

Hepatic Radioembolisation of Yttrium-90 Microspheres in Animal Model

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Abstract

Background and Aim: Liver directed therapy utilizing yttrium-90 microspheres represents a recently introduced in situ multidisciplinary cancer therapy that has caught the attention of many physicians faced with the challenges of treating these complex patients. Radioactive particle in capillary liver system were assessed through the in vivo test and the leakage to lung or other organ was defined. The concentration of Y-90 in liver tumor without leakage to the other organ was seen which has the important role in radioactive drug successes by radioimbolization method.

Method: Four different phases of Y 90 injection were performed in rabbits; 1. Preparation of Y-90 glasses microspheres, 2. Preservation, preparation and tumorization of the animal lab before and after drug injection, 3. Animal Angiography and injection of radioactive drug in animal liver, 4. Radionucleotide imaging of the animal; an assessment of stabilization of the radioactive particle in liver tumor. Early and late anterior and posterior injection of Y90 microspheres on rabbit showed. Yttrium 90 microspheres concentrated in liver, background, left and right lung were calculated. The mean \pm SD was defined for the particle localization.

Result: The most Y90 microspheres were localized in late posterior view in rabbit and the less in background; 67.79 ± 19.9 and 13.65 ± 7.97 respectively. Considering the late posterior view the highest total count of particles were mostly seen in the liver and then in the background, 68804 and 12026 respectively. Early posterior injection of Y90 demonstrated the most particles were concentrated in liver 57.82 ± 17.66 and the smallest in the background 19.61 ± 6.63 . Regarding early anterior injection, the most average number of the particles was reported 44.35 ± 13.10 in liver and the fewer particles were in background 17.93 ± 5.44 . Concerning the late anterior view, the great total numbers of particles were concentrated in liver 1020 and the less in left and right lung with the number of 342. The average particles counts were calculated 79.33 ± 21.55 in the liver and 36.17 ± 8.7 in background.

Conclusion: Significantly higher doses of radiation can be delivered to a liver mass by intra-hepatic arterial administration of 90Y-microspheres and the most concentration of the particles were seen in the liver in comparison to the other organ. This treatment appears to be beneficial in non-respectable tumors with acceptable toxicity.

Keywords: Yttrium-90; Radioembolisation; Liver; Tumors

Introduction

Hepatocellular cancer is amongst the commonest causes of cancer mortality worldwide [1] and is the fourth most common cause of death from cancer and rapidly increasing in incidence in the United States [2]. Recurrent, most often unrespectable disease in the hepatic remnant contributes significantly to this inability to achieve long term cure rates for colorectal cancer patients [3]. Five year survival estimates range between 30-50% following hepatic resection and less than 20% following transplantation for hepatocellular cancer [4].

It is obvious that the altered arterial supply to hepatic tumors could potentially be exploited to deliver lethal doses of radiation. A high energy radiation source combined with an appropriately sized trans-

hepatic arterial administered embolic microscopic particle would allow radiation to be distributed preferentially to the tumors [5]. While we're on the subject, is also noted of excessive hepato pulmonary shunting. Yttrium-90 (Y90), a pure β emitter is produced by neutron bombardment of yttrium-89 in a reactor. Y90 has a physical half-life of 64.2 hours and decomposes to stable zirconium 90. Treatment with Y90 microspheres must be based on cross-sectional images and arteriograms in the individual patient. The work-up should include CT or MR imaging of the liver for assessment of tumoural and non-tumoural volume, portal vein patency, and extent of extra hepatic disease.

Two factors suggest that the hepatic arterial administration of radiopharmaceuticals embedded in microspheres is a potential therapeutic choice for patients with HCC: The tumor nodules are often more vascular compared with the surrounding normal liver, and

the nodules receive their blood supply predominately from hepatic arterial rather than portal venous circulation. Administration of microspheres through hepatic artery branches with consequent deposition in the tumor terminal vasculature could result in an, 3-fold or greater radiation dose in tumor nodules relative to normal liver [6]. ⁹⁰Y surrounded into non-biodegradable glass microspheres can be administered safely by intrahepatic arterial injection to patients with HCC at a dose of 100 Gy [7,8]. We report an investigation of intrahepatic arterial ⁹⁰Y-microspheres at this dose in an experimental study on rabbits with non-respectable tumor designed to determine the proportion of the particles concentration in Liver in comparison to the background and left and right lung.

Material and Method

Animal angiography and hepatic artery injection of Yttrium 90

Radioembolisation was conducted on one Persian male rabbit weighing 3.5 kg. Animal was anesthetized with intramuscular mixture of ketamine (50 mg/kg), xylazine (5 mg/kg) and atropine (0.4 mg/kg). A 20 F catheter was introduced through the right femoral artery by cut down technique after preliminary local sedation with xylocain (1 mg/kg) Subcutaneous. A 0.5-1 cm length 4F sheath was placed into the artery and after 4F sheath placement with heparin in 0.9% sodium chloride solution (50 U/kg) was intravenously injected. Then a guide wire 0.014 (BMW abbot vascular, ca, USA) placed into the Right judkins catheter (cordis corporation, USA) and enter both in the sheath, followed by the guide wire in the artery Under the fluoroscopy, then catheter placed into the artery and Follow the Guide Wire going forward first into the right femoral artery toward right iliac, abdominal aorta, siliac artery and at the end of the hepatic artery. To find the true path of the injected contrast material (visipaque GE Health care, cork, Ireland) is used, after getting into the hepatic artery, catheter removed and Micro catheter 2/3 f with guide wire 0.014 placed into the arteries that supply blood to the Right liver lobe and then after injection of Y90 microsphere in 2 ml of 0.9% sodium chloride solution, the cannula was flushed with 5 ml in 0.9% sodium chloride solution and removed. Angiographic assessment revealed that the supply blood to the right liver lobe hepatic artery was not contrasted and so microsphere was sedimented.

Preparing and tumorization of the animal lab before and after radioactive drug injection

Totally 10 rabbit were used in this procedures and were preserved in sterilized condition, the sheep were refuse to eat before surgery and for the rabbit nothing was forbidden. Ketamin and xylazine were used as aesthetic drug and after intubation isofloran was used. The animals were monitored and all vital sign were determined during angiography. All important factors as blood volume were provided. After angiography the animals underwent antibiotic therapy and heparinasion. For the means of tumorisation we used two method; 1) laparotomy and injection of 0.1 mil cancer cell suspension of VX2 including one million carcinoma cancer of anterior lobe and inferior part of the capsule and significant lobe liver lobe of the patients, 2) inserting a piece of carcinoma tumor with the volume size of 1 mm in liver through laparotomy. Early and late anterior and posterior injection of Yttrium 90 intervention on rabbit showed the number of Yttrium 90 pixel concentrated in liver, background, left and right lung

which were calculated and manifested. The mean \pm SD was defined for localized Yttrium 90 pixels.

Radioneuclotid imaging of the animal lab and assessment of stability of radioactive particle in liver tumor

The work-up should include CT or MR imaging of the liver for assessment of tumoural and non-tumoural volume, portal vein patency, and extent of extra hepatic disease. A triple phase CT to delineate the geographical distribution, the volume and the partition between hepatic parenchyma and tumour is essential in therapy planning. Adjunct information on portal vein patency and aberrant hepatic arterial anatomy is obtained. Distribution of the disease is typically characterized as uni-lobar or bi-lobar, however the correlation of tumour with hepatic arterial supply is variable and can only be ascertained with arteriography. As cites indicates poor hepatic preserve or peritoneal metastasis, both of which have a poor prognosis.

Statistical analysis

Survival curves were generated by the Kaplan-Meier technique (15). Multivariable stratified Cox regression (16) was used to evaluate the influence of liver dose, TNR, and Okuda's staging on survival time. SPSS 18.0 (Chicago, USA) was used for all the statistical analyses. Continuous and categorical variables are presented as means (\pm standard deviation) or medians and as counts (percentage), and were assessed with appropriate tests. Student t test was used to compare the quantitative variables and Chi-square test was used to compare the categorical variables.

Results

Late posterior intervention on rabbit showed the number of Yttrium 90 particles concentrated in liver, background, left and right lung were respectively 1015 pixel out of the total count of 68804, 380 out of 12026, 361 out of 13345 and 362 out of 12983 which were showed particles were mostly concentrated the in liver than the other sites. The mean \pm SD was defined for localized Yttrium 90 absorption which was 67.79 ± 19.9 for the liver, 13.65 ± 7.97 for the background, 13.97 ± 8.27 for the left lung and 37.96 ± 8.91 for the right lung.

The size of the particles was also calculated and from the greatest to smallest one were defined respectively; 5834.71 mm^2 for the liver, 2184.42 mm^2 for the background, 2075.2 mm^2 for the left lung and 1965 mm^2 for the right lung. Figure 1 depicted the concentration of yttrium 90 in liver in comparison to left and right lung and the background.

Considering the late posterior view in injection, the total numbers of particles were mostly accumulated in the liver 68804 and the less one in background 12026. The average particles number were mostly considered in liver with the number of 67.79 ± 19.9 and the less one in background with the number of 31.65 ± 7.97 . The greatest particles were seen in liver 5834.71 mm^2 , and the smallest was in right lung 1965.98 mm^2 .

Early posterior intervention on rabbit injection demonstrated that the total count for the particles was mostly reported in left lung with the number of 18668 and the less one in liver with the number of 118997.

The great number of particles which were concentrated in early posterior view in was seen in the rabbit liver with the number of 2058

and the less one in left and right lung with the number of 648. Particles were mostly concentrated in liver with the average number of 57.82 ± 17.66 and the less average was seen in the background with the number of 19.61 ± 6.63 . The particles had the greatest dimension in liver with the number of 118390.38 mm^2 and the fewer dimensions in the left lung 3725.02 mm^2 (Table 1).

Regarding early anterior injection of Yttrium 90 in rabbit, the most of the particles were seen in the liver with the number of 2058 and the less one in left and right lung with the number of 624. The most average number of the particles was reported 44.35 ± 13.10 and the fewer one was in the background with the number of 17.93 ± 5.44 . The greatest numbers of the particles were 11830.38 mm^2 in liver and 3587.05 mm^2 in the left lung (Table 1).

With regards to late anterior view, P articles mostly were demonstrated in liver with the number of 1020 and the less in left and right lung with the number of 342. The average of the particle counts were 79.33 ± 21.55 in the rabbit liver and the less in background with the number of 36.17 ± 8.7 . The greatest particles were found in liver 5863.46 and the less in left and right lung with the number of 1965.98 mm^2 (Table 1).

According to the analysis of the volume of the interest (VOI) in SPECT-CT after 20 min (early phase), the mean count of the particles was 1369 ± 331.9 and in the late phase (after 24 hours) was 395 ± 78.6 .

ROI		Early		Late	
		Ant	post	Ant	post
Liver	Ave count	44.35 ± 13.10	57.82 ± 17.66	79.33 ± 21.55	67.79 ± 19.9
	Total count	91280	118997	80918	68804
Background	Ave count	17.93 ± 5.44	91.61 ± 6.63	36.17 ± 8.7	31.65 ± 7.97
	Total count	12102	12745	13058	12026
Left lung	Ave count	22.44 ± 6.21	28.84 ± 8.95	39.51 ± 9.44	36.97 ± 8.27
	Total count	14004	18688	342342	13345
Right Lung	Ave count	20.86 ± 5.97	23.1 ± 7.37	40 ± 8.99	37.96 ± 8.91
	Total count	13015	14415	13679	12983

Table 1: Early and late posterior injection of yttrium 90 characteristics in rabbit.

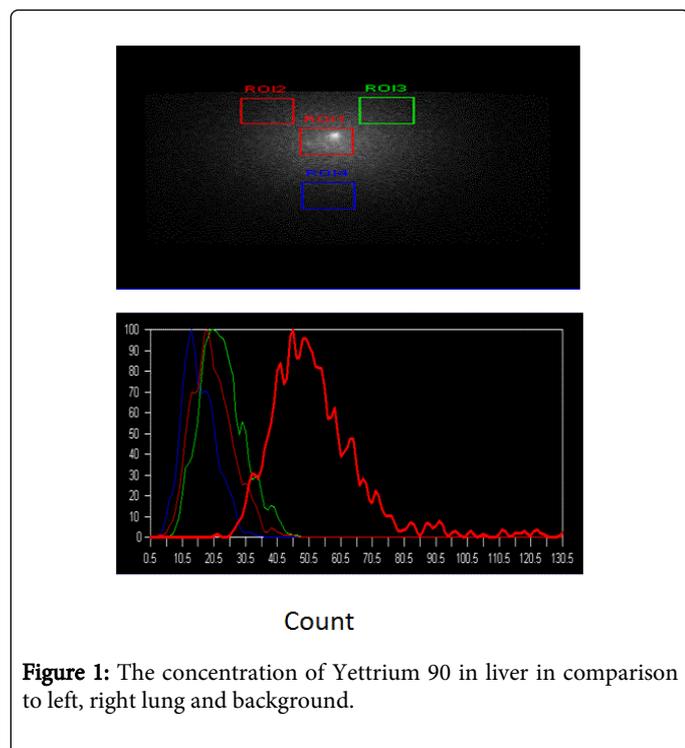


Figure 1: The concentration of Yttrium 90 in liver in comparison to left, right lung and background.

Discussion

We hypothesize that according to radioactive particle size and blood flow in liver through successful catheterization, the particles would be concentrated in injected area and do not leak to other organ specially lung. If particles concentrated in injected area in liver there would be no leakage in sensitive organs as lung and no necrotic effect would be reflected on liver and around area; consequently radiotherapy should be performed with beta wave. In this study radioactive particles in capillary liver system were assessed through the in vivo test and defining the leakage to lung or other organs. The concentration of Y-90 in liver tumor without leakage to the other organ has the important role in effectiveness of this radioactive drug by radioembolization method.

Early studies demonstrated the practicability of Y90 microsphere therapy for a variety of disease types [9,10]. Y90 microsphere therapy have since been applied mainly for the treatment of unresectable hepatic metastatic colorectal and hepatocellular carcinoma. The application of Y90 resin microspheres to a patient population with hepatic colorectal metastases demonstrated favourable responses, augmented with the addition of hepatic arterial 5FU. In a fundamental trial, patients were randomised to receive intra arterial FUDR with or without a single dose of the resin microspheres. The results demonstrated a benefit in all clinical indices favouring the combination therapy, specifically a time to tumor progression and formed the basis for FDA approval in the US. An important lesson was learnt during this trial; the great number of the patients developed

extra hepatic disease that adversely affected survival and this observation was supported by a separate large clinical experience.

In Asia, Y90 resin microspheres as an effective treatment option was first delineated by an 18 patient phase I/II trial and supported by an observational study in 71 patients conducted by the same group. These studies found that tumor response and clinical benefit was comparative to the dose delivered. Repeat treatments with Y90 microspheres provided additional survival benefits. A Canadian study published in 2000 reported on 22 patients to determine response parameters, survival and toxicity after intra-arterial injection of 90Y glass microspheres. The median dose delivered was 104 Gy (range 45-145 Gy). Interestingly the median survival of 54 weeks (range 7-180 weeks) and the trend for enhanced survival with higher doses (>104 Gy) was similar to the results seen for resin microspheres. Several retrospective patient studies have emerged from the centers treating with glass Y90 microspheres in the USA. Our study showed that due to Yttrium 90 microspheres resolution, after 24 hours nearly 1/4 of the particles has been remained This is the unique investigation considering the total count of the particle and calculated the concentration of Y90 microspheres in rabbit liver lung and background were compared a So far, a few study found to calculate the mentioned criteria of Y90. Gesch wind reported on 80 patients from a relatively large database of 121 patients who were treated with glass microspheres.

In a study, treatment with 90Y-microspheres was associated with a 20% response rate with less toxicity than with hepatic arterial embolization or high-dose external beam radiotherapy. In addition, 8 patients had durable stable disease. Lau et al. also found 8 partial responses in 18 patients with inoperable HCC. In their larger follow-up series, objective tumor regression of 50% in tumor volume was seen in 26% (19/71) of patients. In that study fewer objective responses because of either their stricter response criteria or a lower dose; however, many of their patients had prolonged stable disease suggesting that treatment with 90Y-microspheres does have anti-tumoral effects that may be dose related.

The disposition of 90Y-microspheres into tumor compared with non-tumorous liver tissue is clearly an important determinant of therapeutic index. More vascular tumors are likely to receive greater deposition of 90Y-microspheres and radiation dose compared with normal liver tissue. One of the most appealing aspects of intrahepatic arterial 90Y-microsphere therapy is selective deposition in tumor vasculature with sparing of normal tissue.

The present study showed, Y90 microspheres which was localized in late posterior view in rabbit were mostly found in liver (67.79 ± 19.9), and the less found in background (13.65 ± 7.97). The size of the particles was calculated and was greatest in the liver 5834.71 mm^2 2184.42 mm^2 and the less (1965 mm^2) was in the right lung. Considering the late posterior view, particles was totally higher in number in the liver (68804) and lower in number in the background (12026). The average count in this view mostly was considered in liver (67.79 ± 19.9) and the less in background (31.65 ± 7.97). The greatest particles were seen in liver (5834.71 mm^2), and the smallest were in the right lung (1965.98 mm^2).

Early posterior injection demonstrated that the total particles count for the Y90 microspheres were mostly in left lung (18668) and the less ones was in the background (118997).

The greatest particles number, in early posterior view was concentrated, in liver (2058) and the less delivered in left and right

lung with the number (648). Particles were mostly concentrated in liver (57.82 ± 17.66) and the less were delivered in the background (19.61 ± 6.63). The particles had the greatest dimension in liver (118390.38 mm^2) and the smallest dimension in the left lung (3725.02 mm^2).

Regarding early anterior injection, the most of the particles were seen in the liver (2058) and the fewer seen in left and right lung (624). The greatest size of the particles was 11830.38 mm^2 in liver and 3587.05 mm^2 in the left lung. As a result of the other study, the tumors treated with Y90 microspheres have responded to Y90 microspheres therapy. This is confirmed by reduction in tumor volume and markers, ability to convert to a respectable status, and improvements in the time to tumor progression. Our study suggested that we might use this method for treatment of liver tumors.

In anterior view, most of the particles were concentrated in liver (1020) and the fewer was transferred in to the left and right lung (342). The average of the particle count was seen in the liver (79.33 ± 21.55) and the less was seen in the background (36.17 ± 8.7). The greatest particles were found in the liver (5863.46 mm^2) and the less in the left and right lung (1965.98 mm^2).

According to our data it could be suggested that that treatment with 90Y-microspheres does have anti tumoral effects. As our best knowledge this is one of the one of the few study manifested the localized Y90 microspheres characteristics and accumulation in liver, background left and right by radio-nucleotide imaging technique. Our study showed that due to Yttrium 90 microspheres resolution, after 24 hours nearly 1/4 of the particles have been remained.

Conclusion

We showed that the most of the pixels were accumulated in the liver and the least was concentrated in background and the left and right lung. Randomized clinical trials and registry data will assist to better answer these important questions.

Y90 microspheres represent an intriguing therapy for the treatment of liver cancer. However, the utility of Y90 microsphere therapy remains to be determined within the context of the other currently available therapies. Standardisation of dosimetry and treatment techniques, achievable only in the robust randomized clinical trials, is necessary to arrive at conclusions that support clinical effectiveness. Registry data will be necessary to provide guidance on therapeutic effectiveness and for disease types for which clinical trials are not historically feasible due to their low incidence and for many patients who do not meet traditional eligibility criteria. Such efforts are underway. However, there are many unanswered critical questions; who would be the 'optimal' patient? Should the radiation dose be fractionated, and at what dose and frequency? Does a dose response to tumors volume correlation exist, that might be answered in larger study in human population. This treatment involves injection of plastic or glass microspheres incorporating the radioactive isotope Yttrium-90 directly into the tumor.

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Conflicts of Interest

There are no conflicts of interest.

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