Safety of Transarterial ^{Y90} Radioembolization in Management for Unresectable-Intermediate and Locally Advanced-HCC

MOHAMED M. HAMED, M.D.*; ABDELHAY A. ABDELHAY, M.D.*;
MOHAMED H. ABD ALFATTAH, M.D.** and GAMAL AL-DEIN E. GAMEEL, M.D.**

The Departments of Radiology* and Tropical Medicine**, Faculty of Medicine, Cairo University, Egypt

Abstract

Background: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide. However, most patients present with either unresectable (intermediate or advanced) tumors, cirrhosis, or both, eliminating these surgical treatment choices. Many institutions have adopted the Barcelona Clinic Liver Cancer (BCLC) staging classification, which links the stage of the disease to a specific treatment strategy. Current guidelines recommend transarterial chemoembolization (TACE) as the standard treatment of Barcelona-Clinic Liver Cancer (BCLC)-B patients, however, the long-term survival outcomes of patients managed with this technique do not appear fully satisfactory. In addition, HCC has traditionally been regarded as a radioresistant tumor due to the limited ability to deliver lethal doses using external beam techniques. Radioembolization with yttrium-90 (Y^{90}) is a recently introduced liver-directed therapy. It is brachy therapy by arterially injected Y^{90} microspheres for the treatment of malignancies. Growing data suggest that Y^{90} radioembolization has a potent anticancer effect with negligible adverse events.

Aim of Study: This study aims to present and discuss the safety and adverse effects of Y^{90} radioembolization for management of patients with intermediate and locally advanced (BCLC-B and BCLC-C1) Hepato-Cellular Carcinoma (HCC).

Patients and Methods: This is a prospective study carried out between June 2014 and May 2016 for patients with hepatocellular carcinoma and liver restricted disease. All patients underwent treatment by Y^{90} microsphere radioembolization (SIR-Tex).

A total number of 20 patients with intermediate and locally hepatocellular carcinoma and liver restricted disease, not eligible for curative treatment.

Results: Follow-up was done using laboratory tests and clinical assessment. We found accepted toxicity profile in patients treated with Y^{90} radioembolization. The most frequent symptoms we encountered were the transient fatigue, abdominal pain and post embolization syndrome. The sever adverse effects (pneumonitis and GI ulceration) were not encountered in our study due to careful selection and pretreatment diagnostic preparation angiograph.

Conclusion: Y^{90} microspheres radioembolization is safe therapeutic option for patients with intermediate and advanced HCC which can be utilized even in patients with compromised liver function.

Key Words: *Hepatocellular carcinoma (HCC) – Transcatheter arterial chemoembolization (TACE) – Barcelona Clinic Liver Cancer (BCLC) – Y^{90} Radioembolization.*

Introduction

HEPATOCELLULAR carcinoma is the most frequent primary tumor of the liver, the incidence of which is increasing worldwide [1]. To best assess the prognosis of hepatocellular carcinoma patients, it is recommended that the staging system takes into account tumor stage, liver function and physical status. Many institutions have considered the Barcelona Clinic Liver Cancer (BCLC) staging system as the most accepted one for HCC as it accomplishes this aim. Therapy of HCC follows defined treatment algorithms been proposed by the Barcelona Clinic Liver Cancer (BCLC) [2].

BCLC takes into account the number, size and extent of the tumor, liver functions and incorporates the Okuda stage and Child-Pugh score. There is a corresponding treatment schedule for each stage of the disease. According to the BCLC staging system, image-guided tumor ablation is recommended in patients with early stage HCC [3]. Patients who have intermediate-stage hepatocellular carcinoma according to the BCLC staging system are the optimal candidates for transcatheter arterial chemoembolization (TACE) as a palliative treatment. Palliative options should aim to improve survival without greatly impairing the quality of life [3].

Correspondence to: Dr. Abdelhay A. Abdelhay,
E-Mail: Abdelhayalsayed@hotmail.com.

Recently, Y^{90} radioembolization has been as a treatment option for interventional management of locally advanced HCC, s(BCLC-B and BCLC-C), primary and secondary liver tumors [4]. It is a liver-directed therapy using a catheter-based approach, Y^{90} Radioembolization is an internal brachytherapy by arterially injected yttrium-90 (Y^{90}) microspheres for the treatment of malignancies [5].

This modality involves the arterial infusion of glass or resin microspheres labeled with a radio-therapeutic agent Yttrium-90 (Y^{90}) which are similarly administered via percutaneously placed catheters positioned in the hepatic arterial system. Radioembolization is a form of brachytherapy that allows for concentrated beta-radiation administration to tumor tissue while minimizing damage to surrounding liver parenchyma [6].

Moreover, in a randomized controlled trial done by LoCM et al., [7] they concluded that in cases where there is an invasion of the portal vein, embolic forms of liver-directed therapy for HCC such as TAE or TACE are relatively contraindicated. This relative contraindication is attributable to the embolic effect of TAE/TACE on the hepatic artery, leaving the portal vein as the sole source of blood supply to the liver. If this supply is compromised, such as in the presence of PVT (malignant or bland) ischemic necrosis becomes a possibility [8]. So, despite the fact that this therapy Y^{90} Radioembolization-is an embolization procedure, the small sizes of the Y^{90} particles causes an embolization at a microvascular level for permanent vascular blockade.

Growing data suggest that Y^{90} radioembolization has a potent anticancer effect with negligible adverse events if appropriate pretreatment evaluations including dosimetry, calculation of lung shunt fraction and assessment of vascular anatomy are performed. Retrospective and small prospective studies have shown response rates and survival after (90) Y therapy which are comparable to TACE and sorafenib in the intermediate and advanced stages, respectively [4].

Patients and Methods

Patients:

This is a prospective study carried out in private hospitals between June 2014 and May 2016 for patients with hepatocellular carcinoma and liver restricted disease. All patients underwent treatment by Y^{90} microsphere radioembolization (SIR-Tex).

A total number of 20 patients (18 males and 2 females), with intermediate (BCLC class B) and locally advanced (BCLC class C-1) hepatocellular carcinoma and liver restricted disease, not eligible for curative treatment with Eastern Cooperative Oncology Group (ECOG) performance status 0,1 or 2 and Child-Pugh A to B.

Inclusion criteria:

• Patients with HCC, by typical appearance on imaging and/or cytohistological evaluation (liver biopsy).

• Accurate staging: CT and/or MRI of the liver, CT-scan of the abdomen and thorax.

• Cooperative Oncology Group (ECOG) performance status 0,1 or 2.

• Child-Pugh A to B.

• BCLC class B to C-1.

• Bilirubin level < 2.

• Liver restricted disease.

Exclusion criteria:

• Unmanageable intolerance to the contrast medium.

• Pregnancy or breast feeding.

• Child-Pugh score >B.

• Bilirubin >2mg/dl.

• Other contraindications to hepatic embolization procedures (e.g coagulopathy).

Intervention:

The procedure was carried out over two separate sessions; a work-up session and a treatment session.

A- *Preparation Angiogram:* Once a patient has been selected as a candidate for Y^{90} radioembolization, an initial angiographic evaluation is performed. This is done primarily to document the visceral anatomy, identify anatomic variants, and isolate the hepatic circulation by occluding extra-hepatic vessels. This is very important; because it determines the overall safety of the treatment.

The technique includes standard visceral angiography using a hooked catheter such as a Cobra-2 or a Simmons 1 or 2. First, an aortic angiogram is performed, seconed step is the superior mesenteric arteriogram, to assess for the presence of accessory or replaced hepatic arteries arising from the superior mesenteric artery (SMA). Next, the celiac trunk is selectively catheterized to evaluate the hepatic arterial supply. Subsequent to celiac injec-

tion, it is imperative that selective right and left hepatic angiography with power injection angiography be performed.

Other arteries should be catheterized include, Proper hepatic angiogram, right hepatic angiogram, left hepatic angiogram, gastroduodenal artery and phrenic arteries. This detailed visceral angiogram allows for the identification of variant mesenteric anatomy, and the extrahepatic vessels, as the radio-active microspheres, administered into the hepatic artery, should be prevented from ending up in extrahepatic organs. Accordingly, prophylactic embolization (using coils) of extrahepatic vessels such as the gastroduodenal, right gastric, or falciform artery maybe performed. Once the anatomy has been established, selective arteriography is performed in the expected location of the Y^{90} radioembolization treatment. Microcatheters should be used (Renegade Hi-flow [Boston Scientific, Natick, MA], Progreat [Terumo, Somerset, NJ], or 2.3-French Prowler Plus [Cordis, Miami, FL]).

B- Injection of (^{99m}Tc-MAA): Once a catheter has been placed into the appropriate location, 150 MBq Technetium-99 labeled macro aggregated albumin (^{99m}Tc-MAA) was injected. It is recommended that ^{99m}Tc-MAA injection be performed once all vessels of concern have been embolized. ^{99m}Tc-MAA is used as a surrogate in order to predict the distribution pattern of Y^{90}-microspheres. The distribution of ^{99m}Tc-MAA will be visualized by whole body planar imaging. Accordingly, lung shunt fraction can be calculated and deposition of ^{99m}Tc-MAA in the abdominal organs, such as the stomach, duodenum and pancreas, can indicate patent extrahepatic vessels distal to the injection site. In case a lung dose exceeding 30Gy (610 MBq) is predicted, an activity reduction was prescribed.

The ^{99m}Tc-MAA scan can also demonstrate the presence of any GI flow. The shunting evaluation allows the physician to plan for radioembolization therapy and minimize any uncertainty in microspheres distribution at the time of treatment.

C- Y^{90} microsphere injection: Finally, the last step of Y^{90} microspheres injection should take place within two weeks of the 1st seesion. The hepatic artery will be catheterized and the Y^{90} microspheres will be administered from the exact same microcatheter position as where the ^{99m}Tc-MAA was administered.

Post-procedure care All patients underwent Y^{90} radioembolization were hospitalized overnight for observation and administration of medications as needed. All patients were monitored for mild side effects and symptoms including pain requiring oral analgesics, fever, vomiting or nausea and for severe symptoms including pain requiring parenteral analgesics or hemorrhage.

Imaging analysis: Quantifying size reduction and necrosis.

Tumor response by cross-sectional imaging either by CT and/or MRI was evaluated on all surviving patients 1 and 3 months after treatment and approximately every 3 months thereafter, and was categorized according to Response Evaluation Criteria in Solid Tumors (RECIST) and the modified RECIST criteria. Responding disease are seen in patient had complete response (CR) or partial response (PR) while patients had either stable disease (SD) or progressive disease (PD) considered non responding disease.

Results

Twenty patients with Hepato-Cellular Carcinoma underwent Y90 radioembolization were included in this study and were retrospectively evaluated.

Clinical adverse effects:

The most commonly reported adverse effects (AE) was a transient fatigue syndrome, starting the next day after the procedure, with a maximum between 3 days and 7 days post therapy, representing general complications.

These mild adverse effects were well tolerated by most of the patients, requiring only bed rest and symptomatic treatment.

In one case, these symptoms were severe, requiring hospitalization 2 days after therapy, and was managed conservatively.

No patient experienced treatment-induced ulcerations in stomach or duodenum. In addition, we detected no patients with radiation-induced pneumonitis. (No complications related to non target radiation).

A mild worsening of ascites from baseline was seen in one patient with main PVT.

There were two cases who developed pleural effusions.

There were no significant complications or mortalities secondary to the technical aspects of radioembolization.

However, there was 1 death in the short follow-up period (3 month) that was possibly attributed to treatment. In this patient, the immediate post procedure and the during the 1 st month of post treatment passed eventless, with partial-yet mini-mal-recanalization of the PV was noted.

After 8 weeks, acute elevation of bilirubin level, liver enzymes and kidney functions was noted, with rapid deterioration of the conscious level and death.

Laboratory toxicities (Impact on Liver Functions):

Compared with baseline laboratory parameters for patient underwent adequate follow-up at, 3 and 6 months, there was a slight increase in the bilirubin levels at month follow-up with mean about 0.5mg/dl.

It has to be noted that, these elevated bilirubin levels returned to normal within 6 to 8 weeks post treatment.

Although the highest incidence of bilirubin elevation occurred in the main PVT group, this was not statistically different from the no-PVT or lobar PVT groups (p=0.2 10).

ECOG Performance status:

According to performance status (ECOG criteria), 6 patients were graded as grade 0 (30%), 11 patients were grade 1 (55%) and only 3 patients were grade 2 (15%).

Statistical analysis:

• Results were expressed as mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate or number (%).

• Comparison between categorical data was performed using Chi square test. Statistical analysis was performed with the aid of the SPSS computer program (version 19 windows).

• The data were considered significant if p-value was ≤0.05 and highly significant if p-value was <0.01.
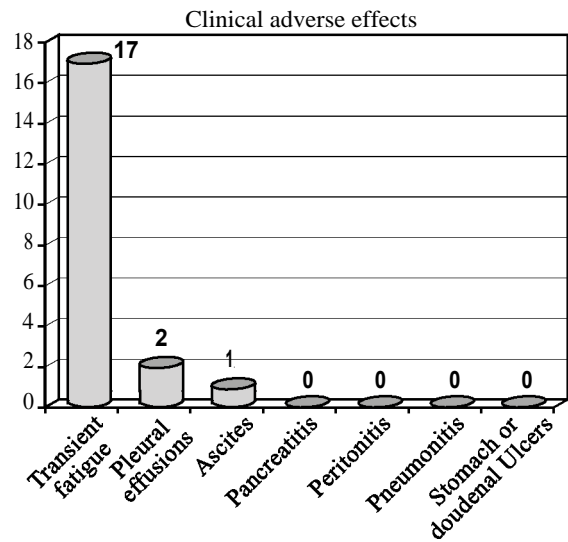

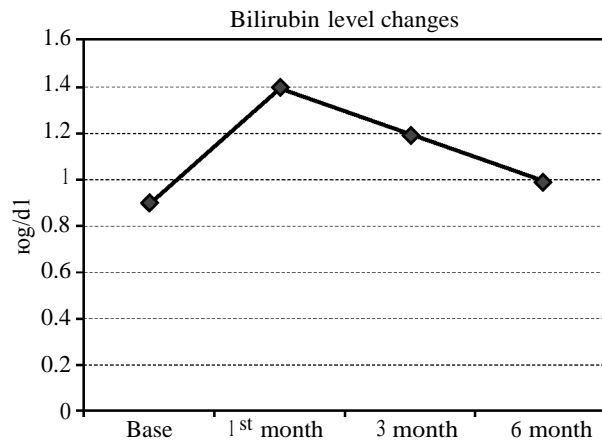Fig. (1): Clinical adverse effects post Y^{90} radioembolization.

Fig. (2): Changes in bilirubin levels post radioembolization.
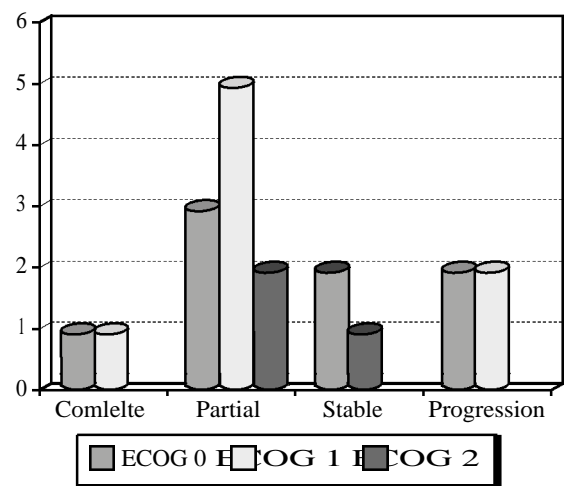

Fig. (3): 6 month response in relation to ECOG performance status of the patients.
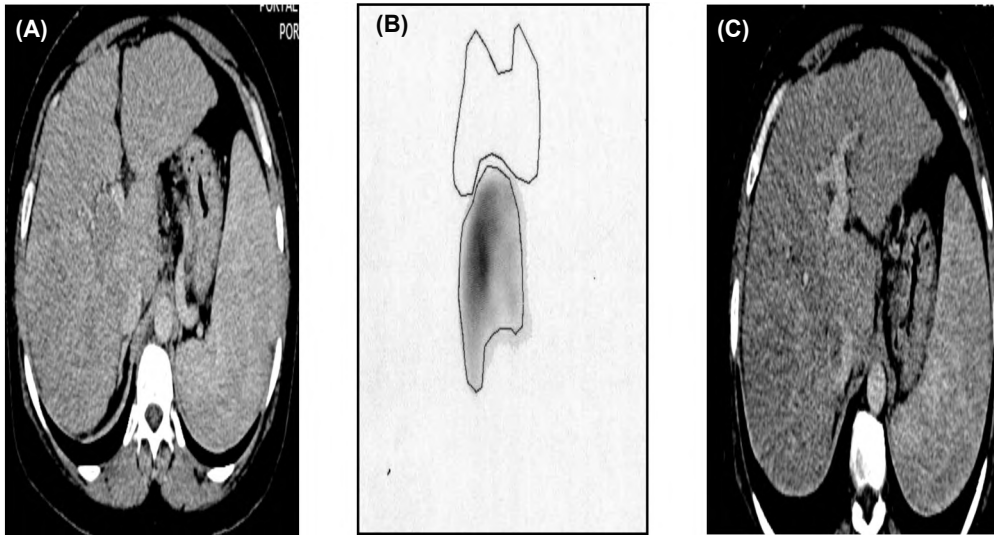
Illustrative
Cases:

Fig. (4): (A): CT scan showing infiltrative right lobe lesion with portal vein thrombosis. (B): Liver/lung shunt (anterior-posterior). (C): CT scan 6 months post Y^{90} radioemolization with still seen unchanged portal vein thrombus and IVC thrombus.
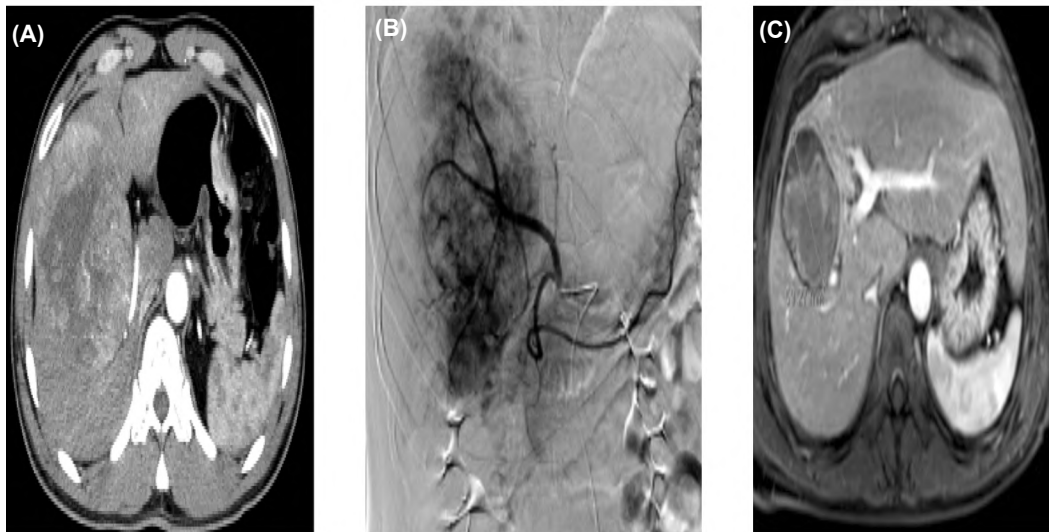

Fig. (5): (A): Multicentric right lobar HCC, the largest exceeded 10cm and there were multiple atellite nodules at segments 6 and 8 in liver dynamic CT scan. (B): Hepatic angiography showing the hypervascular tumoral blush. (C): At 6 months post-radioembolization, liver dynamic MRI showed significantly decreased main tumor, atrophy of right lobe and hypertrophy of left lobe.
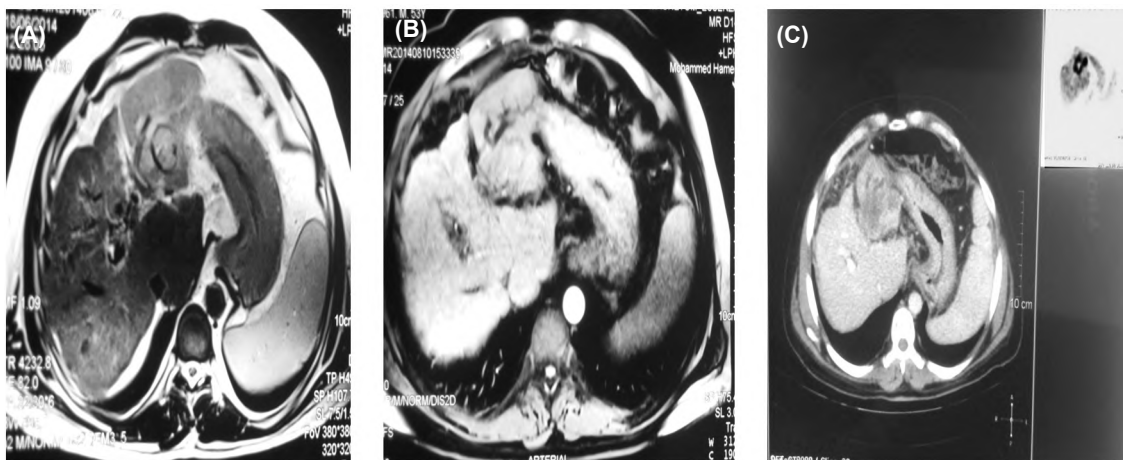

Fig. (6): (A): MRI scan showing left lobe lesion with segmental left portal vein thrombosis and cholestasis. (B): MRI scan 3 months post Y^{90} radioemboliztion showing stable lesion size yet with differential tumoral enhancement. (C): PET/CT scan 6 month post radioemboliztion showing partial response, with tumor size reduction and residual peripheral activity.

Discussion

Hepatocellular carcinoma is the most frequent primary tumor of the liver, the incidence of which is increasing worldwide [1].

Patients who have intermediate-stage hepatocellular carcinoma according to the BCLC staging system are the optimal candidates for transcatheter arterial chemoembolization (TACE) as a palliative treatment. Palliative options should aim to improve survival without greatly impairing the quality of life [4].

Over the last decade, radioembolization has emerged as a treatment option for the locoregional management of locally advanced HCC, stage B-Multinodular- and stage C-portal invasion- primary and secondary liver tumors [2]. One advantage of this treatment option in treatment of cases of multicentric HCC is that Y 90 radioembolization can be performed in an unselective fashion [9].

Kooby et al., [5], stated that; in contrast to conventional trans-catheter arterial hepatic chemoembolization, AEs after such "unselective" injection pattern, as performed as a lobar pattern of the hepatic artery, is not significantly increased as compared to segmental or even subsegmental microsphere application, although the tumor response rate may vary. Moreover, in a randomized controlled trial done in 2002 [8], they concluded that in cases where there is an invasion of the portal vein, embolic forms of liver-directed therapy for HCC such as TAE or TACE are relatively contraindicated. This relative contraindication is attributable to the embolic effect of TAE/TACE on the hepatic artery, leaving the portal vein as the sole source of blood supply to the liver. If this supply is compromised, such as in the presence of PVT (malignant or bland) ischemic necrosis becomes a possibility.

However, clinical experience has shown that intraarterial hepatic regional therapies can be performed in the presence of PVT. Investigators have demonstrated that TACE can be performed safely in patients with PVT and cavernous transformation or patients with partial portal vein occlusion and hepatopedal flow providing modified techniques are used such as (A): Low-dose, segmental; or (B): Use of partial arterial occlusion as the endpoint [8].

So, despite the fact that this therapy-Y ^{90} Radioembolization-is an embolization procedure, the small sizes of the Y 90 particles causes an embolization at a microvascular level for permanent vascular blockade.

The most frequent symptom we encountered was the transient fatigue and abdominal pain, which has been reported by other investigator [4,9,10], to be the most common adverse reaction following Y 90 radioembolization.

Super selective radioembolztion led to minimization of the adverse effects of Y 90 radioembolization, a conclusion by chow et al., [11], with the most common clinical toxicities were fatigue (30%), abdominal pain (10%), and post embolization syndrome (10%).

Severe AEs that may be associated with Y 90 radioembolization are radiation pneumonitis and gastrointestinal ulcerations. They are caused by the unintentional deposition of microspheres either through tumor-associated arteriovenous shunting into the lungs, or by way of collateral vessels to the intestine originating in the hepatic arterial system.

Pneumonitis is now generally considered a rare event in Y^{90} radioembolization, as the introduction of the pretreatment ^{99m}Tc-MAA scan allows pretreatment estimation of the lung shunt, definition of maximal lung doses and dose reduction if needed [8].

In the case of significant hepatopulmonary shunting, the prescribed activity should be reduced according to recommendations on the package insert (shunt10%-15%, 20% reduction; shunt 15%-20%, 40% reduction;shunt >20%, no treatment) [12].

Kim et al., [13] stated that about 50% of aborted Y90 radioembolization after the mapping angiography and ^{99m}Tc-MAA injection was attributed to high lung shunt.

In contrast, gastrointestinal ulcerations are occasionally reported, as when injecting the Y 90 microspheres, stasis within the artery supplying the tumor occurs, this increases the probability of a backflow of spheres into small collateral arteries to the stomach, the duodenum, or the pancreas [14].

This risk is probably lower than 5% when a very active search for collateral vessels connecting the hepatic arteries to the GI area is performed. But abdominal pain persisting or developing 1-2 months after Y^{90} radioembolization should prompt the performance of an upper endoscopy that may rule out gastric lesions.

Philip et al., [10], suggested that this phenomenon may be avoided by introducing SPECT-CT after application of ^{99m}Tc-MAA, as this cross-

sectional imaging of the ^{99m}Tc-MAA significantly enhanced the detection of accidental non intentional deposition of microspheres in the gastrointestinal tract.

Both of these AEs (pneumonitis and GI ulceration) were not observed in our study due to careful selection and pretreatment diagnostic preparation Angiography.

The detailed visceral angiogram allowed for the identification of variant mesenteric anatomy, and the extrahepatic vessels, accordingly, prophylactic embolization (using coils) of extrahepatic vessels such as the gastroduodenal, right gastric, or falciform artery were performed.

In our study, we aborted a case due to unintended peritoneal radiation activity detected after ^{99m}Tc-MAA injection. A finding that was confirmed by doing SPECT. Active search for the vascular supply was conducted and collaterals with small falcifine artery found as well as small vessels from gastro-hepatic trunk (which is an anatomical variant encountered in this case), it was difficult to catheterize and embolize.

The third and probably most important safety issue was hepatotoxicity by non-target irradiation of liver tissue. The significance of hepatotoxicity is emphasized by the fact that most HCC in Egypt is present in patients with liver cirrhosis.

In our cohort, more than half of the patients showed a transient bilirubin elevation, corresponding to other reports of patients treated with Y^{90} radioembolization [15].

However, elevation of bilirubin, as a surrogate marker for hepatotoxicity, was only mild and not related to clinically relevant symptoms, requiring no hospitalization.

It worth mentioning that in the current study, there was a case that had a clinical picture suggestive of fulminant hepatitis during the short term follow up. This was possibly attributed to treatment (radiation induced liver disease (RILD).

RILD is often what is called "radiation hepatitis" and classically was described as occurring within 3 months of initiation of radiation, with increase in abdominal girth, liver enlargement, and occasionally ascites or jaundice, with elevation in serum alkaline phosphatase. The clinical picture resembles Budd-Chiari syndrome, but most patients survive, although some die of this condition without proven tumor progression [16].

In our patient, the immediate post procedure and the 1st month of post treatment passed eventless, with partial recanalization of the PV proven by Doppler (partial response according to both RECIST and mRECIST criteria). After 8 weeks, the patient experienced acute elevation of bilirubin level, liver enzymes and kidney functions, jaundice and ascites, with rapid deterioration of the conscious level and death. This is not typically the clinical scenario of RILD, yet it still a possibility.

Sangro et al., [17], studied liver disease induced by Y^{90} radioembolization of liver tumors in 45 patients who underwent the treatment for primary or secondary liver tumors. Three patients (6.7%) developed findings consistent with RILD. All 3 of these patients had received prior chemotherapy while none of the patients who had not been given chemotherapy prior to Y^{90} radioembolization developed RILD.

Also, Meyer et al., [18] had a five patient analysis on the use of degradable starch microspheres as an embolizate to normal hepatic parenchyma during Y^{90} radioembolization. Post treatment SPECT/CT demonstrated sparing of normal parenchyma. This is an interesting concept, which needs validation.

Limitations:

The findings from this study are encouraging but must be considered in the context of its limitations.

The small study sample was due to tight selection criteria, which were deemed necessary to create a homogeneous cohort.

The lack of control group-especially in cases with PVTT and financial constrictions remain as challenges.

Follow-up for this report was limited to 6 months with only two time points for objective response assessment. Later response and maximal response were not analyzed because of high variability in chronology and availability of follow-up.

Conclusion

Radioembolization with Y^{90} microspheres for advanced HCC is a safe treatment option which can be utilized even in patients with compromised liver function. We demonstrate a good toxicity profile and our data further underline the role of Y^{90} radioembolization as a locoregional therapy in patients with locally advanced tumor stages with or without PVT. Moreover, our data highlight the necessity for randomized controlled trials compar-

ing and/or combining Y^{90} radioembolization with TACE in BCLC B patients and with systemic therapy in BCLC C patients.

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تقييم أمان علاج المراحل المتوسطة والمتقدمة ـ غير القابلة للإستئصال ـ من الأورام الكبدية الأولية بالحقن بالحبيبات المشعة عن طريق الشريان الكبدى

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إن الحقن الكيميائى عن طريق القسطرة من خلال الشريان الكبدى هو العلاج المتاح الآن للمراحل المتوسطة من الأورام الأولية الكبدية، ولكن النتائج على المدى الطويل غير مرضية، كما أن الحقن الكيميائى يعتبر من الممنوعات الجزئية فى المراحل المتقدمة موضعياً.

وفى العقد الأخير، ظهر حقن الحبيبات المشعة عن طريق الشريان الكبدى- وهو يعتبر نوعاً من العلاج الأشعاعى الداخلى- كعلاج جديد لمثل هذه الحالات، حيث أوردت الكثير من التقارير والأبحاث تأثيره القوى على الأورام وإمكانية إستخدامه فى علاج هذه الحالات، حتى فى المرضى الذين يعانون من تدهور جزئى فى وظائف الكبد، إذا تم عمل التقييم المبدئى قبل العلاج بطريقة ملائمة.

وقد تطرق هذا البحث لإمكانية إستخدام العلاج بالحبيبات المشعة عن طريق الشريان الكبدى فى حالات الأورام الكبدية الأولية المتوسطة والمتقدمة موضعياً، كما تمت دراسة نجاحه، أمان هذه الطريقة الجديدة.

وقد جاءت نتائجنا متوافقة مع الأبحاث المنشورة سابقاً والتى تبشر بنجاح هذه الطريقة.

ولكن يلزم المزيد من الوقت والعديد من الأبحاث المستقبلية لتحديد أفضل الطرق والتطبيقات وكذا المكان الأفضل لهذا العلاج بين أساليب العلاج الأخرى المستخدمة حالياً .