After the procedure, measurements should be made and recorded with a Geiger Müller counter measuring the radiation levels lower than 0.1 mR/hour by the health physician to determine possible radioactivity contaminations of the applicators' hands, room, and waste to be applied.

After administration of the treatment, the catheter connection of the dosing set is separated. The interventional radiologist also applies pubic pressure to the patient to avoid bleeding by drawing the catheter. Once these procedures are completed, it is recommended that radiation measurements be made from the patient's liver area over the skin and at a distance of 1 m.

4. Bremsstrahlung imaging after treatment

Although the saline in treatment application vial can be determined with the measurements during the procedure that the dose is given to the patient by interventional radiologists and nuclear medicine practitioners, the imaging immediately after treatment is of great importance to ensure that the activity is delivered to the desired site in the liver and that there are no undesirable activity leaks in the nonliver tissues.

Since the Y-90 is a pure beta emitter, X-rays that are generated by Bremsstrahlung effect can be displayed under the gamma camera. As well as Bremsstrahlung imaging may be carried

out without collimator, if low leveled collimator is settled it may be done in 20% windows that adjusted to 80 keV energy, or if medium-energy collimator is used in 20% windows that adjusted to 159 keV by taking plenary images similar to Tc99m-MAA hepatic artery perfusion scintigraphy, but more preferred method is to take planar images similar to 20% pencil Tc99m-MAA hepatic artery perfusion scintigraphy with 20% pencil adjusted to 80 keV energy or 20% pencil adjusted to average 159 keV if medium-energy collimator is used if low energy collimator is placed. Imaging is recommended within the first 24 hours after treatment [5].

As an alternative to Bremsstrahlung imaging, post-treatment biodistributions of Y-90 microspheres can be displayed by PET/CT imaging in recent years. However, the Y-90 is a pure beta emitter radionuclide, but it also degrades the radioactive decay of the positrons by 1 per 32 million. Based on this characteristic, patients can be monitored directly at the PET/CT unit after treatment. However, in order to obtain a good quality image, it is recommended imaging for at least 30 min per bed position and placing a 2.5-mm thick copper ring in the gantry to prevent the detector from saturation [6].

5. Patient management after treatment

Since Y-90 is a pure beta emitter radionuclide, it is not necessary to take special radiation safety precautions in patients after treatment. After Y-90 microsphere treatment, the patient can be discharged similar to planned angiography procedure after for several hours following time for hemorrhage control. However, since the vast majority of patients are terminal period cancer patients and are likely to have additional internal problems it is suggested that it will be good to hospitalize these patients and the patients are admitted at least 1 day after treatment in most centers.

It is recommended that antipyretic and antiemetic and antiacid medications be given to the patient on the day of treatment against nausea-vomiting and fever which are early side effects of treatment. In patients, the same drugs are continued after treatment and full blood counts and blood biochemical values of the patients are followed. In patients, the same drugs are continued after treatment and full blood counts and blood biochemical values of the patients are followed. Patients can usually be discharged on the day after the treatment without any symptoms or signs, since the primary mechanism of action of the treatment is not embolization but internal radiotherapy, so that almost no cases of post-embolism syndrome like after chemoembolization are observed.

Whole blood counts and blood biochemical control are performed weekly for 1 month from the patients. FDG-PET/CT imaging is performed to determine early treatment response in patients with indications on 4–6th weeks after treatment. On 2–3rd months after the treatment, assessment of treatment response with CT and/or MRI is done.

Side effects and complications: As well as intra-arterial Y-90 microsphere treatment is effective, it is also a safe local treatment method because of its theoretical basis. As a result, side effects and complications are less common than systemic treatments and other similar local

treatments. The most common side effects associated with treatment are mostly seen in the acute phase, most of these are self-repairing minor side effects. Serious side effects and complications are rarely observed after treatment, most of which are subacute and chronic effects that arise after the 3rd month [1–5]. Although radiomicromicrospheres are directed intra-arterially to the tumor veining and emitted radiation to the tumor from the inside via embolization, the main action mechanism of the treatment is not embolism, causing internal radiation damage. For this reason, the embolization syndrome observed in chemoembolization is not an expected side effect of Y-90 microsphere treatment.

However, side effects such as fever, abdominal pain, nausea, and vomiting can be observed in the first hours of treatment because of the systemic endothelial damage response in patients due to intravascular intervention. It is possible to prevent these side effects with premedication with appropriate drugs such as antipyretics, analgesic, and antiacid-antiemetics and maintenance with same drugs in the first week after treatment; however most of these effects are self-limiting and low to moderate in severity.

The most common side effects in patients are anorexia and fatigue. These constitutional effects may take over 4–6 weeks after treatment. These symptoms usually improve without requiring additional treatment, as patients receive regular oral nutrition and hydration at rest and after rest.

Transient increment may occur in liver transaminases beginning in the first 4–6 weeks and continuing for 2–3 months in the majority of patients taking Y-90 microsphere treatment. This increment is mostly low to medium, and is self-limiting. Patients are advised to check their blood biochemical values during the first 4–6 weeks following treatment.

Especially thrombocytopenia can be observed in the blood counts in the first 3 months after Y-90 microsphere treatment. It is believed that this effect arises due to the fact that Y-90 is given localized and it is a radiopharmaceutical with good in-vivo stability, so that it is not directly affected to bone marrow, it is mostly due to not to production of some blood proteins in the liver as a result of the liver damage and transient failure. For this reason, it is recommended that blood counts followed up for the first few months.

Apart from these effects, cholecystitis may arise within the first 4–6 weeks after treatment in Y-90 microsphere treatment. Cholecystitis usually arises due to a radiomicromicroscopic leak in the bile of the cystic artery, which is an accessory artery, in patients who do not undergo coil embolization. In some patients, leakage may be seen to the bile duct due to reflux caused by vasospasm during the treatment. Cholecystitis due to Y-90 microsphere treatment gives clinical signs of cholecystitis due to other factors and the treatment does not show any difference.

Transient blockage may develop in the intrahepatic bile ducts due to tissue edema, which is often caused by radiation damage due to treatment. In this case, the symptoms and signs such as an increase in biochemical values that show bile functions such as ALP and GGT, and sudden onset and increased jaundice, abdominal swelling, and severe abdominal pain may be observed. In this case, first cholecystectomy metics and biliary function increasing antiedema medical treatments are applied. If the patient does not respond to these medical treatments, a temporary stent may be placed to the bile ducts.

The most serious complication of Y-90 microsphere treatment is “radiation-induced liver disease”. Radiation-induced liver disease is a liver failure table characterized by sudden and excessive increases of total bilirubin levels without significant increases of liver transaminases, a sudden decrease in albumin level, and a sudden onset of progressive liver disease with abrupt onset and increased acidity, jaundice. Although its mechanism is not completely known, it is thought to be inflammation due to radiation damage and subsequent fibrosis. In radiation-induced liver disease, the patient is treated with anti-inflammatory, anti-inflammatory, and anti-inflammatory treatments to support liver function. Fulminant hepatitis and related deaths can be observed in patients who do not respond to treatment. In studies, the incidence of radiation-induced liver disease after Y-90 microsphere treatment is reported to be about 3% [7].

Another serious complication of Y-90 microsphere treatment is pulmonary fibrosis. Performing hepatic artery perfusion scintigraphy with Tc99m-MAA before treatment and treatment dose adjustment by calculating hepatopulmonary shunt ratio treatment complications are rarely encountered [3, 4].

6. Y-90 microsphere treatment in primer and metastatic liver tumors

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and is still among the deadliest cancers. The main treatment of HCC is the curative surgery. However, other treatment approaches, including Y-90 microsphere treatment, are on the way to patients in whom surgical treatment is not possible. It is preferable that a council consisting of a gastroenterologist, a surgeon, a medical oncologist, an interventional radiologist, and a nuclear medicine doctor should be established for the decision of treatment of HCC patients.

In the study conducted by Salem et al. with 291 HCC patients, it has been reported that Child-Pugh A patients are the patients who got greatest benefit from Y-90 microsphere treatment and treatment respond did not change for this patient group whether vascular invasion is seen or not [8]. In the same study, it was reported that the patients had the most fatigue side effects with 57% frequency and the third and fourth degree bilirubin toxicity was observed with 19%.

In a study conducted by Inarrairaegui et al. with 72 HHC patients, it has been reported that median survival was 13 months [9]. The treatment respond of the patients with more than five lesions, bilobar disease, and alpha-fetoprotein >52 IU/mL was lower and prognosis of these cases was worse.

Studies have been published the report on the success of the Y-90 microsphere treatment in the case of portal vein thrombosis in HCC patients.

In a study conducted by Kulik et al. who considered the patients with lung and adrenal metastasis HCC contradicted to the treatment, it has been reported that Y-90 microsphere treatment in patients with vascular invasion had a survival of approximately 3 months (10.1 months versus 10.1 months) [10].

Kooby et al. compared the chemoembolization and Y-90 microsphere treatment in their studies. As a result of the study, they have reported that these two treatment methods showed similar progression-free survival rates in HCC patients [11].

Carr et al. compared the patients with advanced phase and inoperable biopsy diagnosed HCC patients in their study conducted in North America. As a result of the study, they have reported that treatment success was similar for both groups [12].

In patients with HCC, a significant decrease in tumor burden is achieved after Y-90 microsphere treatment, and in some patients, the possibility of surgery or transplantation arises and treatment at appropriate centers serves this purpose as well [13].

In addition to HCC, Y-90 microsphere treatment for cholangiocarcinomas from primary liver tumors is performed in eligible patients.

In a meta-analysis study conducted by Al-Adra et al. in a recent year that included a total of 12 studies that examined Y-90 microsphere treatment efficiency, it has been reported that median survival of the patients was 15.5 months, the partial response rate in treatment responses assessed by radiological methods was 28%, and stable disease was reported to be 54% [14]. In the same study, it was emphasized that Y-90 microsphere treatment provided much better survival rates than all other treatments in cholangiocarcinomas.

Serum alpha-fetoprotein levels and radiological imaging methods are preferred in patients with HCC in the follow-up of Y-90 microsphere treatment in primary liver tumors. Riaz et al. reported that a 50% reduction in alpha-fetoprotein levels after treatment is correlated with treatment response [15].

The great majority of liver malignancies are secondary cancers. After the lymph nodes, the liver is the most metastasized organ. Cancers that frequently metastasize to liver are colorectal cancer, pancreatic cancer, breast cancer, and neuroendocrine tumors. However, ocular malignant melanoma may recur with liver metastases even after many years. If there is a possibility of resection in liver metastatic disease, surgical treatment is generally the first choice. However, it is possible to administer Y-90 microsphere treatment independently from histopathology of primer tumor that makes metastasis if the surgical contraindication is met or if compliance criteria are met for patients with liver metastasis that cannot be resected.

In patients with colorectal cancer, Y-90 microspheres can be used in combination with chemotherapy, after chemotherapy, as a rescue treatment in advanced phase disease in the treatment of liver metastases without surgery. Y-90 microsphere treatment combination with chemotherapy strengthens the response to systemic chemotherapy in patients with colorectal cancer that no chance of surgery option [16].

In a study conducted by Van Hazel et al., it was reported that the Y-90 microsphere treatment added to the 5-fluorouracil/leukoplovan chemotherapy protocol at 3rd month significantly increased the quality of life compared to the chemotherapy treated group [17].

There are studies reported that Y-90 microsphere therapy alone or as an effective and safe treatment modality when combined with a radiosensitizing chemotherapy regimen as rescue treatment in chemotherapy refractory metastatic colorectal cancer advanced phase patients [18, 19].

In a study conducted by Kennedy et al. with 208 colorectal cancer patients with liver metastases, it has been reported that there is a decrement in tumor size in 35.5% of the patients, stable respond in 55% of the patients with BT imaging; well metabolic respond is seen in 85% of the patient with the PET imaging method [20].

Although all chemotherapy regimens have been tried, disease burden is reduced with Y-90 microsphere treatment in patients colorectal cancer that have continuing metastatic disease in liver and that have metastases in different regions or not, in this context other treatment modalities such as surgical treatment or radiofrequency ablation treatment are possible [21].

About 60% of patients with breast cancer lose their lives because of liver failure, which is caused by liver metastases. Because of this reason, Y-90 microsphere treatment plays an important alternative therapeutic role in patients who have no chance of surgical treatment of breast cancer with liver metastasis. Coldwell et al. reported that when the decrement of tumor burden in liver metastases in breast cancer provided with Y-90 microsphere treatment and systemic chemotherapy, it has been seen that Y-90 microsphere treatment provided a significant increase in median survival (11 months versus 30 months, $p < 0.001$) [22].

Surgical treatment of neuroendocrine tumor liver metastases is still a controversial topic, and alternative local treatment modalities are needed to surgery. It has been emphasized that extensive patient-participated clinical trials and retrospective studies in this regard have shown that Y-90 microsphere treatment of neuroendocrine tumor liver metastases is a well-tolerated, symptomatic healing, and highly effective treatment [23, 24].

In the literature, it has been reported that Y-90 microsphere treatment provides a significant survival advantage in uveal malign melanoma from tumors that frequently metastasize to liver [25].

Y-90 microsphere treatment is considered to be an effective and reliable treatment approach in the treatment of liver metastases in all gastrointestinal cancers, especially in pancreatic cancer, as it is in colorectal cancers [26].

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