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Is Radioembolization a Safer Treatment than Chemoembolization in Patients with Primary Liver Cancer (HCC)?

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ABSTRACT

OBJECTIVES: The objective of this selective EBM review is to determine whether or not radioembolization is safer treatment comparing to chemoembolization in patients with primary liver cancer (HCC)

STUDY DESIGN: Review of three English language primary randomized controlled studies published between 2014 and 2016.

DATA SOURCES: Three randomized controlled trials (RCT) were found using PubMed and Medline database.

OUTCOMES MEASURED: Eligible patients were randomly selected and divided into two groups: one group received radioembolization with Y-90 (TARE Y-90) while the other group received chemoembolization (TACE). Adverse events after post treatment were recorded and compared between TARE Y-90 and TACE

RESULTS: The study by El Fouly et al. (2014) found that less adverse events occurred in patients receiving TARE Y-90 comparing to patients receiving TACE. The study by Kolligs et al. (2015) found that gastrointestinal (GI) adverse events were more common in TARE Y-90 treatment group than TACE treatment group. Overall, the results from Kolligs et al. study showed no significant difference of adverse events between TARE Y-90 and TACE group. The study by Salem et al. (2016) also found that the frequency of adverse events in both TARE Y-90 and TACE group was similar.

CONCLUSIONS: Results from two randomized controlled trials demonstrate that both TARE Y-90 and TACE could cause similar adverse events in HCC patients. The third randomized controlled trial indicate that TARE Y-90 is superior than TACE regarding safety.

KEYWORDS: Hepatocellular carcinoma, chemoembolization, Y-90 radioembolization

INTRODUCTION

Primary liver cancer is a form of cancer that originates in the cells of the liver. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It accounts for 85% to 90% of all primary liver cases. [1] HCC is considered as the fifth most common cancer with over half a million new cases diagnosed annually worldwide.[8] According to the World Health Organization, HCC is the second leading cause of cancer related mortality in the world.[4] "Most HCC cases (>80%) occur in either sub-Saharan Africa and in Eastern Asia". [2] Over the past two decades, the incidence and prevalence of HCC have significantly increased in the United States. There are approximately 20,000 new cases diagnosed in the United States each year. [6] HCC creates a heavy economic burden on the patients and society. In order to manage the 20,000 new cases, it would roughly cost one billion U.S dollars not including morbidity and mortality cost. [6] In the United States, the incidence of HCC is two times higher in Asians and African Americans compared to Caucasian. [2,8] "During recent years as incidence rate increased the age distribution of HCC patients has shifted toward relatively younger ages, with the greatest proportional increases between ages 45 and 60". [2] HCC is more commonly seen in males than females with a ratio of 2:1 due to the greater risk of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection as well as higher alcohol consumption and tobacco use .[2,8]

The exact causes of HCC are still unknown due to the complexity of the disease. However, there are several risk factors associated with the development of HCC including cirrhosis, HBV infection, HCV infection, alcoholic liver disease, nonalcoholic steatohepatitis (NASH), aflatoxin-contaminated food intake, diabetes, and obesity. [9] Major risk factors of HCC vary based on the region. Worldwide, chronic infection of HBV and HCV are known as the most common risk factors for developing HCC. [8] In the United States, the incidence of HCC caused

by HCV is much higher than HBV. [2] The pathophysiology of developing HCC varies based on the etiology. In chronic infection of HBV or HCV, the viral damage to the hepatocytes causes chronic inflammation, hepatocyte proliferation, fibrosis, cirrhosis, and eventually leads to liver cancer. [9]

During the early stages of HCC, patients may present asymptomatically with no physical signs due to the ability of the liver to regenerate its damaged tissues. Thus, a majority of patients with HCC are diagnosed when the disease has already progressed into advanced stages. "Between 90-95% of HCC patients will present with the triad of right upper quadrant pain, palpable mass, and weight loss". [10] Other common signs and symptoms of HCC include pruritus, fever, early satiety, nausea, and vomiting. Abdominal pain is reported to be one of the most common symptoms of HCC primarily due to the visceral involvement of the abdominal or pelvic region. [10] On the physical exams, patients with an advanced stage of HCC will typically present with palpable liver masses, nodular liver, hepatic bruits, ascites, splenomegaly, jaundice, or peripheral edema.

Several different diagnostic tools can be performed to detect HCC including blood tests, imaging studies, biopsy, and genetic tests. Blood tests are used to assess the liver functions and the serum level of alpha fetoprotein (AFP), a key tumor marker of HCC. The serum marker AFP is highly sensitive, but it has a low specificity. Thus, blood tests should not be used alone as a diagnostic tool for HCC. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, imaging studies should be obtained in conjunction with blood tests. [7] Ultrasound (US) is often the first diagnostic test of choice because it is a low cost, non-invasive test with no radiation exposure to the patients. However, one of the disadvantages of US is that "the reliability is influenced by the expertise of the operator as well as the provision of dedicated

equipment". [9] In addition, sensitivity and specificity of US are limited by the size of the tumors. US is best used to detect 80%-95% of tumors with 3-5 cm in diameter and 60%-80% of tumors <1 cm in diameter. [7,9] Thus, multiple phase computed tomography (CT) or magnetic resonance imaging (MRI) are subsequently performed to further evaluate and confirm the disease. [7]

Treatments of HCC are determined based on multiple factors such as patient performance status, stage of the disease, and liver reserve function. For early stage of HCC, liver transplantation and hepatic resection are the definitive treatments. [7] Ablative techniques such as radiofrequency ablation or cryotherapy are also considered as potential curative treatments of HCC. However, ablative techniques offer best efficacy only when the maximum diameter of the tumors is less than 3 cm. [7] Patients with cirrhosis and advanced stage of HCC are not eligible for liver transplantation, hepatic resection, or ablative techniques due to the high rate of recurrence and the risk of postoperative decompensation. [9] Transarterial radioembolization with Y-90 (TARE Y-90) and transarterial chemoembolization (TACE) are the best therapeutic treatments and also most commonly used in patients, who are unable to receive curative treatments. [1,11] TARE Y-90 and TACE are similar regarding general concepts and techniques. In both treatments, the primary goal is to block the blood supply by direct delivery of embolic agents to the arteries supplying the liver tumors through a catheter. While TACE utilizes a combination of microspheres and chemotherapeutic agents mixed with an oil medium, microspheres loaded with radioactive isotope Yttrium 90 are used as embolic agents to deliver radiation to the tumors in TARE Y-90.

OBJECTIVE

The objective of this systemic review is to determine whether TARE Y-90 is a safer treatment option compared to TACE in patients with primary liver cancer (HCC).

METHODS

The studies used for this review were selected based on the following criteria. The article must be a randomized controlled trial, peer reviewed journal, and published in English after 2008. All three of the articles in this review were selected through a detailed search of articles via the Cochrane, PubMed, and Medline databases. Studies from these selected articles were based on importance of outcomes to the patient (Patient-Oriented Evidence that Matters). The objective of all three articles was to compare the adverse events in post-treatment of TARE Y-90 and TACE. Statistics used in these studies included relative risk reduction (RRR), absolute risk reduction (ARR), number needed to harm (NNH), and p-values. Key words used in searches were "hepatocellular carcinoma", "primary liver cancer", "chemoembolization", "radioembolization", and "adverse events". Table 1 provides demographic information of all articles included.

In all three studies, patients were randomly selected and divided into two groups. One group of patients received TARE Y-90, while the other group of patients received TACE. The TARE Y-90 group was required to undergo a two-step treatment. First, all patients received an injection of Tc-99 macro-aggregated albumin (Tc-99-MAA) into the hepatic artery. Then, a single photon emission computed tomography (SPECT) scan of the whole body was performed to detect any radiation distribution to the lungs and/or other visceral organs. [11] Embolization using coils, detachable balloons, or vascular plugs, was performed to correct any extrahepatic shunting within the abdomen. [1,5,11]Adverse events were recorded and compared between the two groups after treatments. Inclusive criteria included adults with a diagnosis of intermediate stage of HCC and a life expectancy of 3 months or greater, who are not eligible for surgical transplantation, resection or ablative techniques.

Table 1: Demographic & Characteristics of included studies

Study	Type	# of pts	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
El Fouly [1] (2014)	RCT	n = 42 (TACE)	58 ±7	-Age ≥18 years -Life expectancy >3 months -Diagnosis of HCC made by EASL-AASLD criteria -Liver cirrhosis with good liver functions -Good performance status (PST = 0) -Intermediate stage (BCLC-B) -Absence of evidence of vascular invasion or suspected extra-hepatic disease	Patients who were eligible for curative treatment such as resection, transplantation, or local ablation	0	Chemoembolization was performed using 50 mg Adriamycin mixed with lipiodol and followed with gel-foam
		n = 44 (Y90)	66 ±9			0	Radioembolization was performed with injection of Tc-99-MAAand glass-based microspheres.
Kolligs [2] (2015)	RCT	n = 15 (TACE)	67 ±7	-Age ≥18 years -Diagnosed with unresectable HCC confirmed by either histology/cytology or EASL diagnostic criteria -Preserved liver function -ECOG performance of ≤2 -Absence of any form of vascular invasion or extrahepatic spread.	Patients with resectable HCC Patients with significant extrahepatic uptake on ^{99m}Tc-MAA scan or >15% arteriovenous shunting from liver to lungs	0	Chemoembolization was performed using epirubicin 50mg/m^2, lipiodol, and embolic microspheres
		n = 13 (Y90)	66 ±9			0	Radioembolization was performed 0.5-4 GBq ^{90}Y-resin microspheres
Salem [3] (2016)	RCT	n = 21 (TACE)	62 - 70	-Image/biopsy – proven HCC by guidelines - Unablatable/unresectable disease -No vascular invasion Child-Pugh A/B -Bilirubin ≤2.0 m/dl -AST/ALT ≤5x upper limit of normal	Infiltrative/bulk disease (≥70% tumor burden) - ≥50% tumor burden with albumin <3 g/dL -Cardiac comorbidities	0	Chemoembolization was performed with 75 mg/m2 of drug/lipiodol combination and followed with embolic microspheres
		n = 24 (Y90)	58 - 65			0	Radioembolization was performed with 120 Gy dose of glass microspheres.

OUTCOMES MEASURED

The adverse events after the treatment of TARE Y-90 and TACE were the outcome measured in all three studies. Each study compared the frequency of adverse events between patients in TARE Y-90 group and patients in TACE group. Although there were some variations, common adverse events were measured in all three studies including fatigue, abdominal pain, ascites, peptic ulcers, nausea, vomiting, fever, infection, constipation, and diarrhea. These adverse events were recorded using different methods in all of the studies. Both El Fouly et al. study and Kolligs et al. study used the National Cancer Institute (NCI) common toxicity criteria version 3 (CTCv3) to record and code adverse events during the active treatment and within 2 months of any treatment procedure. In addition, 45-item self-report Functional Assessment of Cancer Therapy (FACT) Hepatobiliary (FACT-Hep) questionnaire was also utilized to assess the adverse events at the baseline and at 6-weekly follow-ups in El Fouly et al. study. In the Salem et al. study, Common Terminology Criteria for Adverse Events (CTCAE) version 4 was used to record the adverse events.

RESULTS

In the El Fouly et al. study, a total of 116 patients were randomly divided into two groups: one group was treated using TARE Y-90 while the other group was treated using TACE. After the screening, 9 (8%) patients in the TARE Y-90 and 21 (19%) patients in the TACE group were excluded from the trial. The remaining 86 patients with intermediate stage HCC met the inclusion criteria and were treated prospectively in a non-randomized controlled study. In TARE Y-90, 44 patients received a two-step treatment, which included a screening test detecting radiation distribution to extrahepatic organs and embolization with angiography. Arterial embolization was performed using TheraSphere, a type of glass-based microsphere composing of

20-30 μm large B-emitting particles. In TACE, 42 patients received a conventional technique using 500-700 μm chemo-particles, gel foam, and a combination of 50 mg Adriamycin mixed with lipiodol. In both groups, any adverse events within 30 days following any treatments were evaluated and recorded. Based on the data in table 2, the number of patients with abdominal pain after TACE was much higher compared to the number of patients after TARE Y-90 (85% in TACE vs. 5% in TARE Y-90; P <0.001). The most common adverse events (40%) after TARE Y-90 treatment was fatigue syndrome. However, it was still significantly less than TACE group with 73% patients experiencing fatigue syndrome (P <0.01). While nausea and vomiting was reported in 38% of patients after TACE, there was no patients in TARE Y-90 group with the same adverse event (P <0.001)

Table 2: Post-therapy adverse events by El Fouly et al. [1]

Adverse Events	**TACE, n (%)**	**TARE Y-90, n (%)**	**P-value**
Abdominal pain	35 (83)	2 (5)	<0.01
Fatigue syndrome	30 (73)	18 (40)	<0.001
Nausea/vomiting	16 (38)	0 (0)	<0.001

In the study by Kolligs et al., 13 patients were randomly selected to receive TACE Y-90 treatment, and 15 patients were randomly selected to receive TACE treatment. Similar to El Fouly et al. study, patients in TACE Y-90 group were required to go through a two-step treatment to minimize visceral shunt. After 14 days of the initial step, all TACE Y-90 patients received a single session of arterial embolization using 0.5-5 GBq SIR-Spheres, a commercial Y-90 microspheres from Sirtex Medical in Sydney, Australia. In TACE group, 15 patients received a combination of 50 mg/ m2 epirubicin and lipiodol in conjunction with 150-300 μm or 300-500

μm Embosphere, chemo-particles from Merit Medical. In both groups, adverse events within 2 months following any treatments were evaluated and recorded. Gastrointestinal (GI) events were statistically difference between two groups. As illustrated in table 3, the number of patients experiencing GI events after TARE Y-90 was more frequent comparing TACE ((40% in TARE Y-90 vs. 8% in TACE; P <0.029). Out of 6 patients with GI adverse events in TARE Y-90 group, 2 patients were reported with abdominal pain.

Table 3: Post-therapy adverse events Kolligs et al. [5]

Adverse Events	**TACE, n (%)**	**TARE Y-90, n (%)**	**P-value**
Gastrointestinal events	1 (8)	6 (40)	0.029

In Salem et al. study, a total of 179 patients with intermediate stage (BCLC A or B) HCC were eligible for either TARE Y-90 or TACE. However, only 45 patients met the inclusion criteria after screening. Twenty-four patients were randomly selected to receive TARE Y-90, and 21 patients were randomly selected to receive TACE. Before transarterial embolization, patients in TARE Y-90 group underwent angiography and technetium-99m scintigraphy to identify extrahepatic perfusion of radiation. Coil embolization was performed if any shunting was detected. A median dose of 126 Gy TheraSphere was administered to TARE Y-90 patients during the last step of the treatment. In TACE group, 42 patients were treated using a drug/lipiodol combination at a maximum dose of 150 mg and followed by transarterial embolization using Embospheres. The results from table 4 demonstrated a higher number of patients experiencing abdominal pain after TACE than TARE Y-90 (53% in TACE vs. 25% in TARE Y-90; P <0.11). However, more patients (88%) in TARE Y-90 were reported with fatigue

syndrome than in TACE (63%). Nausea and vomiting occurred in both TACE and TARE Y-90 groups, but there was no significant difference between two groups.

Table 4: Post-therapy adverse events by Salem et al. [11]

Adverse Events	**TACE, n (%)**	**TARE Y-90, n (%)**	**P-value**
Abdominal pain	10 (53)	6 (25)	0.11
Fatigue syndrome	12 (63)	21 (88)	0.08
Nausea	8 (42)	7 (29)	0.52
Vomiting	3 (16)	1 (4)	0.31

Abdominal pain was used to compare the relative risk increase (RRI), absolute risk increase (ARI), and number needed to harm (NNH) between the three studies. In order to obtain these results, it was essential to find the Experimental Event Rate (EER) and Control Event Rate (CER). EER was calculated by using the number of people who was treated with TARE Y-90 and developed abdominal pain (a) dividing by the sum of (a) and the number of people who were treated with TARE Y-90 but did not develop abdominal pain (c), CER was calculated by using the number of people who were treated with TACE and developed abdominal pain (b) dividing by the sum of (b) and the number of people who were treated with TACE and did not develop abdominal pain. As illustrated in table 5, the results of Salem et al. showed NNH was 3.62, which indicated that for every 4 patient treated, 1 more patient would experience abdominal pain. The results of Kolligs et al. study showed NNH was 3.086, which indicated that for every 3 patients treated, 1 more patient would experience abdominal pain. The results of El Fouly et al. showed NNH was 1.269, which indicated that for every 1 patient treated, 1 more patient would experience abdominal pain.

Table 5: Results of adverse events - Abdominal pain

Study	RRI (%)	ARI (%)	NNH
Salem et al	47.5	27.6	3.62
Kolligs et al	526.3	32.4	3.086
El Fouly et al	5.4	78.8	1.269

DISCUSSION

This systemic review of three randomized controlled trials evaluated and compared the adverse events in patients with HCC after TACE or TARE Y-90. In the United States, embolization using chemo particles is the treatment of choice for patients with intermediate HCC, those who are not eligible for liver transplantation, hepatic resection, or ablative techniques. In early 2000, a new technique using microspheres with high doses of radiation was introduced as a possible therapeutic treatment option for intermediate HCC. Since then, it has become one of the most common HCC treatment in both teaching and community hospitals. Currently, TheraSphere and SIR-Spheres are the two commercial Y-90 microsphere products available on the market. Both TheraSphere and SIR-Spheres are approved by The Food and Drug Administration (FDA) for the use in the treatment of unresectable intermediate stage HCC. TheraSphere is eligible for reimbursement by Medicare, Medicaid, and majority of commercial health insurance plans.

There were noteworthy limitations within all three randomized controlled trial studies. The first limitation was the lack of consistency in adverse events measuring methods between the three trials. While both Koligs et al. and El Fouly et al. studies used the NCI common toxicity criteria version 3 (CTCv3), the adverse events in the study by Salem et al. was recorded by CTCAEv4.0. Second limitation involved the variability in dosages, types of chemotherapy

agents as well as the sizes of chemo particles used in TACE. Although lipiodol was used as a radiopaque contrast agent in all three studies, there was a discrepancy between these studies. In El Fouly et al. study, patients in TACE group received a combination of 50 mg Adriamycin mixed with lipiodol, gel foam, and 500-700 μm chemo embolizing particles. On the other hand, TACE patients in the study by Kolligs et al. received a combination of 50 mg/ m2 epirubicin mixed with lipiodol, and 150-300 μm or 300-500 μm chemo embolizing particles. Even though both Epirubicin and Adriamycin are members of the same chemotherapy class called anthracyclines, they have different chemical structures, and thus they yield distinctive side effects [3]. In Salem et al study, the name of chemotherapy agent was not mentioned.

CONCLUSION

Based on this systemic review, it is difficult to conclude whether radioembolization is a safer treatment than chemoembolization in patients with HCC due to the highly complex nature of the disease. Symptoms such as fatigue, abdominal pain, nausea, and vomiting are commonly presented in HCC patients at the time of diagnoses. It is not possible to identify whether these symptoms adverse events of the treatments or symptoms of HCC.

All three randomized controlled studies indicate that both TARE Y-90 and TACE could cause adverse events in HCC patients. Two out of three randomized controlled studies suggest that the frequency of adverse events between TARE Y-90 and TACE are not significantly different. The results of the third study demonstrate that TARE-90 is more superior than TACE regarding safety. Overall, both TARE Y-90 and TACE are good treatment of choice for patients with unresectable HCC. It is important to focus on the patient profile when selecting an appropriate treatment. Future studies are warranted to larger studies and establish a standard method to measure adverse events in post treatment.

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