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A Review: Radioactive Microspheres as a Theranostics

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Abstract

Microspheres as a drug delivery system hold great promise in reaching the goal of controlled drug delivery as well as site specific delivery. In the last few decades, scientific and technological advancements have been made in the research and development of radio labeled microspheres. These are used successfully for the treatment of various cancers and tumors. Since response to chemotherapy and external radiotherapy is not so effective and hazardous too, so an alternative to this is internal radiation therapy. These radio labeled microspheres are very stable and have a proven efficacy in the field of primary as well as metastatic cancers. Radioactive microspheres can be selectively targeted to various tumors without undue radiation to the non tumorous tissues. The radioactive microspheres are injected to halt tumor growth via the blood supply, thereby enabling surgical removal once the tumor size decreases. This review provides an outlook to various aspects of radioactive microspheres and their role in treatment of various tumors and cancers.

Keywords: Radioactive microspheres, Radionuclide, Radiation therapy.

1. Introduction

In connection with aim of maximizing the bioavailability of conventional drugs with minimum side effects, new drug delivery systems continue to attract much attention. Such systems include microspheres, liposomes, nanospheres etc. These drug delivery systems lend themselves to parenteral administration and are useful for sustained release of drugs. There is also the possibility of directing the drug to an appropriate organ or target site within the body through these colloidal drug delivery systems. Microspheres form the basis of colloidal drug delivery systems; hence they have received a great impetus. Microspheres are solid, approximately spherical particles ranging from 1 to 1000 mm in size. They are made of polymeric, waxy or other protective materials that include biodegradable synthetic polymers and modified natural products such as starches, proteins, fats and waxes.

The natural polymers include albumin and gelatin whereas the synthetic polymers include polylactic acid, polyglycolic acid etc. In the past few decades, microspheres have been extensively exploited for therapeutic purposes, especially for the treatment of various cancers. This approach involves the use of microspheres labeled with suitable radionuclides or isotopes instead of a drug. For therapeutic purposes, radiolabeled microspheres are used for radioembolization therapy of tumors and cancers. Radioactive microspheres have an advantage of delivering high concentration of radioactivity to the target area without causing any damage to the surrounding tissues and organs. Following administration, these microspheres get entrapped in the web of small blood vessels feeding a tumor and thus deliver the required concentration of radioactivity at the target site. The radioactivity is never released from the microspheres and acts from within. The effective treatment

range is up to 90 mm for alpha emitters, for beta emitters the range is not more than 12 mm and for gamma emitters the range is up to several centimeters. In chemotherapeutic approach, the drugs have to be withdrawn even before the complete removal of the tumor, which finally leads to revival of tumor tissue. Withdrawal problems are not there in the case of radioactive microspheres and thus the use of radioactive microspheres shows better chances for complete eradication of tumors. Another important advantage of radioactive microspheres is patient compliance since the radioactivity dose persists at a target site for at least four weeks and high concentrations can be achieved at the target site.[1-5]

2. Types of Radioactive Microsphere

2.1 Therapeutic Radioactive Microspheres

Many radio labeled microspheres are appropriate for therapy once the encapsulated diagnostic radioisotope has been exchanged for a therapeutic one from the α- or β-emitter group. Typical uses in the last 20 to 40 years include local applications for the treatment of rheumatoid arthritis, liver tumors and cystic brain tumors. However, their use remains experimental because of smaller than expected target uptake, unwanted toxicity and insufficient treatment effects that have resulted from radio chemical instability and suboptimal biodistribution of the radiopharmaceutical. In addition there exists a general negative attitude towards the use of radioactive substances in spite of proven superior results of many radiation therapies. Few therapeutic applications of radioactive microspheres are tabulated as follow [6-7]:

Table 1: Therapeutic applications of microspheres

Type of radioactive microspheres	Applications
^{90Y}-glass microspheres, ^{186}Re/188Re-glass microspheres	Radioembolisation of liver and spleen Tumors
^{35}S-colloid, ^{90Y}-resin microspheres, ^{169}Er.citrate	Radiosynovectomy of arthritis joints
^{90Y}-labeled poly(lactic acid) microspheres, ^{211}At-microspheres, ^{212}Pb-sulfur colloid	Local radiotherapy
Chromium ^{32}P-phosphate, ^{90Y}-silicate	Intracavity treatment

2.2 Diagnostic radioactive microspheres

Diagnostic studies with radiopharmaceuticals include dynamic and static imaging and *in vivo* function tests. Dynamic imaging provides information about the Bio distribution and pharmacokinetics of drugs in organs. Performed with a γ-camera, dynamic studies are generally carried over a preset length of time and provide clues to the functioning of the organ being examined. The first such microspheres in clinical use were red and white blood cells, which were taken from a patient, labelled with ^{111}In or ^{51}Cr, and then re-injected. Red blood cells labelled with ^{51}Cr commonly used for the measurement of red blood cell mass and imaging of the spleen. Another common application of radiolabelled red blood cells is the accurate determination of total systemic arterial flow or venous return, as well as for blood flow determination within specific organs. Various diagnostic applications of radioactive microspheres are as follows [8-9]:

Table 2: Diagnostic applications of radioactive microspheres

Type of radioactive microspheres	Applications
^{111}In or ^{51}Cr-labelled red blood cells	Gated blood pool study
^{111}In-labeled platelets, ^{99m}Tc-sulfur colloid	Thrombus imaging in deep vein thrombosis
Polystyrene microspheres labeled with γ-emitters ^{141}Ce, ^{57}Co, ^{114m}In, ^{85}Sr, ^{51}Cr	Blood flow measurements
^{3}H, ^{14}C-labelled microspheres ^{141}Ce-polystyrene microspheres	Investigation of biodistribution and fate of drug loaded microspheres
^{99m}Tc-impregnated carbon particles ^{99m}Tc-macro aggregated human serum albumin	Lung scintigraphy
^{99m}Tc-macro aggregated human serum Albumin	Radioembolisation
^{99m}Tc-macro aggregated human serum albumin	Liver and spleen imaging
^{99m}Tc-sulfur colloid ^{99m}Tc-antimony sulfide colloid	Bone marrow imaging

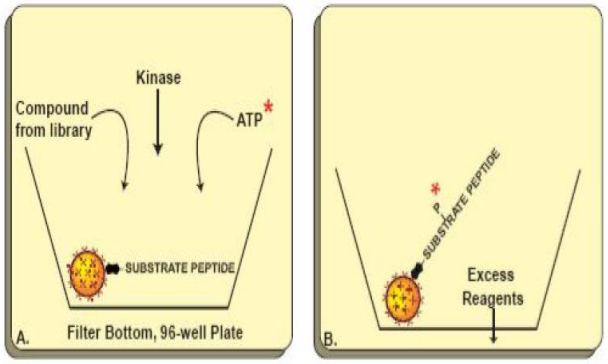

Figure 1: Radioactive protein kinase assay

3. Selection of radionuclide

The choice of radionuclide is determined by the organ/tissue to be treated. Absorption, distribution, metabolism and excretion of radiopharmaceuticals can be followed by scintigraphy. Depending upon their use, they may be administered orally or by injection. The uses of radionuclides for the treatment of various types of cancers have been an effective alternative to other therapies such as chemotherapy and external radiation therapy.

General requirements for the selection of radionuclides include lack of toxicity, ease of elimination from the body, small size to allow intravenous injection, sufficient radiation spectrum, simple labeling procedures and no leakage of isotope from particles surface. Most routinely used radiopharmaceuticals are technetium-^{99m} (^{99m}Tc) labeled compounds that are prepared by adding sodium pertechnetate to nonradioactive lyophilized ingredients supplied in a "kit" form suitable for administration. ^{99m}Tc has ideal physical characteristics. It emits only gamma radiation in the range of a gamma camera detector. Its half-life of 6 h limits the radiation dose to the patient. Other important radioisotopes are ^{90}Y (Yttrium), ^{188}Re (Rhenium) and ^{166}Ho (Holmium). [10-12]

3.1 Yttrium [10-12]

^{90}Y is the decay product of strontium-90. Also produced by ^{89}Y(n, g). ^{90}Y is a high energy pure beta emitting isotope with a half life of 64.1 h. The maximum energy of beta particles is 2.27 MeV and the maximum range of emission in tissue is 11 mm. ^{90}Y has two major disadvantages. Firstly, a long neutron activation time (> 2 weeks) is needed to attain therapeutic activities of yttrium. Secondly, Bio distribution of ^{90}Y loaded microspheres cannot be directly determined in clinical trials since ^{90}Y is a pure beta emitter and does not produce imageable gamma rays.

3.2 Rhenium [10-12]

The radioisotopes of rhenium ^{188}Re and ^{186}Re have unique physical properties that make them attractive for radiotherapy. ^{188}Re has a half life of 3.78 days with maximum beta energy of 1.07 MeV whereas ^{186}Re has a shorter half life of 17 h and maximum beta energy of 2.12 MeV. Both isotopes have imageable gamma rays.

3.3 Holmium [10-12]

^{166}Ho is produced by neutron capture of ^{165}Ho which has a natural abundance of 100%. ^{166}Ho has a half-life of 26.83 h and decays by emission of 1.855 MeV and 1.776 MeV maximum energy beta particles. Its physical properties are suitable for plenty of medical applications, for example, skin and hepatic malignancies, rheumatoid arthritis etc.

3.4 Radioactive microspheres for radiation therapy [13-15]

An early approach in radiation therapy involved the use of yttrium oxide powder suspended in a viscous media. Yttrium was selected as it emits nearly 100% beta radiation. But the major disadvantage of yttrium oxide powder is its high density (5.01 g/cm^3) and irregular particle size. The high density makes it difficult to suspend the particles in the medium and this accelerates their tendency to settle in the blood stream prior to reaching the tumor as desired. Sharp corners and edges of the particles irritate the surrounding tissues and interfere with uniform distribution. In recent applications, microspheres comprising of glass material, polymer or resin are being used. Depending upon the application it is desirable to link the microspheres with a suitable radionuclide. The stability of these microspheres is such that they do not release a significant amount of radiation emitting material into the surrounding tissues. The suitability of the microspheres for radiation therapy is based upon the properties of targeted delivery of radioactivity, uniform distribution of radioactive material throughout the microsphere material, easy activation by neutron irradiation of microspheres bearing a suitable isotope, low leakage or leaching of radioactive material, suitability for parenteral administration, uniform size distribution and easy labeling. The three major microsphere materials viz glass-based, resin-based and polymer-based are preferably used for microsphere preparation.

3.5 Glass microspheres [16-20]

The glass microspheres are incredibly small (20–30 mm) in size. Glass has minimum radionuclide impurities and is non-toxic, non-resistant to radiation damage. Glass microspheres can be easily prepared in uniform sizes and easily administered. Each injection contains five to ten million microspheres for delivering radioactive material to the desired target. The manufacturing process was described by Ehrhardt and Day [9]. A beta-emitting radioisotope was chemically dissolved in and distributed uniformly throughout the glass material. The glass based materials used were aluminosilicate, magnesium aluminosilicate, lithium silicate, potassium silicate etc. containing 166Ho, 186Re, 90Y as radioisotopes. Glass has many advantages over nonglass materials: it confers targeted delivery of radioactivity to the tumor site; sufficient dosage of radiation and ease in the preparation of glass microspheres. But the major drawback of glass microspheres is their high density (3.29 g/ml) and non-biodegradability [24].

The high density results in side effects due to premature intravenous settling and falling back into the gastroduodenum. In radiotherapy, glass microspheres labeled with radionuclide have been used. This eliminates the problem of leaching of radionuclide material. More recently, new yttrium based glass microspheres in which the leaching problem has been eliminated have been developed under the trade name "Theraspheres". Theraspheres with a diameter of 15–30 mm contain a stable ^{89}Y isotope which is activated by neutron bombardment in a nuclear reactor to ^{90}Y. Houle *et al* [18], used ^{90}Y glass microspheres in the treatment of hepatocellular carcinoma (HCC). The ^{90}Y microspheres were injected via a hepatic artery catheter. No toxicity was observed for doses between 50 and 100 Gy to the liver and up to ^{320}Gy to the tumor itself. Thus as desired, the large absorbed doses of internal radiation can be safely delivered to hepatic tumors if the presence of extrahepatic shunting is excluded. Radioactive rhenium glass microspheres are an alternative to yttrium glass microspheres as the production of ^{90}Y is time consuming and include costly neutron activation in a nuclear reactor. Rhenium microspheres are used for the in vivo irradiation of diseased organs in the body, for example, malignant tumors and the inflammed synovium of the joints. The radioactive microspheres are directly injected into the synovial sac where they deliver enough radiation (^{100}Gy) to destroy the inflammed lining of the diseased synovial membrane.

3.6 Polymer based microspheres [16-20]

Polymers are used as vehicles for the immobilization and local delivery of radionuclides or radiopharmaceuticals. Radionuclides are either physically adsorbed or chemically linked to a polymeric surface. Polymer based microspheres have many advantages over glass microspheres which include biodegradability, biocompatibility, systemic and controlled release of radionuclide from polymer etc. This provides a way to control local dosage of radiation without the need for physical removal of the implanted radionuclide. The best known biodegradable polymers which are hydrolysed without enzymes and metabolized by the body are polylactic acid, polyglycolic acid and their copolymers poly (lactic-co-glycolic acid). Preferred radioisotopes are those which have a particle range in tissue according to the tissue layer which is to be targeted. For example beta particles emitting radioisotopes like carbon-14, sulphur-35 and phosphorous-33 will be absorbed in the first 70 microns of tissue whereas more energetic beta particles emitting the radioisotope phosphorous-32 have a longer range of about a centimeter and can be used to treat thicker tumors [20]. Polymeric microspheres are prepared by the solvent evaporation technique. The polymer is dissolved in a suitable volatile solvent and dispersed in a continuous medium using a stabilizing agent, Controlled evaporation of solvent results in the formation of solid microspheres. The solvent evaporation method has been used for the preparation of polylactic acid microspheres containing ^{166}Ho, ^{90}Y, ^{186}Re as radioisotopes [19]. Radioactive ^{166}Ho loaded polylactic acid microspheres were prepared by Mumper *et al* [23]. Holmium-165-acetylacetonate (HoAcAc) and polylactic acid were dissolved in chloroform and the solution was added to polyvinyl alcohol solution. The final solution was stirred until the evaporation of the solvent. Microspheres were graded and collected according to size. These microspheres were recently tested for the treatment of hepatic malignancies in rabbits. The bio-distribution and histological analysis confirmed that radioactive microspheres got heterogeneously distributed over the liver and accumulated preferentially in the tumor area. It was demonstrated that ^{166}Ho polylactic acid microspheres were the promising systems for the liver tumor treatment [26]. Van *et al* used ^{166}Ho loaded polylactic acid microspheres for radio-embolization of unresectable head and neck cancer in rabbits. Complete tumor remissions were obtained in 79% of rabbits. Over 95% of the microspheres retained in the tumors indicated that polymeric microspheres could be used for the embolization of tumors. Magnetic polylactic acid microspheres loaded with a beta emitting radioisotope like ^{90}Y were made by Hafeli *et al*[14]. It was reported that magnetic microspheres could be selectively delivered to the target site after incorporating 10% Fe_3O_4 (magnetite). Magnetic microspheres get slowly hydrolysed into lactic acid after the complete decay of radioactivity. These microspheres were used for intracavital tumor therapy. Experiments showed a twelve fold increase in the activity in tumor with a directional magnet fixed over the tumor.

3.7 Albumin based microspheres [16-20]

Albumin is a type of globular protein and is present in blood and tissues. When human serum albumin is to be used for organ imaging, it is denatured to produce albumin aggregates and then selectively sieved to obtain desired particle size. When used diagnostically, albumin is combined with a radioisotope such as ^{99}Tc, ^{131}I. Albumin microspheres received considerable attention because of their biodegradability, biocompatibility, non-antigenicity and organ specific targeting properties. Various methods have been reported for the preparation of albumin microspheres. Microspheres of ovalbumin (OVA), prepared by emulsifying an aqueous solution of albumin in soybean oil have been labeled with technetium after reduction by thiosulfate or stannous chloride. Currently ^{99}mTc microspheres of human serum albumin are widely used for lung scanning [28]. More recently ^{99m}Tc human serum

albumin microspheres have been used successfully for the treatment and assessment of the radiation induced gastritis, pneumonitis, lungs shunting etc. The tumor to normal tissue (T/N) ratio determines how safe and effective the treatment is Ho *et al*[17]. This determination of tumor to normal tissue ratio by simulation with ^{99m}Tc albumin microspheres is recommended before internal radiation therapy. Lau *et al*[20] in 1994 used ^{99m}Tc macro aggregated albumin (MAA) to assess the vascularity of liver metastasis and to predict the tumor to normal (T/N) tissue ratio in selective internal radiation therapy. It was estimated that if T/N ratio is not less than 2, then selective internal radiation therapy should be followed. This allowed the radioactive dose to be delivered to the tumor while keeping the radiation dose to the nontumorous liver within the tolerance limit. In 2000 Wunderlich *et al* reported human serum albumin (HSA) microspheres labeled with ^{188}Re for internal radiotherapy of tumors. These microspheres were uniform in size, with a mean diameter of 25 mm and were biocompatible and biodegradable. Intravenous injection in Wistar rats, using the lungs as a model for a well-perfused tumor, demonstrated sufficient in vivo stability. Yttrium was also used with human serum albumin for internal radiotherapy of lung tumors. Experiments were carried out in mice using ^{90}Y macroaggregates of human serum albumin for whole lung irradiation. Based on its rapid clearance from the lung, it was suggested for internal radiotherapy.

3.8 Resin based microspheres [16-20]

Microspheres based on ion exchange resins are favoured for radioembolization due to lower density compared with glass, ease in labeling and their commercial availability. In comparison to polymers and glass, resin microspheres are suspended in physiological saline, thus avoiding any complications whereas ceramic microspheres must be suspended in either viscous or dense solutions. Zielinksi and Kasprzyk, prepared cation exchange resin microspheres labeled with ^{32}P for radiation therapy of hepatic neoplasms. The maximum energy of the ^{32}P beta particle was 1.71 MeV resulting in tissue penetration of 8 mm thickness. The range was short enough to minimize unwanted irradiation to sensitive adjacent organs. Approximately ^{15m}Ci of ^{32}P labeled microspheres distributed uniformly in a 2100 g liver and delivered a dose of 5000 rads. ^{99}Tc labeled anion exchange resin (AG1-X8) microspheres were also prepared and studied. Microspheres of AG1-X8 (60 mm diameter) were mixed with 5–200 mCi of 99Tc pertechnetate in physiological saline. The labeled microspheres were washed with water, supernatant was removed and placed into an oven for 15 min (270^{0}C). The ^{99}Tc labeled microspheres were ultrasonically dispersed in saline. ^{99}Tc radiopharmaceuticals are used routinely in nuclear medicine practice. Turner *et al* prepared microspheres by the addition of ^{166}Ho-chloride to the cation exchange resin Aminex A- 5. A reproducible, nonuniform distribution of the 166 Homicrospheres throughout the liver was observed on scintigraphic images, following intrahepatic arterial administration in pigs. This predictable distribution allowed these investigators to determine the radiation absorbed dose and to define the administered activity required to provide a therapeutic dose. Aminex A-27 was labeled with 188Re by adding ^{188}Re-perrhenate and $SnCl_2$ to vacuum dried resin particles by Wang *et al*. These ^{188}Re labeled microspheres were injected by direct intratumoral injection into rats with hepatoma. In the treated group, survival over 60 days was better than in a control group. Campbell *et al* [5] investigated the microscopic distribution of microspheres in human liver following hepatic infusion of 32 mm resin microspheres labeled with ^{90}Y as a treatment for a liver cancer with a diameter of 80 mm. The observed deposition patterns indicated that the vascular tumor periphery received much greater radiation doses from radioactive microspheres than both normal and the a vascular tumor centre.

4. Applications of radioactive microspheres

In the past few decades, radioactive microspheres are being exploited for therapeutic applications. But owing to their ability to deliver high concentrations of radioactivity to the target site without damaging normal surrounding tissues, they are extensively exploited for the treatment of cancer.

The limited efficacy of current approaches to the treatment of cancer has reawakened interest in the use of radio labeled therapy which involves the use of radio labeled microspheres. Microspheres labeled with a radioactive isotope are injected directly into the diseased areas. External beam radiation requires about ten treatments over a period of 30 days to deliver a dose of 2000 to 2500 rads. In contrast, radioactive microspheres safely deliver an average dose of 15000 rads in a single treatment with minimal damage to healthy surrounding tissues. Currently this novel approach is finding success in fighting different cancers viz. liver cancer, head and neck cancer, spleen cancer etc. [21-24]

4.1 Applications in oncology [25,26]

4.1.1 Treatment of liver metastases or secondary cancer

Hepatic tumors derive most of their blood supply from the hepatic artery, whereas the non tumorous part of the liver gets 80% of its blood supply from the portal vein and only 20% from the hepatic artery. So most of the radioactive substances including microspheres injected through the hepatic artery are delivered to the tumor, giving a favourable uptake ratio of tumor to normal tissue (T/N). In early studies Grady [12] estimated the good objective

regression of cancers, improvement of symptoms and prolongation of life in seventeen of the twenty five patients treated by ^{90}Y resin microspheres. Blanchard *et al*[3] carried out a study by injecting ^{90}Y plastic microspheres (15 mm diameter) into the hepatic artery of fifteen patients with liver metastases and one patient with hepatoma. The study revealed that there was reduction in tumor volume by more than 50% while the mean survival rate was 62 weeks. However there was gastric ulceration due to unintended infusion of the radio labeled microspheres into the gastric circulation. By measuring the radiation doses received by the tumor and the nontumorous liver parenchyma separately, it was found that non tumorous liver could tolerate more than 30 Gy which is currently considered the limit for whole liver irradiation using external beams without any evidence of radiation hepatitis. Based upon the observation that patients who received up to 138.9 Gy to the nontumorous liver did not develop radiation hepatitis, an arbitrary safety limit of 80 Gy to the normal liver delivered by ^{90}Y microspheres was recommended [13]. Magnesium alumino borate glass microspheres containing radioactive rhenium were prepared and successfully used to treat liver tumors by radio embolization. The microspheres were made radioactive by neutron activation and then injected into the hepatic artery of sprague-dawley rats with one week old hepatoma. The bio-distribution studies showed a sevenfold increase of microsphere uptake by hepatoma as compared to healthy liver tissue. Tumor growth in the animals receiving radioactive microspheres was significantly lower than in the animals receiving nonradioactive microspheres. So it was concluded that radioactive rhenium microspheres were effective in slowing down or even diminishing liver tumor growth without altering hepatic enzyme levels [15]. Recently, biodegradable polylactic acid microspheres labeled with ^{166}Ho have been manufactured for internal radiation therapy of hepatic tumors. Nijsen *et al* [25], investigated the therapeutic effects of 166Ho loaded polylactic acid microspheres in rabbits with liver tumors. Rabbits were divided into three groups as Sham treated rabbits (n ¼ 3), "cold" microspheres treated rabbits (n ¼ 3) and ^{166}Ho microspheres treated rabbits. Biodistribution and histological analysis confirmed that radioactive microspheres got heterogeneously distributed over the liver and accumulated preferentially in the tumor area. Sham treated and cold microspheres treated rabbits showed an exponential tumor growth. The study demonstrated that ^{166}Ho polylactic acid microspheres were the promising systems for liver tumor treatment.

4.1.2 Treatment of hepatocellular carcinoma

Encouraged by the results achieved in the case of liver metastases, the therapy was extended to patients with hepatocellular carcinoma. In the late 1960's and early 1970's, ^{90}Y labeled inert ceramic or resin microspheres were injected into hepatic arteries of patients at an estimated dose ranging from 50 to 200 Gy. Inspite of striking response and survival rates, complications arised due to unexpected leaching of yttrium from the surface of microspheres and due to subsequent uptake of free yttrium by the bone marrow which led to lethal myelosuppression and radiation hepatitis. Largely as a result of these complications interest in this approach declined until the late 1980's. The recently developed 22 mm glass microspheres (Theraspheres1) incorporate ^{89}Y oxide into a glass matrix from which yttrium is unable to leach out. Wollner *et al* found that injection of cold theraspheres to be well tolerated. Moreover microspheres did not appear in the bone-marrow causing no myelosuppression. Burton *et al*[4] demonstrated that pretreatment with angiotensin II increased the microspheres uptake by the tumor by threefold in rabbits with VX_2 hepatoma and Walker carcinoma in rats. Accessibility of the microspheres to the central portion of the tumors had also increased. Earlier there were no reports on the effect of ^{90}Y glass microspheres in the treatment of liver cancer via the portal vein. In 1993 Yan *et al* studied the administration of ^{90}Y glass microspheres via the portal vein. It was concluded that ^{90}Y glass microspheres were effective in the treatment of liver cancer. In the study, conducted by Wang *et al*, ^{188}Re was used to label microspheres. The authors analysed the biodistribution and survival times after the intratumoral injection of ^{188}Re microspheres into rats suffering from hepatoma. The bio distribution studies revealed that radioactivity in the tumor was very high while in all other organs it was quite low. In addition, it was concluded that direct injection of ^{188}Re microspheres was extremely attractive as a therapeutic alternative in hepatoma patients. Hepatocellular carcinoma constitutes a difficult health challenge because of its poor prognosis and limited treatment options. UPCI (2002) reported a new treatment for inoperable primary liver cancer with Theraspheres1 which appeared to be safe and effective for liver cancer patients. Recently a new attractive approach was suggested to selectively deliver therapeutic doses of radiation to hepatic tumors. In a recent study by Georgiades *et al* [10] ^{90}Y microspheres were administered via the hepatic artery to patients with liver malignancies. This procedure provided a way of delivering radiation doses in excess of 100 Gy to the tumors by sparing the normal tissue. Carr *et al*[6] used ^{90}Y glass microspheres for the treatment of unrespectable and transplantable advanced stage hepatocellular carcinoma. These ^{90}Y labeled glass microspheres were delivered via the hepatic artery in 43 patients. It was observed that 27 out of 43 patients were evaluable for the

response and 12 patients had stable disease. From the study, it was estimated that Theraspheres1 appeared to be a promising, nontoxic and effective treatment for unresectable hepatocellular carcinoma. More recently in 2003, Sarfaraz *et al*., administered 90Y microspheres via the hepatic artery to selectively deliver therapeutic doses of radiation to liver malignancies. This procedure allowed to deliver radiation absorbed doses in excess of 100 Gy to the tumors without significant liver toxicity. Microspheres were administered via a catheter placed into the hepatic artery. The actual radiation absorbed doses to tumors and normal liver tissue was calculated based on the ^{99}mTc macro aggregated albumin study and computed tomography scans. As expected, the activity uptake within the liver was found to be highly non-uniform and a multi fold increase of uptake in tumor compared to nontumor tissue was observed. The radiation absorbed dose for tumor and liver were 402 Gy and 118 Gy, respectively.

4.1.3 Bone tumor

A traditional and definite method for bone tumor diagnosis is bone biopsy but this procedure has many risks and also increases the rate and extent of tumor cell metastases. An alternative to this traditional approach is the use of radioactive microspheres. In 1985, Robertson *et al*. Used radioactive microspheres of 15 mm (diameter) to explore the spread of tumor cells from the distal femur into the lymphatic system, venous drainage and local tissue. Radioactive microspheres have been used for the study of bone microcirculation in aseptic osteonecrosis of the femoral head. With the injection of radioactive microspheres it was possible to show that aseptic necrosis begins with global ischaemia and is followed by incomplete revascularization leaving a necrotic area. On the border between the two areas hypervascularity produced a zone of fragility where micro fractures developed with detachment of a sequestrum.

4.1.4 Head and neck cancer

The role of intra-arterial radioisotope therapy in the treatment of head and neck cancer was studied. From an experimental study in rabbits, it was found that 166Ho loaded polylactic acid microspheres are promising candidates for studies on radio embolization of unrespectable head and neck cancer. The effects on tumor growth, retaining efficiency of microspheres in primary tumor and the excretion of free 166 Ho were analysed by embolizing the radioactive Ho-labeled PLA microspheres into rabbits with VX2 squamous cell carcinoma. Complete tumor remission was obtained in 79% of the rabbits following embolization with radioactive microspheres. Over 95% of the microspheres were retained in the tumor. Dextran hydrogel microspheres for chemoembolization and holmium-polylactic acid microspheres for radio embolization proved to be promising candidates for the embolization of head and neck cancer. Particles with a mean diameter of at least 40 mm and volume weight mean size up to 70 mm are preferably used for the embolization of head and neck cancer.

4.1.5 Spleen tumors

Spleen imaging illustrates anatomic changes in the spleen and radiocolloids have been successfully used for the purpose. Radio colloids get concentrated in splenic tissues by phagocytosis. Therefore by spleen scanning we can depict the size, shape and position of the splenic tissue. Conventional splenic embolization with radio labeled microspheres was introduced as an alternative to splenectomy. Hypersplenism is characterized by inappropriate sequestration and destruction of blood elements and results in a diminished number of circulating thrombocytes or RBCs, WBCs. Hypersplenism may occur in patients with a variety of haematologic, inflammatory, metabolic and neoplastic disorders. Many patients with hypersplenism have an increased risk at surgery. Partial embolization of the spleen serves as an alternative to surgery. In 1995 Becker *et al*[2] successfully used ^{90}Y labeled microspheres (diameter 45–75 mm) in radio embolization of the spleen. In patients with severe thrombocytopenia attributable to congestive hypersplensim the necessary therapeutic dose was estimated to be 100 Gy and a computer tomography (CT) study was performed after radio embolization. It was found that the splenic volume decreased from 1400 to 470 cm^3 and the platelet count increased to almost normal levels. The treatment showed no evidence of any complications so intraarterial radioembolization with 90Y resin microspheres was clinically effective and well tolerated in hypersplenism.

4.1.6 Treatment of rheumatoid arthritis

Radioisotope synovectomy (Synoviorthesis) is a noninvasive used for the treatment of rheumatoid arthritis. Radioisotope synovectomy constitutes an effective alternative to operative therapy. Advantages of radioisotope synovectomy include a simple technique, decreased or no hospitalization, lower costs, early and easier mobilization of the patients, reliable results and free of side effects. Radioisotope synovectomy involves the intraarticular injection of a radionuclide to alter or ablate the inflammed synovium. The treatment controls the synovial inflammation and maintains joint function. Upon administration, microspheres get uniformly distributed along the synovial membrane and emit beta radiation to fully irradiate the membrane while sparing the more distant joint structures [7]. Mumper *et al*[24] investigated poly-L-lactic acid (PLA) microspheres containing neutron activated 166Ho as potential agents for radionuclide synovectomy. In vivo retention studies were conducted by administering

irradiated ^{166}Ho polylactic acid microspheres into the joint space of normal rabbits (n ¼ 6). Biodistribution data for ^{166}Ho was acquired by killing the rabbits 44 h (n ¼ 1) or 120 h (n ¼ 5) after administration of polylactic acid microspheres. It appeared that the majority of ^{166}Ho leaching occurred from the joint in the first 44 h after administration. However no ^{166}Ho activity was observed in the feces or lymph nodes after 120 h. The maximum soft tissue penetration of a beta particle emitted from ^{166}Ho is 8.4 mm. This appears ideal for the treatment of an inflamed knee synovium, which may become 1–7 mm thick depending on the severity of the disease. Thus the potential use of ^{166}Ho in rheumatoid arthritis is very promising. In 1998, Wang *et al* administered ^{188}Re microspheres via intra-articular injection in rabbits with antigen induced arthritis. A bio distribution study was carried out. The study revealed that leakage of the radiotracer from the knee was negligible. Ultimately ^{188}Re microspheres proved to be effective radiopharmaceuticals for radiation synovectomy. Recently Wang *et al* conducted the histologic study to assess the effect of radiation synovectomy on synovium and articular cartilage. ^{188}Re microspheres were administered into the knee joints of rabbits via intra-articular injection. This resulted in mild reactive inflammation and thrombotic occlusion of vessels which subsided rapidly. After 12 weeks of injection, sclerosis of the sub synovium was studied. There was no significant difference in the articular pattern after injection of 0.3 or 0.6 mCi ^{188}Re microspheres. It was reported that a treatment dose of ^{188}Re microspheres caused transient inflammation of the synovium without causing any detectable damage to the articular cartilage of knee joint. The selection of the radioisotope depends upon the size of the joint. Usually ^{90}Y and ^{188}Re are used for knee and shoulder, ^{186}Re for finger or elbow etc. The traditionally used radiation colloids were not ideal since their large size distribution led to radiation leakage from the joint leading to toxicity problems. The agents for potential use in radiation synovectomy are ^{90}Y glass microspheres, ^{166}Ho polylactic acid microspheres, ^{188}Re human skin albumin microspheres.

4.1.7 Selective internal radiation therapy (SIRT) [24-27]

A new approach regarding the use of radioactive microspheres in the treatment of liver tumors and cancer is selective internal radiation therapy (SIRT). SIRT is another means of attack in the battle against liver cancer. SIRT is a treatment for both hepatocellular carcinoma and colorectal liver metastasis. It involves the delivery of millions of microscopic radioactive microspheres containing ^{90}Y directly to the liver tumor. The targeted nature of SIRT enables the delivery of up to 40 times more radiation than would be possible using conventional radiotherapy. In Australia, approximately 200 patients have been treated in various phase I and phase II trials with SIRT. A phase III trial in Perth compared the treatment with fluorodeoxyuridine (FUDR) hepatic artery chemotherapy as the control group against the same chemotherapy plus SIRT. The patients who received SIRT had a better outcome than those treated with chemotherapy alone. Patients treated with SIRT showed an increase of 2 years in survival time from 26% to 39% and an increase of 3 years in survival time from 6% to 17%. SIRT targets a very high radiation dose to tissue in close contact with microspheres, but this diminishes rapidly with distance away from the microspheres. Thus the area close to the microspheres is highly effected while areas distant from the microspheres are spared. This is in contrast to the delivery of radiation to a tumor by external beam therapy where the prescribed dose is delivered evenly to every element of the target tissue. Thus SIRT causes harm only to the tumorous cells and is sparing the healthy hepatic cells [4]. By selective internal radiation therapy, established liver cancer can be effectively treated by the use of intrahepatic articular injection of 90Y resin microspheres. 25 out of 25 patients treated by Grady in 1979 showed good results thus leading to the prolongation of their life. For adjuvant therapy of colon cancer internal radiation therapy of the liver was done with phosphorous-32 colloid. 4 patients with colon cancer were selected. Out of 4 patients 3 did well without significant side effects and no evidence of liver cancer was found after 2 years. The fourth one died of brain metastases but having reduced liver cancer. Side effects of SIRT include post procedural fever, abdominal pain, radiation hepatitis and peptic ulcer. Recently in 2001, Stubbs *et al*. treated 50 patients with advanced, nonresectable colorectal liver metastases and a median age of 61.5 years with SIRT. A titrated single dose of 2.0–3.0 of ^{90}Y microspheres was injected into the hepatic artery. This was followed by regional chemotherapy with 5-fluorouracil at four weekly intervals for four days by continuous infusion. Responses to SIRT were assessed by falling tumour markers CEA (Carcinoembryonic antigen) and by CT (computer tomography) scans. Tumour marker data suggested that there was a destruction of liver tumour in 90% of the patients by a single treatment with SIRT. Thus it was concluded that selective internal radiation therapy was well tolerated though accompanied by liver pain and nausea. There was no treatment related mortality in the patients.

5. Future prospects [24-27]

For radioactive microspheres more exhaustive search is required for the materials which are more biocompatible and biodegradable after the delivery of radioisotopes. The labeling methods are to be improved so that highly stable radio labeled microspheres can be

produced in a single, short step using a simple radio labeling kit. There is a need for the preparation of more homogenous, monosized microspheres that will allow for better and more reliable bio distribution results. The advances in molecular biology and engineering are required for the design of very selective and site specific therapeutic microspheres. Direct intra tumoral injection of radio labeled microspheres is a sound technique in terms of localization of the radiation dose, but the technique still needs further evaluation, particularly in terms of the safety of both the patient and the operating staff. Internal radiation therapy is likely to play a substantial role in the control of hepatic cancer in the near future.

6. Conclusions

Internal radionuclide therapy using radioactive microspheres plays a substantial role in the control of hepatic and other types of cancers. Radioactive microspheres are very stable and have a proven efficacy in the field of treatment of diseases especially cancer. Radioactive microspheres are an ideal tool for the treatment of diseases like rheumatoid arthritis, spleen tumors etc. Radioactive microspheres are able to deliver high concentrations of radioactivity to the target area without damaging normal surrounding tissue. Improvements in radio labeling techniques have resulted in increasingly stable microspheres with a leakage of less than 0.1% of the activity. This is the major reason of their gaining popularity in therapeutic applications. These radiolabeled microspheres serve as one of the future materials in the battle against cancer and tumors. Acknowledgements: We are grateful to University Grants Commission for providing us financial assistance.

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