Radioisotopic Pulmonary Lobectomy: Feasibility Study in Dogs

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In search for an alternate treatment for inoperable cancer of the lung in humans, we investigated the possibility that introduction of radioactive material into a selected lobe of the canine lung would effectively destroy that lobe without systemic effects or radiation injury to adjacent organs. Ten million ion exchange microspheres labeled with 740 MBq of phosphorus-32 (^{32}P) were injected through a catheter placed in a selected lobar branch of a pulmonary artery in 12 anesthetized dogs. Six additional dogs served as controls and received 10 million microspheres not labeled with ^{32}P. Organs were harvested from 1 wk to 12 mo after injection and examined grossly and histologically. There was progressive organization and contraction of each necrosed ^{32}P treated lobe which was reduced to a scarred remnant by 12 mo, whereas only minimal inflammatory changes occurred in controls. Of the ^{32}P injected dose, 94% remained in injected lobe, 4%–5% in nontargeted lobes and <0.08% in blood. Radioactivity in liver, kidneys, spleen, heart, and bone marrow was <0.1% for each organ. Thus, large doses of radiation in the order of 1,500 Gy can be effectively delivered to a selected lobe to produce a "radioisotopic pulmonary lobectomy."

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Internally administered radiopharmaceuticals for treatment of neoplasias, as pointed out by Beierwaltes, offer the potential to outmode present approaches of conventional radiation therapy and chemotherapy because of three characteristics (*1,2*):

1. Radiopharmaceuticals may selectively irradiate target tissues in a single administration with a radiation dose which is 20–30 times larger than that of conventional radiation therapy.
2. Therapeutic use of radiopharmaceuticals is followed by a lower incidence of leukemia, second cancers, and generalized reactions.
3. Treatment is comparatively noninvasive and nontraumatic.

Although surgical removal is the preferred treatment for cancer of the lung, many patients when first seen are beyond the operative stage or have superimposed conditions which make them inoperable or high risk cases. Statistical surveys reveal that surgery is possible in only one-fourth of the cases of all diagnosed pulmonary cancers.

External radiation therapy is limited by the effects of transit radiation on pulmonary and cardiac tissues. High doses cause radiation sickness, a further deterrent to its use in debilitated patients.

Chemotherapy, although of some value in temporarily arresting the disease, is accompanied by drastic side effects.

Many patients with *localized cancer of the lung* have severe *emphysema* and *cardiac disease*, which contraindicate any pulmonary resection. With the aim of establishing a treatment for these patients, we have done experimental work on a method of delivering high-energy beta radiation selectively to a localized portion of the lung without significant damage to adjacent tissues and without generalized radiation sickness.

The radionuclide phosphorous-32 (^{32}P) was selected because of its advantageous physical properties. The maximum energy of a ^{32}P beta particle is 1.71 MeV, resulting in a maximum range in tissue of 8 mm. The average range is 2 mm; thus, the range is short enough to minimize unwanted irradiation to sensitive adjacent organs. Radiation hazards to attending personnel are likewise minimized. Finally, ^{32}P is readily available world-wide at low cost.

MATERIALS AND METHODS

Dogs of mixed breed and either sex of ~20–30 kg in size were obtained, examined, immunized, and dewormed by the staff veterinarian and then quarantined for 3 wk after arrival at our animal research facility. They were housed in individual runs and humanely treated according to AAALAC (American Association for Accreditation of Laboratory Animal Care) standards.

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The two main variables involved in this approach are the dose of radioactivity and the number of microspheres to be administered. After some theoretical considerations supported by pilot experiments, we decided to standardize the methodology to be described herein on the basis of a dose of 740 MBq (20 mCi) ^{32}P-labeled to 10 million ion exchange resin microspheres. The choice of 740 MBq ^{32}P dose was motivated by Beierwaltes' first characteristic (*1,2*) on the desirability of irradiating tumors with doses 20–30 times larger than those in conventional radiotherapy. Since a conventional radiotherapeutic dose is 60 Gy (6,000 rad), 20–30 times this dose amounts to 1,200–1,800 Gy (120,000–180,000 rad). By working backwards on the MIRD system calculations (*3*), we arrived at the dose of 740 MBq. On the other hand, since good geographic lobar distribution was obtained with 10 and 1 million microspheres in pilot experiments, we decided to use 10 million microspheres in order to make the experimental conditions more stringent.

To establish feasibility for this study, 18 animals were utilized: 12 dogs were treated with 10 million ^{32}P-labeled microspheres. Six dogs served as controls and were treated with 10 million microspheres not labeled with ^{32}P, henceforth referred to as "non-^{32}P-microspheres."

Administration of Phosphorus-32-Microspheres

On the day the microspheres were administered, the dogs were anesthetized with an intravenous (i.v.) injection of sodium pentobarbital (25 mg/kg) and treated prophylactically with a broad spectrum antibiotic. Chest radiographs and lung perfusion scintigraphs (technetium-99m-macroaggregated albumin) had been obtained as baselines a few days earlier. An occlusion balloon catheter (size 7F, double lumen) was introduced via the jugular vein under fluoroscopic guidance into a preselected lobar branch of the right or left pulmonary artery. The balloon was radiographically delineated by filling it with radiopaque contrast medium; then the pulmonary lobe was visualized by injecting 3 ml of a contrast medium (Renographin 76). Another chest radiograph was then obtained.

Immediately thereafter, 10 million ion exchange resin microspheres (diameter 53–63 μm) labeled with ~740 MBq (20 mCi) ^{32}P mixed with 1 million microspheres labeled with ~185 MBq (5 mCi) ^{99m}Tc for scintigraphy were delivered into the preselected pulmonary lobe with the aid of the device shown in Figure 1. This device was connected to a catheter placed into the pulmonary artery branch. The radioactive microspheres were suspended in physiologic saline solution by continuous magnetic stirring and were delivered into the pulmonary lobe by a saline flush. More than 90% of the microspheres inside the 10-ml vial shielded by lead glass was flushed out with 50 ml saline. Additional flushing saline solution up to a total of 150 ml was used to maximize the number of microspheres transferred. The balloon was then deflated, the catheter removed, and pulmonary scintigraphs were obtained with a gamma camera shortly afterwards and subsequently at weekly, and later monthly, intervals.

Control animals were subjected to exactly the same procedure as the treated group except that the 10 million microspheres were not labeled with ^{32}P.

Images of 300,000 counts each were obtained for both ^{99m}Tc and ^{32}P scintigraphs by using a Pho/Gamma V scintillation camera (Searle Radiographics, Des Plaines, IL) with a low-energy DIVCON collimator in the diverging mode except

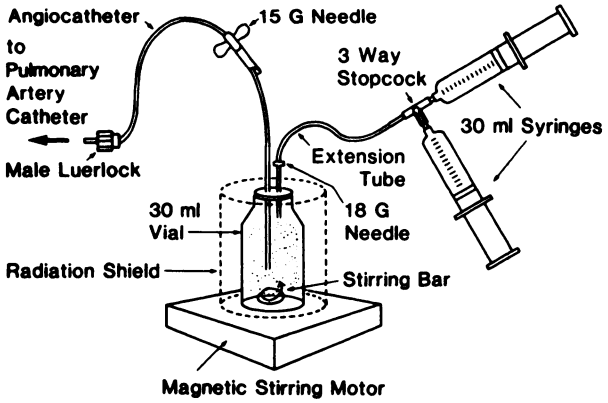

FIGURE 1
Delivery system. Suspended microspheres inside a vial shielded with lead glass are flushed with saline through an angio-catheter into the targeted region of the lung via the selected branch of a pulmonary artery.

for the 25,000 count images of ^{32}P Bremsstrahlung obtained at 2 mo after injection. A 20% energy window (FWHM) setting was used for ^{99m}Tc imaging and a 40% window for ^{32}P Bremsstrahlung.

Prior to and throughout the experimental period, blood samples were obtained for analyses consisting of RBC, Hgb, PCV, MCV, WBC differential count, serum glucose, sodium, potassium, chloride, BUN, creatinine, BUN/creatinine ratio, calcium, cholesterol, total protein, albumin, globulin, direct bilirubin, alkaline phosphatase, g-glutamyl transpeptidase, transaminase-SGO, LDH, uric acid, and total bilirubin (VetPath, Rancho Cucamonga, CA).

Additionally, blood samples were analyzed for radioactivity by counting 3 ml of blood in a deep well gamma counter for 1 min as described below.

Following an anesthetic overdose, organs (all pulmonary lobes, heart, aorta, esophagus, spleen, liver, kidneys, and bone marrow) were harvested at periods ranging from 1 wk to 1 yr after intrapulmonary administration of microspheres. These organs were studied by gross pathology and microscopic histologic examinations. Specimens from the excised organs were placed in vials and weighed on a laboratory balance; their Bremsstrahlung radiation was counted in a deep well gamma counter (Beckman 4000, Irvine, CA) with a wide-open energy spectrum window and compared to a ^{32}P standard of similar geometry.

Microsphere Type and Size

The types of microspheres used were analytical grade cation exchange resin (AG 50W × 12, minus 400 mesh hydrogen form) for ^{32}P labeling and analytical grade anion exchange resin (AG 1 × 8, minus 400 mesh, chloride form) for ^{99m}Tc labeling. Resin beads were separated into narrow particle size ranges by a combination of wet and dry sieving through Standard Testing Sieves and differential sedimentation. This separation process was monitored by optical microscopic analysis of samples placed into a hemacytometer counting chamber until the desired size 53–63 μm was reached.

The detailed radiochemical preparation of the ^{32}P-labeled microspheres is described elsewhere (*4*). Basically, they were labeled with ^{32}P-phosphate by exchange at pH 2–4 and con-

version to a stable product at pH 9. Quality control testing of chemical stability and biologic behavior of these microspheres suspended in physiologic saline solution established their stability (*4*). Chemical synthesis operations were conducted with emphasis on pharmaceutical purity (sterility and apyrogenicity) and radiation safety.

Dosimetry

In calculating the absorbed dose it was assumed:

1. Uniform distribution of ^{32}P-microspheres within the preselected lobe.
2. No biologic elimination (the effective half-life is equal to the physical half-life).
3. The range of beta particles in lung tissue is very short (a few millimeters), so that beta particles impart their energy essentially at the point of emission.
4. A small fraction of the beta particle energy converted into Bremsstrahlung x-ray (<1%) was ignored and not included in the calculations.

The following data and nuclear parameters from Medical Internal Radiation Dose (MIRD) Pamphlet No. 10 were used in dosimetry calculations (*3*):

Decay mode = beta minus
Half-life = 14.3 days = 343 hr
Mean number/disintegration, $n_i = 1.000$
Mean energy/particle, $E_i = 0.695$ MeV
Equilibrium dose constant, i = 1.480 (g.rad/μCi·hr)
Cummulated activity (A) = 1.44 $A_o T_{eff}$ = 1.44 $A_o T_p$.

RESULTS

Tolerance of the Procedure

One dog in the control group did not recover from initial anesthesia. Three animals in the ^{32}P-treated group died during the night at 37, 57, and 62 days after injection; although postmortem examination was done in each instance, no apparent cause of death was found. There were several pleural adhesions in the targeted lobe of two animals (37 and 62 days) with one (62 days) having a yellowish pleural effusion on the targeted side. However, another animal which survived without apparent ill effects until killed at 120 days also developed a pleural adhesion of the targeted lobe.

Intermittent coughing beginning three to nine days was noted in six dogs (two having slightly hemoptic saliva) for up to 11 days after the procedure using ^{32}P. In all six dogs that developed a cough, the catheter had been left in place for 1 hr after injection of the radioactive microspheres before deflating and removing the balloon. No cough developed in five animals when the balloon was deflated and removed within 5 min of injection and in another dog where the catheter was left in place for 1 hr. Otherwise, the procedure was well tolerated with the animals appearing normal in all respects.

The proven fertility of one dog, through a fortuitous pregnancy with subsequent delivery of a litter before any experimental intervention had begun, prompted us intentionally to breed her at 5 mo after the intrapulmonary injection of ^{32}P-labeled microspheres. The pregnancy was borne without any observable difficulty and, in the seventh month after the ^{32}P administration, she delivered a healthy litter at term. Indirectly, this episode corroborates the general tolerance of the procedure.

No changes were noted in blood cell counts and biochemical analyses in animals treated with ^{32}P-labeled microspheres or in control animals.

Biodistribution of Radioactivity

Levels of ^{32}P were determined in blood and several organs at various intervals after administration of ^{32}P-labeled microspheres. Results of these biodistribution studies can be summarized as follows:

1. More than 94% of injected radioactivity remained in the targeted lobe of the lungs.
2. Approximately 4%–5% of injected radioactivity was found in the other lobes of the lungs combined.
3. The level of radioactivity in the blood determined serially for up to 70 days after injection averaged 0.08% of the administered dose (Fig. 2).
4. The amount of radioactivity in liver, kidneys, spleen, heart, and bone marrow was <0.1% of the injected amount for each organ and <0.5% when all these organs were combined.

Using the MIRD system as detailed in the Materials and Methods section and related references (*3,5–8*), the radiation absorbed in the injected lobe was calculated to be ~1,500 Gy.

Pulmonary Images

A scintigraph of the injected lobe with ^{32}P and ^{99m}Tc-labeled microspheres (^{99m}Tc only for control animals)

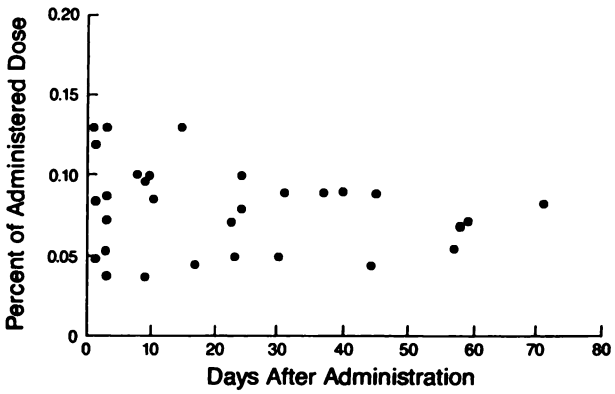

FIGURE 2
Administered dose of ^{32}P averages <0.08% in canine blood. All data points are corrected for decay.

was routinely obtained immediately after the injection procedure. Several lung perfusion scintigraphs with ^{99m}Tc-macroaggregated albumin (MAA) were obtained shortly before the procedure and periodically until the animals were killed. Generally speaking, by the third or fourth week after being injected with ^{32}P-labeled microspheres, the lobe was not perfused. However, for up to 10 wk it was possible to obtain images of the treated lobe from ^{32}P Bremsstrahlung radiation after sufficiently long exposures under the gamma camera.

In Figure 3 some illustrative images obtained at relevant periods show the targeted right lower lobe depicted in the pulmonary angiogram (E) to be well perfused with the rest of the lung prior to treatment (A). It also is visualized with ^{32}P and ^{99m}Tc-labeled microspheres immediately after treatment (B) and with ^{32}P-labeled microspheres at 3 days (F) and 2 mo (G) after treatment.

This lobe was not perfused at 6 mo (C) but at 1 yr some activity was present at its site (D) subsequent to reexpansion of other lobes as seen at the time of necropsy.

Controls typically show that the well-perfused targeted lobe (H) after injection of non-^{32}P microspheres and ^{99m}Tc-labeled microspheres (I) remains as well perfused at 2 mo (J) and at 1 yr (K).

Morphologic Changes in the Pulmonary Lobe Treated with ^{32}P-Labeled Microspheres

Gross Pathology. Changes in the pulmonary lobe following the injection of ^{32}P-labeled microspheres into a lobar branch of a pulmonary artery were studied by serial harvesting of 12 experimental dogs for a period of up to one year.

Early lesions in the injected lobe at 1 wk consisted of red-purple zones of hemorrhagic infarction which at 2 wk had become mottled with pale and hemorrhagic areas. At 1 mo, the infarcted zones were mottled with a central brown area and a peripheral area of pallor representing extensive necrosis. There was a thick fibrinous exudate on the visceral pleural surface. By 2 mo, the necrotic zones blended uniformly throughout the injected lobe which also became contracted.

At later stages, the contraction process continued with the necrotic zones becoming more solid and often densely adherent to the parietal pleura. At 12 mo, the injected lobe had contracted to a rounded dense scar which represented the end stage of the reparative process without outwardly recognizable lung tissue remaining (Fig. 4). Because of this dramatic shrinkage of the treated lobe, we have named this procedure *radioisotopic pulmonary lobectomy.*

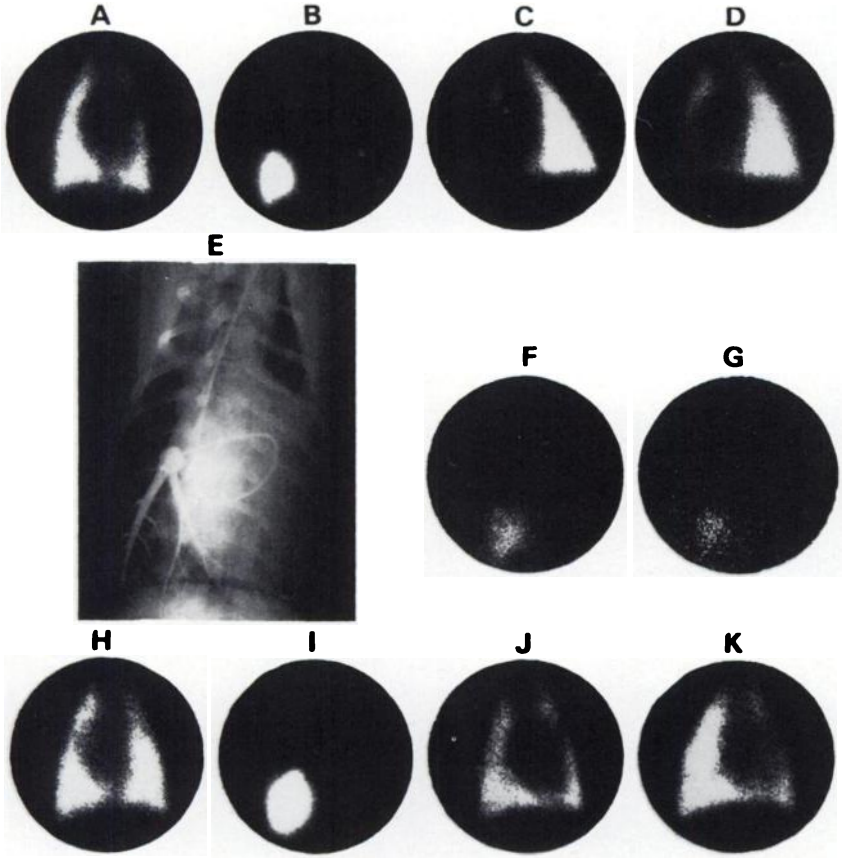

FIGURE 3
Pulmonary images: A–G are of a dog injected with ^{32}P and ^{99m}Tc-labeled microspheres into the right lower lobe; H–K are of control dog injected with non-^{32}P microspheres and ^{99m}Tc-labeled microspheres also into the right lower lobe. All scintigrams are in the anterior projection. (A) Standard ^{99m}Tc-MAA pulmonary perfusion obtained as a baseline prior to the treatment procedure. (B) Image of right lower lobe immediately after intrapulmonary injection of ^{32}P and ^{99m}Tc-labeled microspheres. (C) Standard ^{99m}Tc-macroaggregate perfusion at 6 mo after treatment. (D) Same as (C) at 1 yr. (E) Contrast media angiogram in anteroposterior view delineating the targeted right lower lobe prior to injection of microspheres. (F) Bremsstrahlung image at 3 days post-treatment with ^{32}P. (G) Same as (F) at 2 mo. (H) Standard ^{99m}Tc-MAA pulmonary perfusion obtained as a baseline prior to control procedure. (I) Image of right lower lobe immediately after intrapulmonary injection of non-^{32}P-microspheres and ^{99m}Tc-labeled microspheres. (J) Standard ^{99m}Tc-MAA perfusion at 3 mo after procedure. (K) Same as (J) at 1 yr.

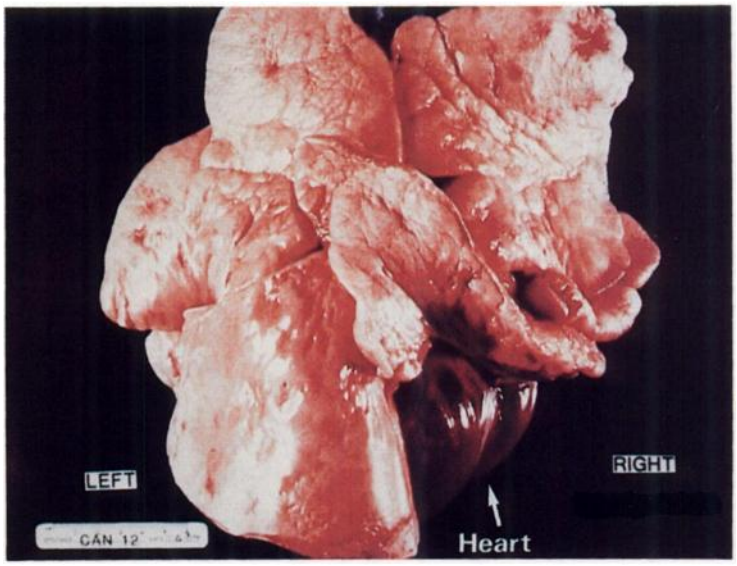

FIGURE 4
Radioisotopic pulmonary lobectomy in a dog. Posterior view of en bloc dissection of lungs and mediastinum 12 mo after administration of 740 MBq of ^{32}P-labeled microspheres into the right lower lobe via a pulmonary artery branch. The so-called "accessory" lobe in the canine right lung has been lifted to show absence of right lower lobe underneath it. The entire *right lower lobe* has been reduced to a nubbin-like structure of solid connective tissue. Absence of this lobe can be more readily appreciated by comparison with Figure 6 where all four lobes of the canine right lung are easily identified.

Microscopic Examination. One week after injection of ^{32}P-labeled microspheres the tissue sections showed intense hemorrhage, extensive coagulative necrosis, and some areas with many inflammatory cells. At 2 wk, massive necrosis and intra-alveolar inflammation were the most prominent changes.

At 2 mo, there was early organization with collagenization and infiltration of the necrotic tissue by macrophages mostly at the periphery of the lesions. At 4 mo, there was extensive fibrosis throughout the necrotized lobe, but the central portion still showed large areas of coagulative necrosis. Occasionally, fine bronchi were seen which had lost support from surrounding tissues and were in early stages of architectural collapse.

At 12 mo, mature organization was dominant. Dense collagen tissue had replaced all necrotic tissue especially where earlier there were large cavities filled with necrotic ghost cells composed of dense collagen (Fig. 5).

At the early stages (up to 2 mo) of examination, microspheres were easily visualized and always located within the lumina of fine arterial branches, arterioles or capillaries. At later stages, after necrosis and during the organizational phase, microspheres were visualized as embedded in collagenous scars.

Morphologic Changes in the Pulmonary Lobe Treated with Non-^{32}P-Microspheres

Gross Pathology. By 3 wk, there was only a slight darkening of the overlying pleura without increase in the hardness of the lung tissue. Cross-sectioned surfaces showed some punctate hemorrhage only. No infarct or gross subcapsular hemorrhages were present. At 3 mo, a slight grayish discoloration was noted in a small area on the periphery of the lobe. There was neither shrinkage nor hardening of the lobe at 12 mo (Fig. 6).

Microscopic Examination. Sections of lungs injected with nonradioactive microspheres showed very little tissue reaction. Pulmonary architecture was unaltered. Changes noted were those associated with tissue reaction to foreign bodies: occasional perivascular congestion and mild round cell infiltrates (Fig. 7).

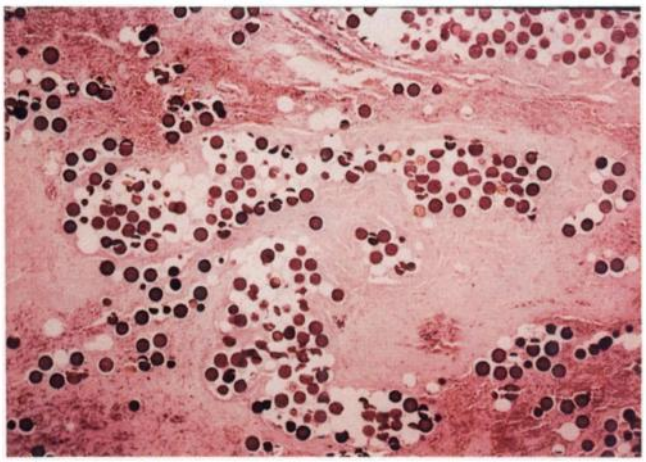

FIGURE 5
Histologic section from right lower lobe remnant shown in Figure 4. Note very dense fibrosis and scarification surrounding the microspheres 12 mo after administration of 740 MBq of ^{32}P-labeled microspheres. Compare with Figure 7.

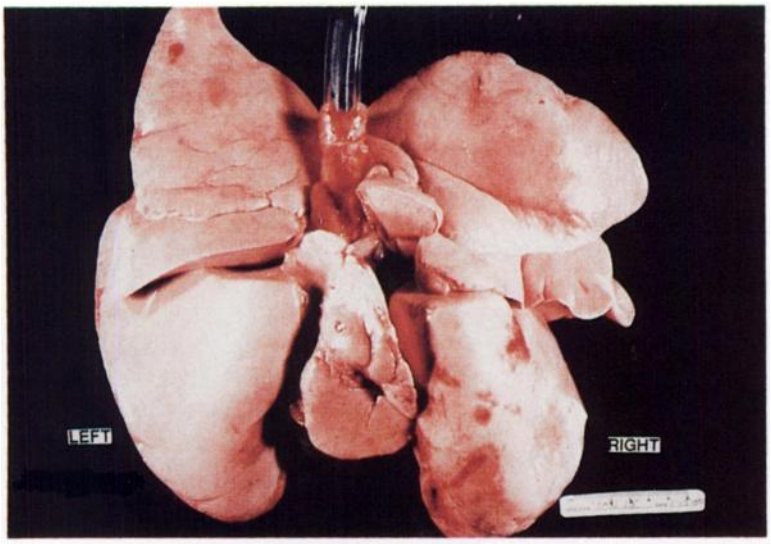

FIGURE 6
Results of injecting non-^{32}P-microspheres into the *right lower lobe* of a dog via a pulmonary artery branch. Posterior view of en bloc dissection of lungs and mediastinum at 12 mo. Some mildly hemorrhagic surface portions on this lobe reflect traumatic injury during excision of the lung at necropsy. The rather medially located structure is the so-called "accessory" lobe of the canine right lung, which here is lying in its anatomical position.

Morphology of Vicinal Organs

Aorta, heart (with pericardium), esophagus, kidneys, spleen, bone marrow (from a vertebra near the targeted pulmonary lung), and nontargeted pulmonary lobes revealed no discernible change at gross examination. Specimens of each organ were obtained from the region closest to the treated lobe. In no case was any abnormality detected at microscopic histologic examination.

DISCUSSION

Results show that large doses of radiation in the order of 1,500 Gy (150,000 rad) can be delivered selectively to destroy a pulmonary lobe (and probably as little as a pulmonary segment with more selective angiographic placement) without damage to the rest of the lungs and other organs, and without systemic leakage of radioactivity. This procedure may be applicable to certain clinical situations to destroy inoperable cancer of the lung and other organs.

Although sporadic attempts were made previously to use radioactive particles for radiation therapy of well delineated regions of the body (*9–13*), several factors hindered the development of this methodology, i.e., *ceramic* microspheres of yttrium-90 (^{90}Y) although chemically stable in vivo are dense (spec. grav. 3) and, therefore, difficult to administer; on the other hand, *ion exchange resin* microspheres labeled with ^{90}Y, although of appropriate specific gravity (ca. 1), proved to be unstable in vivo. In the present study, the minimal levels of radioactivity found in blood indicate that the bond between ^{32}P atoms (or phosphate molecules) and microspheres is very stable in vivo. Stability in vitro had been demonstrated earlier (*4*).

Furthermore, intra-arterial delivery of radioactive microspheres should be evaluated for use in inoperable cancers of the lung on which, by their location and degree of vascularization, the proposed therapy may have a reasonable probability of success. It should not be used as a heroic treatment offered just before the patient dies as was done in some of the earlier attempts by other workers.

Extrapolation to Clinical Situations

Although it might be argued that our animal model involves a healthy lung whereas our objective is to destroy a tumor within a lobe, several considerations

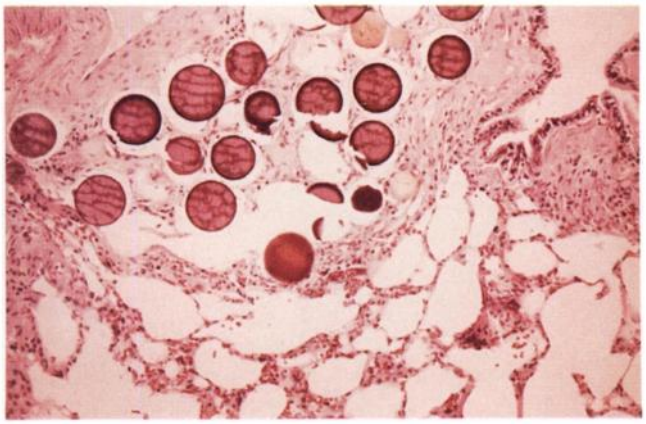

FIGURE 7
Histologic section from right lower lobe specimen shown in Figure 6. Note microspheres surrounded by well-preserved alveoli with slight inflammatory cellular infiltrate.

should be taken into account:

1. It is well established that cancerous cells have a D_0 (an estimate of cell sensitivity to radiation) at least in the same range as normal cells (*14*).
2. That tumors may obtain blood supply from bronchial arteries rather than branches of the pulmonary arteries is not per se an obstacle to the reported methodology. This should facilitate destruction of the tumor because oxygenated tissues are more radio-sensitive than ischemic tissues.

   Since the architecture of the lung is such that all vascular components are in close proximity to each other and our effective radiation doses are high, there is very little chance for any cells in a lung lobe to survive regardless of whether their blood supply is through bronchial or pulmonary arteries.
3. Large unresectable adrenal medullary tumors (up to 8 × 11 × 11 cm) were successfully treated by i.v. injection of ^{131}I-labeled metaiodobenzylguanidine, which concentrates in adrenomedullary tissue (*2*). In our application, the concentration of therapeutic microspheres in pulmonary tissue would be achieved by mechanical trapping of the microspheres in the arteriolar bed of the catheterized lung lobe containing the cancer. The end result is to be the same: massive destruction of the targeted tissue.
4. That a few dogs died spontaneously does not appear a serious impediment to translating carefully the procedure to the clinical field because: (a) the deaths occurred in the early animals when the procedure was still being refined; (b) the catheter had been left with the balloon inflated inside a pulmonary artery branch for 1 hr after injecting the microspheres; (c) although utmost attempts were made to maximize the care given to the dogs under study, there are many aspects of clinical medical care (electrocardiograms, computerized tomography, examinations by specialists, narration of symptoms, social services, etc.), which are generally not available in the experimental situation but are standard in its clinical counterpart. It should be noted that the main objective of the reported work was to establish the feasibility of the procedure.

Aside from inferences regarding clinical extrapolation, it can be concluded that large doses of radiation (1,500 Gy) can be delivered selectively to destroy a pulmonary lobe without damage to vicinal organs or systemic leakage of radioactivity. This procedure appears ready to be tried clinically to attempt the destruction of inoperable cancer of the lung and other organs.

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