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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Yttrium-90 radioembolization for the treatment of unresectable liver cancer: Results of a single center

Rezeke edilemeyen karaciğer tümörlerinde yttrium-90 radyoembolizan tedavi: Tek merkez sonuçları

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ABSTRACT

Objective: To determine the effects of yttrium-90 (Y-90) resin microsphere radioembolization therapy on patients with unresectable liver cancer who do not benefit from chemotherapy.

Methods: Fifty-five patients underwent radioembolization therapy included in the study whose had unresectable primary or metastatic liver cancer originating from the gastrointestinal tract. Three were excluded from the study after pre-evaluation angiography. Thirteen (23.6%) of the remaining 52 patients had hepatocellular carcinoma and 39 (76.4%) had metastatic liver cancer. Fifty-two patients underwent Y-90 radioembolization treatment. Each patient's response to the administered treatment was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) and the overall probability of survival was displayed graphically by the Kaplan-Meier method.

Results: After Y-90 therapy, 47 patients were follow-up. While 57% of the patients responded to treatment as clinical benefit, the disease progressed in 43%. The median hepatic progression-free survival time of the patients was 3.4 months (95% confidence interval (ci):1.4-5.3) and the overall survival time was 11.3 months (95%, CI:8.7-14.03).

Conclusion: This study emphasizes that Y-90 resin microsphere radioembolization treatment is effective in patients with unresectable liver cancer.

Key words: Yttrium-90, radioembolization, angiography, liver cancer

ÖZET

Amaç: Çalışmamızda kemoterapiden fayda görmeyen, rezeke edilemeyen karaciğer kanserlerinde yttrium-90 (Y-90) resin mikrosfer radyoembolizasyon terapisinin etkinliğinin ortaya konması amaçlanmıştır.

Yöntemler: Çalışmaya radyoembolizasyon tedavisi uygulanan, rezeke edilemeyen primer veya gastrointestinal sistemden metastatik 55 hasta dahil edilmiştir. Üç hasta ön değerlendirme anjiografisi sonrasında çalışma dışı bırakılmıştır. Kalan 52 hastanın 13'ü (%23.6) hepatosellüler karsinoma, 39'u (%76.4) metastatik karaciğer kanseri hastasıdır. Elli iki hasta radyoembolizan tedavi görmüştür. Her hastaya verilen tedavi, Solid Tümörlerde Tedaviye Yanıt Kritirleri'ne (RECIST) göre değerlendirilmiş ve tüm sürvi olasılığı Kaplan-Meier metoduna ile grafik olarak gösterilmiştir.

Bulgular: Y-90 tedavisi sonrası 47 hasta takip edilebilmiştir. Hastaların %57'sinde klinik fayda yanıtı alınmış, %43'ünde hastalık progresyon göstermiştir. Hastaların medyan hepatik progresyonsuz survi süresi 3.4 ay (%95 confidence interval (ci): 1.4-5.3), tüm sürvi süresi 11.3 (%95 confidence interval (ci): 8.7-14.03) olarak saptanmıştır.

Sonuç: Bu çalışma Y-90 resin mikrosfer radyoembolizan tedavinin rezeke edilemeyen karaciğer kanseri hastalarında etkin olduğunu ortaya koymaktadır.

Anahtar kelimeler: Yttrium-90, radyoembolizasyon, anjiografi, karaciğer kanseri

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INTRODUCTION

Unresectable liver cancer is a disease with poor prognosis that causes a large number of deaths each year. Without treatment, survival time is less than 6 months, while the average survival time is 1.5 months [1,2,3]. Chemotherapy, transarterial chemoembolization, regional radiotherapy, radiofrequency ablation, radioembolization and transplantation are treatment options for this disease.

Radiotherapy is an alternative choice of treatment for patients that cannot undergo surgery and for those that do not benefit from chemotherapy. While regional irradiation can be performed with external radiotherapy, malign tumors cannot be selectively targeted. Normal hepatocytes have a much lower tolerance for the effects of radiation than do tumoral tissue. Previous reports indicate that when a dose of radiation higher than 43 mGy is administered, liver function deteriorates in 50% of patients [4]. Higher doses of radiation can be more safely administered with conformal or stereotactic radiation therapy. However, the multifocality of metastases and primary foci and their irregular shapes make it difficult to obtain positive results from these types of treatments [5].

Clinical studies for radioembolization therapy began in the 1960s and have received growing attention in the last several years [6,7]. The primary purpose of radioembolization therapy is to provide an alternative treatment option that will reduce the grade of the tumor and extend survival time. While liver tumors receive 90% of their supply from the hepatic artery, the healthy parenchyma receive 80% of their supply from the portal vein [8,9]. This discrimination in vascular perfusion allows for tumor-selective treatment while protecting hepatic function. During radioembolization therapy, microspheres loaded with yttrium-90 (y-90) are selectively infused into the effected hepatic region by transarterial catheterization. Microspheres that reach the tumor microcirculation use beta emission as internal radiation to destroy the tumor. So the treatment is named as selective internal radiation therapy (SIRT). The half-life of Y-90 is 64.2 hours (2.67 days), and it breaks down to zirconium-90. It spreads high energy beta particles (max. 2.27 MeV, average 0.9 MeV) that have average tissue penetration of 2.5 mm and a maximum penetration of 11mm. Y-90 is produced in nuclear reactors by the neutron bombardment of Yttrium-89 [6]. Later, it is bound to resin or glass microspheres so that is can be used for treatment. Currently, there are two microsphere devices available for commercial use, including resin microspheres (SIR-Spheres, Sirtex Medical, Sydney, Australia) and glass microspheres (Therasphere, MDS Nordion, Ottawa, Ontario, Canada).

Publications demonstrating the effectiveness of SIRT are limited in patients with liver metastases from gastrointestinal system cancers.

The results of yttrium-90 (Y-90) resin microsphere radioembolization therapy on patients with unresectable liver cancer who do not benefit from chemotherapy are presented here in. The results of this study are also compared with previously published data.

METHODS

Patients who underwent radioembolization therapy (as determined by the oncology council of our hospital) between 2010 and 2012 were included in the study. After approval from the ethics committee, patient data was analyzed retrospectively with a radiology/patient information program provided by our hospital (MEDI-RIS 11.6 1197/2012 AND MEDİ-HASTA 14.22 1997/2010 Hospital Data Processing Center). All of these patients had unresectable primary or metastatic liver cancer originating from the gastrointestinal tract. Treatment with resin microspheres (SIR-Sphere) was administered to 52 of the 55 patients who were included in the study. Each patient's response to the treatment was evaluated by RECIST (Response Evaluation Criteria in Solid Tumors, second version, 2012) and survival was determined by the Kaplan-Meier method [10]. The average age of the patients was 60 years (Range 43-78 years), and 16 were female (31%) while 36 were male (69%). Thirteen of the patients (23.6%) had hepatocellular carcinoma, 26 (47.3%) had colorectal cancer, 9 (16.4%) had gallbladder and bile duct cancer, 2 (3.6%) had pancreatic cancer, and 5 (9.1%) had gastric cancer. The average time between the diagnosis and the administration of therapy was 15.3 months. 43 of the patients were administered 690 cycles of chemotherapy prior to the treatment without any benefit. Twelve (21.8%) patients did not receive chemotherapy prior to the procedure, 17 (30.9%) patients received level 1 che-

motherapy, and 26 (47.3%) patients received level 2 chemotherapy or higher. Eighteen patients (32.7%) had unilober hepatic involvement while 37 (67.3%) had bilober hepatic involvement. Six patients (10.9%) had a solitary hepatic metastasis, 14 patients had 2-4 (25.5%) metastases, and 35 (63.6%) had more than 5 metastases. The average target tumor diameter in the liver was 59.8mm (20-140mm) and the average Standardized Uptake Value (SUV) in 18-fluoro-deoxyglucose (18-FDG) PET-CT was 11.7 (0-41) (Table-1).

Table 1. Characteristics of patients GIS: gastrointestinal system ALT: alanine aminotransferase

Patient Characteristic	n	%
Sex		
Male	36	69.2
Female	16	30.8
Age		
Median	60	
Range	43 - 78	
Type of primary cancer		
Colorectal	26	47.3
Hepatocellular	13	23.6
Gallbladder and bile ducts	9	16.4
Pancreatic	2	3.6
Upper GIS	5	9.1
Prior lines of treatment		
0	12	21.8
1	17	30.9
≥2	26	47.3
Liver metastases		
Unilober	18	32.7
Bilober	37	67.3
No of liver metastases measured		
1 lesion	6	10.9
2-4 lesions	14	25.5
≥5 lesions	35	63.6
Target lesions diameters, mm		
Median	59.8	
Range	20 – 140	
Baseline ALT, u/l		
Median	28.4	
Range	8 - 141	

When the patients were selected to receive the treatment, hemogram, liver function tests (ALT (alanine aminotransferase), AST(aspartate aminotransferase), bilirubin, renal function tests (BUN (blood urea nitrogen), creatinine) and bleeding disorder tests were performed. ALT and AST values 5 times higher than normal and bilirubin levels above 2mg/dl were considered to be contraindications for receiving therapy [11,12]. Patients were evaluated for hepatic tumor load and hepatic and visceral vascular mapping by dynamic computed tomography (Aquilion 64, Toshiba). The treatment was administered to patients that had a tumor load 70% below the hepatic volume [11]. Positron emission tomography - computed tomography (PET-CT) (Biograph 16, TrueD, Siemens) imaging in the nuclear medicine department of our hospital and tumor-marker lab tests were performed on all of patients before they received treatment. Patients with appropriate laboratory and tumor load evaluations were directed to the interventional radiology angiography unit (Infinix DFP-8000A,Toshiba) of our hospital.

The interventional part of the treatment was conducted in our angiography unit in two stages. In the first stage, hepatic and mesenteric arterial circulation was evaluated by digital subtraction angiography (DSA).

Primary angiographic evaluation and hepatic arterial system isolation were also performed in the first stage.

The routine angiography protocol for radioembolization therapy and the objectives for each step are as follows:

1 - Abdominal aortography: The anatomy of the abdominal aorta and celiac and superior mesenteric artery arising levels are determined and variations are evaluated.

2 - Superior mesenteric arteriography: The objectives are to visualize the hepatic vascular structures originating from the superior mesenteric artery (SMA) and to evaluate the portal vein.

3 - Celiac arteriography: The hepatic artery is anatomically mapped and any variations are noted. The gastroduodenal artery (GDA), right-left gastric arteries, and accessary branches are evaluated.

4 - Selective right hepatic angiography: Hepatic segments 1,5,6,7 and 8, the middle hepatic artery (segment 4), and the cystic artery are evaluated.

5 – Selective left hepatic angiography: Hepatic segments 2,3 and 4, the right hepatic artery, the falciform artery (if present), the phrenic artery, and accessary gastric arteries are evaluated.

6 - Selective gastroduodenal arteriography: Accessary hepatic arteries that originate from the GDA or parasitic arteries supplying the tumor are evaluated.

The hepatic arterial system (evaluated by DSA) was classified according to the Hiatt classification in our study. The region in the liver that was targeted for treatment was classified and evaluated at the same time. Next, the branches in the vascular plexus nourishing the treatment area of the liver that supply the GDA and other determined extrahepatic structures were embolized (Figure 1). Then, the procedure was terminated after Tc-99m macroaggregated albumin (MAA) was administered through the artery selected for treatment. Later, the patient was evaluated with a gamma camera (Symbia S, Siemens) in the nuclear medicine unit and the hepatopulmonary shunt rate, the previously administered MAA, and extrahepatic escape were evaluated.

Patients with a hepatopulmonary shunt rate below 20% who did not have extrahepatic escape were included in the treatment protocol. The dose of y-90 to be administered was determined according to the hepatic tumor load (calculated in CT), body surface area, and shunt rate after MAA administration.

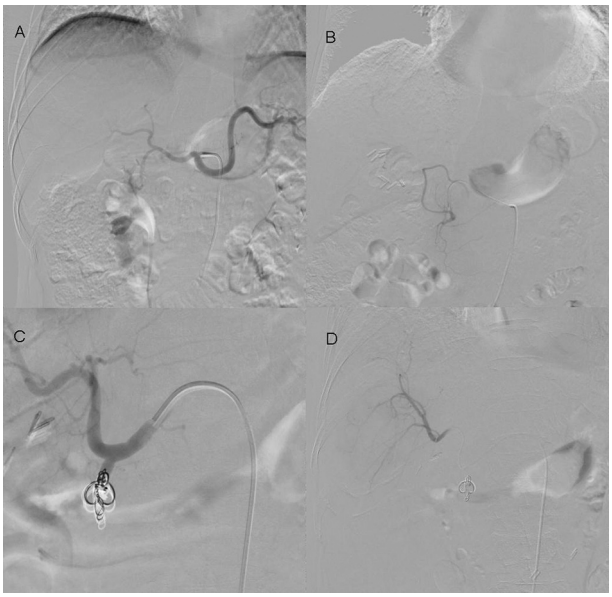

Figure 1. Standard GDA embolization **a.** Selective celiac arteriography, **b.** Selective gastroduodenal arteriography, **c.** Embolized GDA, **d.** Selective right hepatic arteriography after GDA embolization

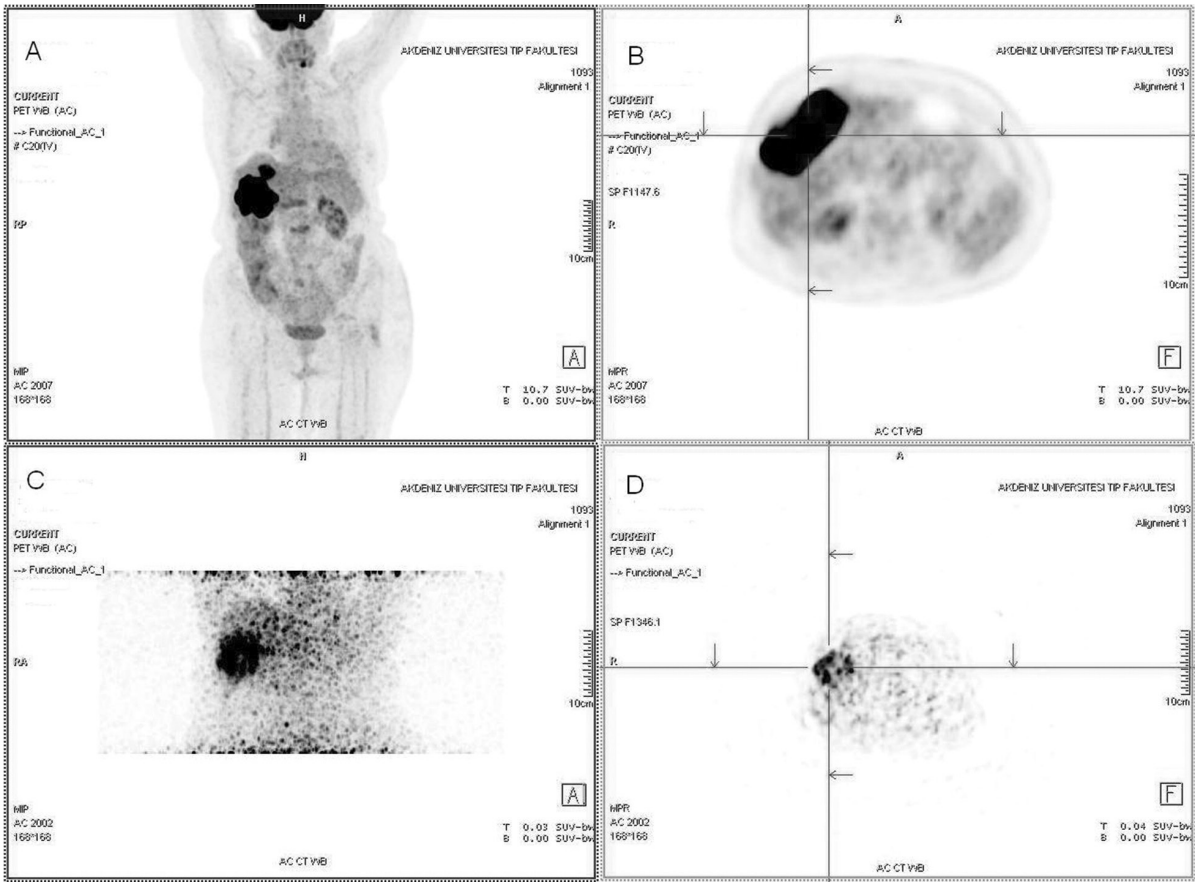

Figure 2. a, b. Coronal (a) and axial (b) 18-FDG PET-CT before the procedure, **c, d.** Coronal (c) and axial (b) Y-90 PET-CT after the procedure

In the second stage, microspheres loaded with y-90 in the calculated dose were administered through selective catheterization in the hepatic artery following the administration of medication for pain control and inflammation. After the procedure, localization of the applied radioactivity was verified with a gamma camera. The patient was observed in the clinic for 24 hours where bleeding was controlled and hepatic and renal functions of the patient were monitored.

After the control PET-CT study, patients were checked weekly for laboratory tests, their general state, any gastrointestinal complications and liver function. Response to treatment was evaluated after 6 weeks by 18-FDG PET-CT and tumor-marker tests (Figure 2).

RESULTS

Fifty five patients were included in the study. Preangiography was performed on all 55 patients and their hepatic arterial anatomy was classified according to the Hiatt classification. Forty-one patients had normal anatomy (type-1), the left hepatic artery originated from the left gastric artery in 3 patients (type 2), and the right hepatic artery branched from the superior mesenteric artery in 11 patients (type 3). The GDA of all of the type 1 and type 2 patients was coil embolized. The GDA was embolized in 5 of the type 3 patients because we planned to treat both lobes of their livers, while we did not embolize the GDA of the remaining 6 patients because treatment was only planned for one lobe. The accessory right gastric artery originating from left hepatic artery in 3 of the type-1 patients was embolized, and the supraduodenal artery branching from the arteria hepatica propria in 2 of the type-1 patients was embolized. Fifty-one extrahepatic branches were embolized in the patient group for arterial isolation (46 GDA, 3 accessory right gastric artery, and 2 supraduodenal artery). One patient was excluded from the study due to the critical narrowing of the celiac artery, and two patients were excluded due to high hepatopulmonary shunt (20% and above) after MAA administration. The remaining 52 patients received the treatment. The arteria hepatica propria in 17 patients, the right hepatic artery in 21 patients, the left hepatic artery in 2 patients, and the right and left hepatic arteries in 12 patients were catheterized separately, and radioembolization therapy was administered by y-90 infusion. The patients were infused with an average of 1.6±0.1 GBq (1.4-1.9) from microspheres loaded with Y-90.

Forty-seven of the patients treated with radioembolization were seen regularly for follow-up and their results were documented. We were unable to follow-up with five of the patients.

The patients were examined for the side-effects of the treatment with a weekly clinical examination and laboratory studies. Fifteen patients (31.9%) had symptoms such as weakness, epigastric pain, vomiting and nausea. A gastric ulcer was discovered in the endoscopy results of 3 patients (6.4%), while the epigastric pain, gastritis, and the symptoms of the other patients regressed.

Tumor response to the treatment was evaluated after 6 weeks by PET-CT and tumor-marker analysis according to Response Evaluation Criteria In Solid Tumors (RECIST).

We found stabile disease (SD) in 5 patients (9.1%), a partial response in 19 patients (34.5%), a complete response in 3 patients (5.5%), and progression development in 20 patients (36.4%). Eight of the patients could not be evaluated (14.5%) (Table 2).

Table 2. Response to treatment according to RECIST

Response		No	%
Valid	CR	3	5.5
	PR	19	34.5
	SD	5	9.1
	PD	20	36.4
Non-evaluable		8	14.5
Total		55	100.0

PD: progressive disease, SD: stabile disease, PR: Partial Response, CR; Complete response

The median hepatic progression free survival was 3.4 months (95% ci:1.4-5.3) and overall survival was calculated to be 11.3 (95% ci:8.7-14.03) months. The median survival time for patients with colorectal cancer and liver metastasis after Y-90 radioembolization was 10.6 months (95% ci: 3.8-17.4). Hepatic progression free survival probability as determined by the Kaplan-Meier method is shown in Figure 3. Overall survival probability as

determined by the Kaplan-Meier method is shown in Figure 4. Hepatic progression-free survival for the colorectal cancer patients was 3.2 months and was 3.6 months for the upper gastrointestinal tract, bile duct, hepatocellular and pancreatic cancer patients. There was no statistically significant difference in progression-free survival between the two groups (p= 0.20).

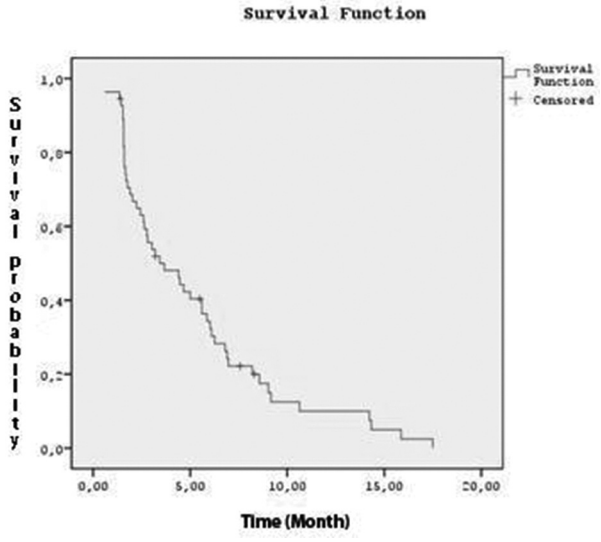

Figure 3. Hepatic progression free survival in 52 patients treated by Y-90 resin microsphere radioembolization. The solid line displays the Kaplan-Meier estimator with marks representing censored events

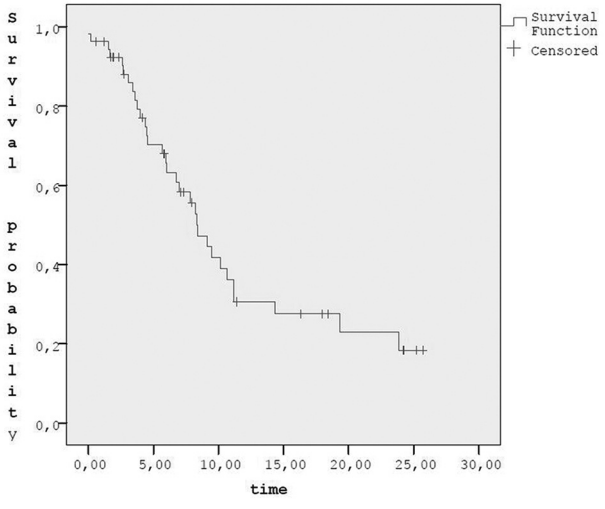

Figure 4. Overall survival in 52 patients treated by Y-90 resin microsphere radioembolization. The solid line displays the Kaplan-Meier estimator with marks representing censored events

DISCUSSION

In most cases, tumors in patients with primary and secondary liver cancer cannot be removed surgically and chemotherapy is often ineffective. Therefore, this patient group suffers a vast amount of pain and deaths each year. Alternative methods of treatment are being studied in order to extend healthy survival in these patients. Alternative choices of treatment include transarterial chemoembolization, regional radiotherapy, RF ablation, and radioembolization.

The effectiveness of Y-90 radioembolization for the treatment of unresectable liver cancer has been emphasized in several studies [13,14,15]. This treatment is clinically well tolerated. In our study, 3 patients (6.4%) developed the major complication of a gastric ulcer. Other general clinical complaints include weakness, epigastric pain, vomiting and nausea. Various experimental clinical studies have been conducted to evaluate the combination of different chemotherapy protocols with Y-90 radioembolization. It has been shown that patients receiving this combination have extended survival rates when compared to patients receiving only chemotherapy or chemotherapy together with biological treatments. Therefore, radioembolization can be accepted as a treatment method used in the first level together with chemotherapy [16,17]. According to a meta-analysis by Vente et al. that covers 19 studies and 792 patients, the response to therapy in salvage treatment (any response involving CR,PR or SD) in combination with 5-fluorouracil/ leucovorin (5-FU/LV) is 79%, in combination with 5-FU/ LV/oxaliplatin or 5-FU/LV/irinotecan is 91%, and is also 91% when used as a first-line therapy [18]. While reported response rates for patients treated only with y-90 radioembolization vary between 44-61% for CR/PR, 34-47% for SD, and 4-22% for PD [19,20,21], the rates were 46.6%, 10.6% and 42.6%, respectively, in our study. The clinical benefit (CR+SD+PR) response rate of Y-90 radioembolization of the patients that we were able to evaluate in our clinic was 57.4%. We believe that the difference between these rates is due to the heterogeneity of the patient groups. The results of this study emphasize that Y-90 resin microsphere radioembolization treatment is effective on lesions in the liver.

In our study, the median survival time for patients with colorectal cancer and liver metastasis after Y-90 radioembolization was 10.6 months and

the toxicities determined were <10%. The overall survival time in our patients was 11.3 months and the requiring hospitalisation toxicity was 6%.

This study emphasizes the effectiveness of Y-90 radioembolization for the treatment of patients with unresectable liver cancer or liver metastases from gastrointestinal system cancers. Radioembolization with Y-90 is a treatment method that should be taken into consideration for appropriate patients with gastrointestinal system cancers.

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