MDS Nordion

NUCLEAR MEDICINE
KANATA OPERATIONS
INVESTIGATION STUDY

PD99099003.08

Investigation Study Radiation Profile on a 20 GBq TheraSphere Dose Vial

Signatures

Prepared by: _____ Date: 99.12.24

Approved by: _____ Date: 24-Dec-99
(Richard Decaire C.H.P.)

Document History

Date	Version	Comments	Prepared by	Reviewed by	Approved by

1. INTRODUCTION

The United States Nuclear Regulatory Commission had requested information to support MDS Nordion application for the registration of TheraSphere. This request is contained in a letter dated November 23, 1999 from a Dr John P. Jankovich. This report contains data collected to address question 7 parts a, b, and c.

The question poised is as follows:

"Regarding external radiation levels, NRC needs information on the device itself, not on the radiation levels around the patient as addressed in the application. Therefore, please specify:

a. External radiation levels around the lucite vial containing the maximum dose of 20 GBq (540 mCi). Provide the data, preferably, at the surface, and at 5, 30, and 100 cm. If there are no meaningful readings at these locations, please state so.

b. Provide similar external radiation levels, if any, outside the lead pot with the lucite vial inside containing a maximum dose of microspheres.

c. Please specify the instrument which you used to perform the radiation profile measurements by listing the instrument manufacturers, model numbers, calibration dates, sensitivity, etc."

To address these questions, information was provided from previous development work. To collect more current data, yttrium-90 chloride solution was added to a TheraSphere dose vial and radiation profiles were determined. The yttrium-90 solution was taken to dryness to represent yttrium-90 microspheres.

TheraSphere is a radioactive product used for the treatment of liver cancer. The radioactive component of TheraSphere is Yttrium-90 microspheres.

2. PURPOSE

The purpose of this investigation study is to collect data for a radiation profile of a 20 GBq TheraSphere dose vial.

3. PROCEDURE

3.1 Preparation of the TheraSphere Dose Vial

3.1.1 To a TheraSphere dose vial (990101.SPE) a total volume of 1.008 mL of a yttrium-90 chloride solution (1400 mCi in 1.56 mL calibrated to Dec 20, 1999) was added in two additions of 0.504mL. The first addition was taken to dryness prior to the second addition which was then taken to dryness.

3.1.2 The TheraSphere dose vial was then crimped sealed (aluminum seal 990102.SPE and septa 990103.SPE) and then placed into a lucite vial shield (990230.SPE). The vial shield was secured closed.

3.1.3 The configuration was then swiped for surface radioactive contamination and none was detected.

3.1.4 After the check for surface contamination, the lucite vial was placed into a F390 lead pot (990201.SPE).

3.2 Radiation Profile Measurements

3.2.1 Radiation profile measurements were performed with a variety of survey instruments to collect data to address the questions from the NRC. These reading were completed by a MDS Nordion Radiation Surveyor.

3.2.2 In all cases the activity quoted is the decay corrected activity (decay corrected to December 22, 1999 at 17:00 hours) based on the addition of 1.008 mL of a yttrium-90 chloride stock (1400 mCi in 1.56 mL calibrated to 12:00 hours on Dec 20, 1999). Therefore, the value is 515 mCi.

3.3 Data

3.3.1 **NOTE:** Background readings in the area that the measurements were performed were completed prior to the source being introduced into the area. The values were 0.1 mR/hr at 5 cm and 0.3 mR/hr at 30 cm. The higher value at the 30 cm mark was due to this area being out of the shielded area that was enclosed at the 5 cm mark. These measurements were completed using a Victoreen Model 471 survey meter.

3.3.2 The following table contains measurements completed using a Victoreen Model 471 survey meter. The Victoreen Model 471 is the standard shipping meter used at MDS Nordion and is calibrated on a monthly basis. The calibration is performed in an on-site facility, approved by the AECB. The MDS Nordion number is 6-144-282 and the calibration due date is December 25, 1999. There is no value for a measurement at the surface for this instrument as the center of the measurement chamber is about 5 cm from the surface of the lead pot and also the lucite vial.

Field Readings

Distance	Activity	Configuration of TheraSphere Dose Vial			
cm	mCi	Lucite Vial		Lucite Vial in F 390 Lead Pot	
		Value mR/hr	Time	Value mR/hr	Time
0	N.A.	N.A.	N.A.	N.A.	N.A.
5	515	300	17:02	31	16:50
30	515	22	17:02	2.2	16:50
100	515	2.3	17:02	0.7	16:50

3.3.3 The following table contains measurements completed using an Extender 2000W survey meter serial # 2808 and manufactured by WM. B. Johnson & Assoc. Montiville, N.J. This meter is calibrated on-site every six months. The MDS Nordion number is 6-144-569 and the calibration due date is May 2000. For the measurements, please note that the radius of the probe is 2 cm and therefore the suface/0 cm is really at 2 cm.

Field Readings

Distance	Activity	Configuration of TheraSphere Dose Vial			
cm	mCi	Lucite Vial		Lucite Vial in F 390 Lead Pot	
		Value mR/hr	Time	Value mR/hr	Time
0	515	810	17:06	85	16:51
5	515	230	17:05	33	16:51
30	515	20	17:05	2.7	16:51
100	515	2.2	17:05	0.6	16:51

OPERATING INSTRUCTIONS

GENERAL PURPOSE SURVEY METER

MODEL 471

Manufactured by

VICTOREEN, INC.
10101 WOODLAND AVE.
CLEVELAND, OHIO 44104

VICTOREEN

SG A Subsidiary of Sheller-Globe

010044D-1

7/85

PRINTED IN USA

Attachment 15

2 SPECIFICATIONS

Feature	Specification
Dimensions (H x W x L)	7 5/8 in. x 5 1/8 in. x 11 1/2 in. (19.4 cm x 13 cm x 29 cm)
Weight	4.9 lbs including batteries (2.2 kg)
Range	Twelve overlapping ranges: 0 to 1, 3, 10, 30, 100, 300 mR/h and R/h (rate) Six overlapping ranges: 0 to 1, 3, 10, 30, 100, 300 mR (integrate)
Radiation Detected	Alpha, beta, gamma and X-ray
Detector	Unsealed, air ionization chamber. The chamber consists of a bakelite wall, 200 mg/cm^2 and a mylar window 1.1 mg/cm^2. The volume of the chamber is 485 cc. An equilibrium cap of 300 mg/cm^2 is provided for the chamber.
Display	Meter, 3 1/8 in. (7.9 cm) scale, taut baud movement
Controls:	
• External	Function Switch: R/h, mR/h, integ. mR Range Switch: Off, batt, 300, 100, 30, 10, 3, 1 Set Zero Knob

2 SPECIFICATIONS (Cont'd)

Feature	Specification
• Internal	Calibration Adjust, Chamber Bias Test Switch, Coarse Zero Adjust
Energy Response	± 10%, 6 keV to 300 keV along chamber axis with equilibrium cap off. ± 10%, 25 keV to 2 MeV with equilibrium cap on, 2 pi solid angle.
Response Time	8 seconds on 3 mR/h range 3 seconds on 10 mR/h range 2 seconds on 30 mR/h range 1.5 seconds on 100 mR/h and 300 mR/h range
Switching Transients	Less than 8 seconds when moving Function Switch or Set Zero knob. No transients on other controls.
Batteries	Two 1.5 V D-cells and four 22.5 V AA Eveready #505 batteries
Battery Life:	
• D-cells, mR/h range	150 hours at 24 hours/day 210 hours at 8 hours/day
• D-cells, R/h range	85 hours at 24 hours/day 120 hours at 8 hours/day
• 22.5 V Battery	Approximately one year
Zero Adjust	Can be properly adjusted in a radiation field.

Feature	Specification
Warm-Up Time	Less than 1 minute
Environmental Effects:	
• Temperature Range	-29°F to +120°F (-34°C to +49°C)
• Humidity Range	0 to 95% noncondensing. Pressure dependent due to detector being unsealed air ionization chamber.
• Geotropism	Negligible, less than two minor divisions on meter scale.
Response to Other Radiation:	
• Minimum Energy to Penetrate Chamber	Alpha 3.5 MeV Beta 70 keV
• Zero Drift with Temperature	6% per 10°C on 3 mR/h and 3 R/h range; 2% per 10°C on 10 mR/h and 10 R/h range; 0.6% per 10°C on 30 mR/h range and 30 R/h range. Can be completely eliminated by rezeroing.
Collection Efficiency	See Figure 2

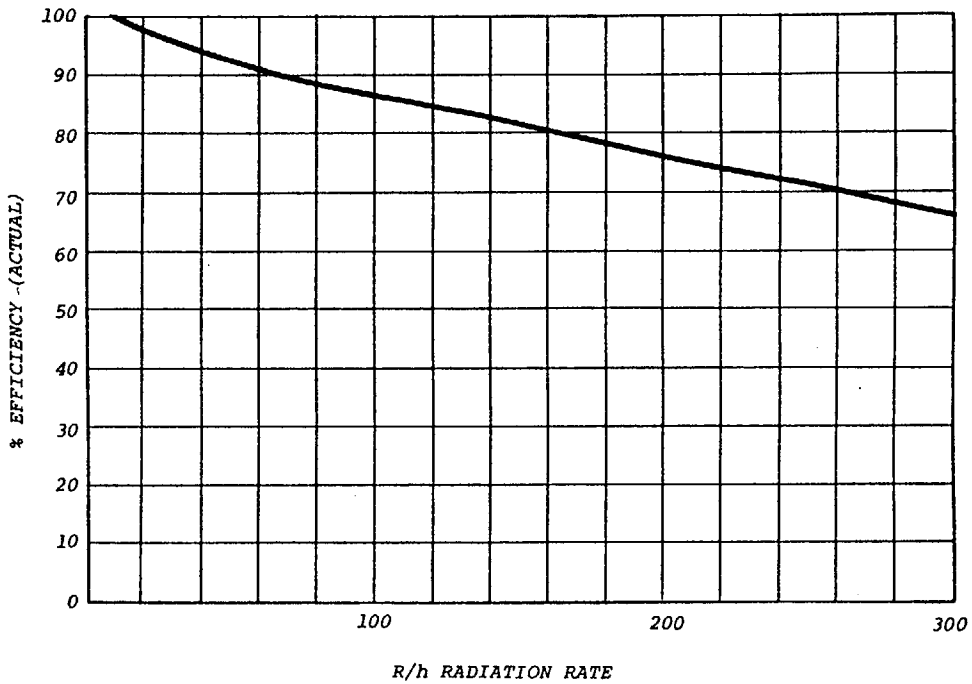

Figure 2. Collection Efficiency Graph

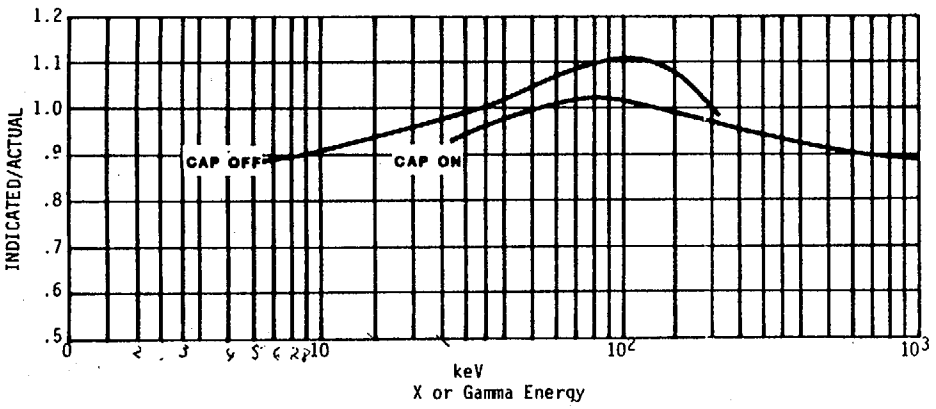

Figure 4. Energy Response Curve

4.3 Directional Dependence - The shape, wall material, center electrode design, and position of the ion chamber in the Model 471 results in an instrument response relatively independent of the direction of the incident radiation. Figure 5 gives the relative angular response of the Model 471 with the equilibrium cap on at 1.3 MeV (^{60}Co), 120 keV, and 40 keV effective.

4.4 Source Distance - If a point source or a collimated beam is used, the 471 chamber must be far enough from the source so that the entire ion chamber is uniformly exposed. In practice this means any point source should be at least one meter from the ion chamber. The center of volume of the chamber is 4.3 cm from the end (Figure 6).

4.5 Calibration Procedure

1. Set the 471 to the 300 mR/h range and zero it.

2. Place the ion chamber in a 100 mR/h field and adjust the calibration potentiometer for the correct reading. Use the equilibrium cap if the effective energy of the source is over 100 keV. Be sure to correct for temperature, pressure, and energy response.

TABLE I: AIR DENSITY CORRECTION TABLE

INCHES	Mm.	F. 60.8 C. 16	64.4 18	68.0 20	71.6 22	75.2 24	78.8 26	82.4 28	86.0 30	89.6 32	93.2 34	96.8 36	100.4 38	104.0 40
19.68	500	1.489	1.499	1.509	1.520	1.530	1.541	1.551	1.561	1.571	1.582	1.592	1.602	1.613
20.08	510	1.460	1.469	1.479	1.490	1.499	1.510	1.520	1.530	1.540	1.551	1.561	1.571	1.581
20.47	520	1.431	1.441	1.451	1.461	1.471	1.481	1.491	1.500	1.510	1.520	1.530	1.540	1.550
20.87	530	1.405	1.414	1.424	1.434	1.444	1.453	1.463	1.473	1.482	1.492	1.502	1.512	1.521
21.26	540	1.378	1.388	1.397	1.407	1.416	1.426	1.435	1.445	1.454	1.464	1.474	1.483	1.493
21.65	550	1.354	1.363	1.373	1.382	1.391	1.401	1.410	1.419	1.429	1.438	1.448	1.457	1.466
22.05	560	1.329	1.338	1.348	1.357	1.366	1.375	1.384	1.394	1.403	1.412	1.421	1.431	1.439
22.44	570	1.306	1.315	1.324	1.333	1.342	1.351	1.360	1.369	1.378	1.387	1.396	1.405	1.414
22.83	580	1.283	1.292	1.301	1.310	1.319	1.328	1.337	1.345	1.354	1.363	1.372	1.381	1.389
23.23	590	1.262	1.270	1.279	1.288	1.297	1.305	1.314	1.323	1.331	1.340	1.349	1.358	1.366
23.62	600	1.241	1.249	1.258	1.267	1.275	1.284	1.293	1.301	1.309	1.318	1.327	1.336	1.344
24.02	610	1.220	1.229	1.237	1.246	1.254	1.263	1.271	1.279	1.288	1.297	1.305	1.314	1.322
24.41	620	1.200	1.208	1.217	1.225	1.233	1.242	1.249	1.258	1.266	1.275	1.283	1.292	1.299
24.80	630	1.181	1.189	1.198	1.206	1.214	1.222	1.230	1.239	1.247	1.255	1.263	1.271	1.279
25.20	640	1.164	1.171	1.180	1.188	1.196	1.204	1.212	1.220	1.228	1.236	1.244	1.252	1.260
25.59	650	1.145	1.153	1.161	1.169	1.177	1.185	1.193	1.201	1.208	1.216	1.224	1.232	1.240
25.98	660	1.127	1.135	1.143	1.151	1.159	1.167	1.174	1.182	1.189	1.198	1.206	1.213	1.221
26.38	670	1.111	1.119	1.126	1.134	1.142	1.149	1.157	1.165	1.172	1.180	1.188	1.195	1.203
26.77	680	1.095	1.103	1.110	1.118	1.125	1.133	1.141	1.148	1.156	1.163	1.171	1.179	1.186
27.16	690	1.078	1.086	1.093	1.101	1.108	1.116	1.123	1.131	1.138	1.146	1.153	1.161	1.168
27.56	700	1.064	1.071	1.079	1.086	1.093	1.101	1.108	1.115	1.123	1.130	1.137	1.145	1.152
27.95	710	1.048	1.055	1.063	1.070	1.077	1.084	1.092	1.098	1.106	1.113	1.121	1.128	1.125
28.35	720	1.033	1.041	1.048	1.055	1.062	1.069	1.076	1.083	1.091	1.098	1.105	1.112	1.119
28.54	725	1.027	1.034	1.041	1.048	1.055	1.062	1.069	1.076	1.083	1.091	1.098	1.105	1.112
28.74	730	1.019	1.027	1.034	1.041	1.048	1.055	1.062	1.069	1.076	1.083	1.090	1.097	1.105
28.94	735	1.013	1.019	1.027	1.034	1.041	1.048	1.055	1.062	1.069	1.076	1.083	1.090	1.097
29.13	740	1.006	1.013	1.020	1.027	1.034	1.041	1.048	1.055	1.062	1.069	1.075	1.083	1.089
29.33	745	0.999	1.006	1.013	1.020	1.027	1.034	1.040	1.048	1.054	1.061	1.068	1.075	1.082
29.53	750	0.992	0.999	1.006	1.013	1.020	1.027	1.033	1.040	1.047	1.054	1.061	1.068	1.075
29.72	755	0.986	0.993	1.000	1.007	1.014	1.021	1.027	1.034	1.041	1.048	1.055	1.062	1.068
29.92	760	0.980	0.986	0.993	1.000	1.007	1.014	1.020	1.027	1.034	1.041	1.047	1.054	1.061
30.12	765	0.972	0.979	0.986	0.993	0.999	1.006	1.013	1.020	1.026	1.033	1.040	1.047	1.054
30.31	770	0.967	0.973	0.980	0.987	0.994	1.000	1.007	1.014	1.020	1.027	1.034	1.041	1.047
30.51	775	0.961	0.968	0.974	0.981	0.987	0.994	1.001	1.007	1.014	1.021	1.027	1.034	1.041
30.71	780	0.954	0.961	0.967	0.974	0.980	0.987	0.994	1.000	1.007	1.014	1.020	1.027	1.033
30.90	785	0.948	0.955	0.961	0.968	0.974	0.981	0.988	0.994	1.001	1.007	1.014	1.021	1.027
31.10	790	0.942	0.949	0.955	0.962	0.968	0.975	0.981	0.988	0.994	1.001	1.008	1.014	1.021

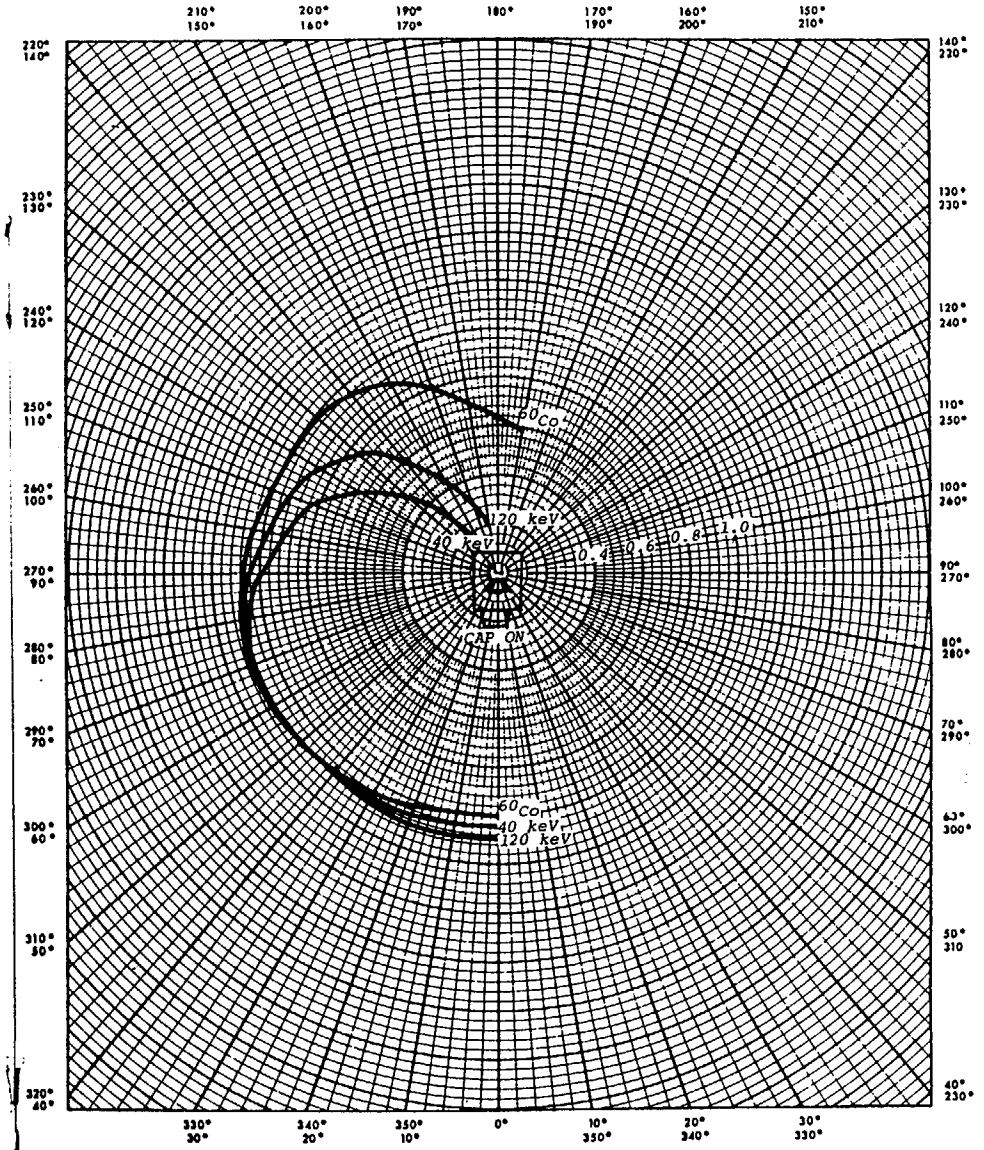

Figure 5. Relative Angular Response

EE700-AJ-OMI-010

WmB JOHNSON

OPERATION and
INSTRUCTION
MANUAL

MODEL IM-260/PD
SURVEY METER
JOHNSON MODEL 2000W
EXTENDER

Wm B. JOHNSON & ASSOCIATES INC.
200 AEI DRIVE
FAIRLEA, WV 24902

Telephone: 304-645-6568 Fax: 304-645-2182

2.0 SPECIFICATIONS

RANGES	7 RANGES - 0-1mR/h, 0-10 mR/h, 0-100 mR/h 0-1 R/h, 0-10 R/h, 0-100 R/h & 0-1000 R/h. EACH RANGE HAS SEPARATE CALIBRATION CONTROLS
ACCURACY	±15%
DETECTORS	HIGH RANGE - 18529 OR ZP-1300 W/COMP. 100 mg/cm^2 SATURATION OVER 10 R/H LOW RANGE - 18504 OR ZP1400 W/COMP. 2 mg/cm^2 SATURATION OVER 20,000 R/h
RESPONSE TIME	RANGES 1,000R, 100R & 100Mr - 1.5 SECONDS 90 % FS RANGES 10R, 1R, 10mR & 1mR - 4 SECONDS 90% FS
HIGH VOLTAGE	530 vdc ±25 vdc
LOW VOLTAGE	REGULATED - 1.7 vdc ± 0.020 vdc UNREGULATED - 2vdc→3.8 vdc
BATTERY	2- "D" CELL ALKALINE 300 HOURS NOMINAL
METER	ROTARY SCALE FOR EACH RANGE METER MOVEMENT SHOCK MOUNTED
AUDIBLE	PIEZO ELECTRIC CLICK FOR EACH PULSE
TEMPERATURE RANGE	-30°CENT. TO 60° CENT.
HUMIDITY RANGE	5 - 95% NON CONDENSING
DIMENSIONS	142" FULLY EXTENDED 38" NOT EXTENDED
WEIGHT	7 POUNDS INCLUDING BATTERIES
HOUSING	CAST ALUMINUM WITH HEAVY DUTY CARRYING STRAP
HOUSING FINISH	BLACK EPOXY

[Reprinted from RADIOLOGY, Vol. 172, No. 3, Pages 857–860, September 1989.]

Attachment 17

Sylvain Houle, MD, PhD • Tsui-Chun K. Yip, MD • Francis A. Shepherd, MD • Lorne E. Rotstein, MD • Kenneth W. Sniderman, MD • Elizabeth Theis, BSc • Richard H. Cawthorn, BSc, RTNM • Katherine Richmond-Cox, RTNM

Hepatocellular Carcinoma: Pilot Trial of Treatment with Y-90 Microspheres[1]

The potential use of yttrium-90 glass microspheres in the treatment of hepatocellular carcinoma was assessed in a pilot study of seven patients. The Y-90 microspheres were injected via a hepatic artery catheter. In this group of patients, no toxicity was observed for absorbed doses of between 5,000 and 10,000 cGy to the liver and up to 32,000 cGy to the tumor itself. Tumor response was seen only at the higher absorbed doses. The new Y-90 glass microspheres can safely deliver large doses of internal radiation to hepatic tumors as long as extrahepatic shunting can be excluded. Extrahepatic shunting will be the main limitation to this form of radiation therapy.

Index terms: Liver neoplasms, therapeutic radiology, 761.321 • Radionuclides, therapeutic • Yttrium, radioactive

Radiology 1989; 172:857–860

PRIMARY hepatocellular carcinoma (HCC) is a relatively rare malignancy in North America. It has been estimated that this tumor results in 3,000–4,000 deaths per year in the United States. Since HCC is almost always lethal, the incidence and mortality per year are approximately the same (1). Most tumors are inoperable at the time of diagnosis due either to extensive bilobar involvement or advanced hepatic cirrhosis. Furthermore, even at presentation, many patients have advanced disease with ascites, jaundice, and a poor performance status. The median survival for untreated patients is approximately 8 weeks.

Chemotherapy has been shown to provide palliation and to prolong survival for some patients. When chemotherapy is administered by means of hepatic arterial infusion, the response rate is approximately 50%. The survival of patients failing to respond to chemotherapy is extremely short (2). Conventional external-beam radiation therapy provides only temporary, modest benefits to some patients with hepatoma. Because of the risk of radiation hepatitis, external radiation therapy has been restricted to doses of 2,000–3,500 cGy (rad) in daily fractions of 200 cGy. The injection of radioactive microspheres via the hepatic artery allows delivery of much higher radiation doses to liver tumors. Therefore, we decided to investigate the potential use of yttrium-90 microspheres as an additional treatment method for primary liver tumors.

Y-90 has desirable properties for internal radiation therapy: It is a pure β emitter with a half-life of 64 hours and a mean β-particle energy of 0.93 MeV (maximum, 2.27 MeV). The average penetration of the β particles in tissue is 2.5 mm (maximum, 10.3 mm). Stable Y-89 is easily incorporated into a glass matrix and can be activated to radioactive Y-90 by means of neutron bombardment in a nuclear reactor.

Y-90–labeled inert ceramic or resin microspheres injected via the hepatic artery have been used for the treatment of metastatic and primary neoplastic disease (3–6). The therapeutic effect results from the radiation field from the radioactive particles trapped within the liver parenchyma. The use of intraarterial microspheres for radiation therapy was recently reviewed (7).

Although very encouraging results were obtained with the Y-90 microspheres in previous studies (3–7), the results were not obtained without difficulty. Due to unexpected leaching of the yttrium from the surface of the resin microspheres, several patients died of myelosuppression from uptake of the free Y-90 by the bone marrow. Several patients had severe gastrointestinal bleeding due to shunting of microspheres to the stomach and gastrointestinal tract. Pulmonary fibrosis in one patient was attributed to arteriovenous shunting of microspheres to the patient's lungs.

More recently, a new Y-90 glass microsphere, for which the leaching problem has been eliminated, has been produced under the trade name Therasphere (Theragenics, Atlanta). These glass microspheres are 15–30 μm in diameter (mean, 20 μm) and contain stable Y-89, which is activated by neutron bombardment in a nuclear reactor to Y-90. The incorporation of the yttrium in an insoluble glass matrix prevents catastrophic leaching of the Y-90 in vivo. The preparation of these microspheres and the problem of leaching have been discussed by Ehrhardt and Day (8). Animal studies conducted at the

[1] From the Departments of Radiology (S.H., T.C.K.Y., K.W.S., R.H.C., K.R.C.), Medicine (F.A.S., E.T.), and Surgery (L.E.R.), Toronto General Hospital, 200 Elizabeth St, Toronto, Ont, Canada, M5N 1L5. From the 1987 RSNA annual meeting. Received December 11, 1987; revision requested February 4, 1988; revision received April 14, 1989; accepted April 17. Address reprint requests to S.H.

Abbreviations: HCC = hepatocellular carcinoma, SPECT = single-photon emission computed tomography.

University of Michigan Medical Center have confirmed the lack of chemical and physical toxicity. No radiation hepatitis–related deaths were observed in dogs receiving doses of up to 18,000 cGy (9).

Herein we report our preliminary experience with these new Y-90 glass microspheres in nine patients with HCC.

MATERIALS AND METHODS

This study is part of a phase 1 clinical trial being carried out at three Canadian centers to assess the toxicity of Y-90 glass microspheres injected via the hepatic artery. The other two centers are evaluating this mode of treatment primarily in patients with hepatic metastases, mostly from colorectal cancer. We have limited ourselves to the treatment of patients with HCC.

For this study, we selected patients with proved HCC in whom chemotherapy had failed and whose tumors were inoperable. One patient with diffuse hepatic spread of tumor who had never received chemotherapy was also included in this series. These patients had good performance status (greater than 60% on the Karnofsky performance scale), no concurrent disease, and normal bone marrow and pulmonary function. The patients who had received chemotherapy had recovered from any toxic effects of the treatment. The experimental nature of Y-90 microsphere therapy and the risks involved were explained to all patients. Informed consent was obtained from all patients before their participation. Of the nine patients entered into the clinical trial at this institution, two could not be treated because of significant extrahepatic shunting.

The following laboratory variables were assessed before treatment and at follow-up: complete blood cell count with differential and platelet count, serum electrolyte status, prothrombin and partial thromboplastin time, and levels of bilirubin, albumin, aspartate transaminase (AST) (formerly SGOT), alanine transaminase (ALT) (formerly SGPT), blood urea nitrogen, creatinine, alkaline phosphatase, and lactic dehydrogenase. Alpha-fetoprotein was used as a tumor marker. Pulmonary function tests and chest radiography were also performed. The extent of hepatic involvement was measured by means of liver ultrasound (US) scans and radionuclide (technetium-99m sulphur colloid) hepatobiliary scans. Changes in the volume of the tumor were monitored by means of serial US examinations. Tumor mass was assessed with transmission computed tomography (CT) only if significant changes were found with US.

In all but one patient, the Y-90 microspheres were injected through a hepatic artery catheter placed percutaneously under fluoroscopic guidance. In five patients the catheter had to be placed in the right hepatic artery to avoid the right gastric artery. Embolization of arterial branches was not allowed in our experimental protocol, designed to assess toxicity. In one patient, surgical implantation of the hepatic artery catheter via the gastroduodenal artery was necessary because of an occlusion at the origin of the hepatic artery.

Immediately before injection of the Y-90 microspheres, the presence of extrahepatic shunting was assessed by injecting Tc-99m–labeled human albumin microspheres (Instant Microspheres; 3M, St Paul, Minn) through the hepatic artery catheter. The size of these albumin microspheres is between 10 and 35 μm (mean, 20 μm) and is similar to that of the Y-90 glass microsphere (15–30 μm). Images of the liver, lungs, and stomach area were obtained with a digital scintillation camera. If activity was noted in the lungs, a shunt fraction was calculated as the ratio of the lung counts to the total counts. Air contrast scintigraphic views of the stomach (10) were obtained when indicated to confirm shunting of microspheres to the stomach.

The administered amount of Y-90 was based on the volume of the patient's liver and the desired total radiation absorbed dose to the liver (5,000 cGy for the first four patients, 7,500 cGy for the next two, and 10,000 cGy for the last patient) assuming a uniform distribution of the microspheres within the hepatic parenchyma. Under this assumption, each megabecquerel of Y-90 per kilogram of liver tissue gives a total absorbed dose of 4.92 cGy over the complete decay of the Y-90 (11). The required activity A (in megabecquerels) for a given hepatic radiation dose D (in centigrays) is thus given by $A = DW/4.92$, where W is the weight of the patient's liver in kilograms. The liver volume was measured on transmission CT scans before treatment. The administered amounts of Y-90 ranged from 1.55 to 6.29 GBq (40–170 mCi).

The dose received by the tumor was estimated with use of a partitioning model for close calculation (Russell et al, unpublished data, 1987). This model assumes that the intrahepatic distribution of the Y-90 microspheres is identical to that of the Tc-99m microspheres. Because of the higher density of the glass microspheres (3.29 g/mL), this assumption may not be strictly true. However, the results of previous animal studies and the bremsstrahlung scans of our own patients indicate that it is a reasonable assumption. The dose to the tumor was calculated from the volume of the tumor, measured with CT, and from the fraction of the injected dose trapped by the tumor mass.

The Y-90 glass microspheres are supplied in a V-bottom microvial with a special flushing system to overcome the problem of microspheres settling in saline due to their high density. A typical patient dose contains 150 mg of Y-90 glass microspheres in 0.05 mL of water. The initial specific activity is about 30–35 MBq/mg. The radioactivity in the dose vial is measured in a dose calibrator from the bremsstrahlung radiation. A 20-gauge needle, attached to a flushing line, is inserted through the rubber septum of the dose vial and its tip positioned at the bottom of the V at the base of the microvial. The other end of the flushing line is connected by a three-way stopcock to a 20 mL syringe containing 0.9% saline and a 5-mL flushing syringe. The tip of a second 20-gauge needle is pushed just below the vial septum. This second needle is attached to the delivery line. Before the dose is administered, the air in the dose vial and tubing is expelled by slowly flushing them with saline. The end of the delivery line is connected to a waste vial to capture the microspheres that escape during this preliminary flushing. Once the air has been removed from the system, the delivery line is connected by a Luer lock to the hepatic artery catheter. The Y-90 microspheres are then administered in three 5-mL slow flushes. The saline entering the vial at the bottom of the V brings the microspheres into suspension. The saline carrying the microspheres leaves the dose vial through the second needle positioned near the septum at the top. After the injection, the residual activity in the microvial, the components of the flushing system, and the arterial catheter was measured in a dose calibrator. The delivery system has proved very effective, with less than 0.5% of the dose remaining in the vial after the injection. Approximately 5% of the Y-90 activity remained in the catheter and delivery system after flushing of the dose. Bremsstrahlung scans were obtained after the injection to demonstrate the distribution of the Y-90 microspheres.

RESULTS

Toxicity

None of our patients showed any evidence of significant toxicity induced by the Y-90 microspheres. The liver enzymes rose transiently in one patient who received 5,000 cGy. However, this patient's liver was already partially compromised by hemochromatosis. This patient also had diffuse cancerous spread throughout his liver. In this particular case, the intrahepatic Y-90 dose was distributed uniformly throughout the organ. In the remaining six patients, the laboratory investigations did not reveal any significant change from baseline. No hematologic toxicity was observed in any of the patients.

Distribution of Microspheres

The Tc-99m microsphere scans revealed that the localized tumor masses were hyperperfused when compared with surrounding liver tis-

sue. The tumor-to-liver perfusion ratios varied from unity to 10: 1.0, 1.0, 1.6, 2.3, 2.4, 6.0, and 10.0. These values are similar to the perfusion ratios observed by other investigators using single-photon emission CT (SPECT) (12). A hypovascular core was not seen on our planar images (SPECT was not used in this pilot study). This could be due to the lower image contrast of planar images when compared to SPECT transverse sections. In our small series there was no distinct correlation between tumor size and hypervascularity. In all cases the bremsstrahlung scans revealed a similar distribution pattern for the Y-90 and Tc-99m microspheres, albeit with less detail. No Y-90 extrahepatic activity was detected.

Administered Dose

As a result of the great inhomogeneity of perfusion observed in our patients, the actual radiation dose to the tumor and normal hepatic tissue was greatly different than that estimated on the basis of a uniform distribution of microspheres throughout the liver. In one extreme case, more tha 80% of the microspheres injected via the right hepatic artery were trapped within the tumor vascular bed. With use of the partitioning model, the estimated dose to the tumor was 32,000 cGy, while the remainder of the right lobe received a total dose of only 2,200 cGy.

Response to Treatment

In the patients who received the lower absorbed doses, disease progressed after yttrium treatment. Two patients who received higher doses (7,500 and 10,000 cGy) became stable for several weeks. In one of these two cases, the tumor stopped growing after therapy, and its size remained unchanged over the next 12 weeks. In another case, there was a slight but definite reduction in the tumor size, although not sufficient to be classified as a partial remission. This patient is still alive after 116 weeks.

Radiation Exposure to Personnel

Despite the large amount of activity handled during these treatments, radiation exposure to personnel was minimal. The vials are sealed in a plastic β shield. Additional lead shielding to guard against bremsstrahlung radiation and the use of a double layer of thick surgical gloves and long forceps kept the extremity exposure to the personnel involved to less than 0.2 mSv per administration. The delivery system allows a rapid setup and a short exposure time to the physician performing the injection.

After treatment, the patients were returned to the nursing units. The dose rate at 1 m from the patient was less than 2 μSv/hr per gigabecquerel administered. At the skin just anterior to the liver, the dose rate was 35 μSv/hr per gigabecquerel injected. No restriction was imposed on the routine nursing care of these patients.

DISCUSSION

Primary HCC is a virulent disease for which conventional therapies have met with limited success. The promising results obtained by other investigators in the treatment of metastatic liver tumors with Y-90 microspheres encouraged us to evaluate this mode of treatment in patients with primary liver tumors. The availability of new Y-90 glass microspheres offered a safe method of delivering large doses of internal radiation to the liver without incurring the risk of catastrophic leaching of the yttrium.

As larger and larger amounts of radioactivity are being injected, it is essential to be able to detect any extrahepatic shunting. In one of our patients, if blood flow shunting to the lungs had not been detected by means of Tc-99m microsphere scanning before Y-90 microsphere injection, we would have delivered a lethal dose of yttrium to the lungs. While shunting to the lungs is relatively easy to detect and quantitate, shunting to the gastrointestinal tract, in particular the stomach, may be more difficult to detect. SPECT and air contrast enhancement of planar views are useful adjuncts to Tc-99m microsphere scanning in distinguishing between gastric and hepatic activity. In the future, as larger doses are used, the detection of even a minute amount of shunting to the gastric mucosa will be even more critical, since the gastric mucosa is much more sensitive to radiation damage than is the hepatic parenchyma.

In addition, depending on the origin of the right gastric artery, it may not be possible to inject the microspheres into the main hepatic artery without a large fraction of the Y-90 microspheres going to the stomach. We encountered this problem in five of our seven patients. Embolization of arterial branches would have been useful in these five patients. If the tumor is detected early, selective injection into either the right or left branch of the hepatic artery could be performed. In addition, tumors are believed to have greater vascularity early in the course of the disease. These two factors—localized tumor and high vascularity—combine to enhance the potential benefit of internal radiation (4).

Further work needs to be done in the area of dosimetry. We expected to see a better response to the internal radiation in tumors that received high doses of absorbed radiation. A possible explanation for this lesser response might be that the assumption of uniform distribution of the microspheres within the tumor does not apply. It may be necessary to develop better dosimetry models based on the microvascular anatomy of the tumors and its effect on the distribution of the Y-90 microspheres within the tumor mass. Humm (13) has discussed this problem in the case of internal radiation therapy with labeled monoclonal antibodies. He has proposed that irregular tumor vasculature leads to irregular distribution of the internal radiation, with some areas receiving much more and other areas much less than the average absorbed dose. Therefore, a large fraction of the tumor cells may be exposed to less radiation damage than required for sterilization. This hypothesis may also apply to radioactive microspheres.

The absence of toxicity in our pilot trial may have been partly due to the preferential trapping of the microspheres by the tumors. Consequently, the normal hepatic tissue suffered less radiation damage than would have been predicted with the assumption of uniform distribution of the microspheres. Therefore, this actual absorbed dose to normal liver tissue should be used to estimate the absorbed dose in order to determine a toxic threshold.

We conclude that large absorbed doses of internal radiation can be safely delivered to hepatic tumors if the presence of extrahepatic shunting can be excluded. Further work is required to define the toxicity and efficacy of the Y-90 glass microspheres. ■

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Radiation Protection Aspects of ^{90}Y Radiotherapy for Malignant Hepatic Tumours

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^{90}Y is a short lived ($t_{1/2}$=64 hours) pure beta emitter which is currently being introduced for radiotherapy of both primary and metastatic malignant tumours of the liver. The procedure involves the introduction of a catheter into the patient's hepatic artery under fluoroscopic control and subsequent injection of 100—300 millicuries of ^{90}Y glass microspheres. The 20 micron diameter microspheres are localized in the microvasculature of the liver lesions by capillary blockage.

The radiological protection aspects of the ^{90}Y administration procedure, which is normally performed in the angiography suite of the X-ray department, are discussed. In normal post-treatment circumstances there is virtually no danger of radioactive contamination (faeces, urine, sweat, etc.) from the patient. Measurements using ionization chambers and TLD's have been performed to determine (bremsstrahlung) dose-rates and time-integrated radiation doses in the immediate environment of the patient for several days post treatment. These are very low, with the total 2 day integrated dose at approximately 2 metres from the patient being less than 10 mrads. These results clearly show that there is no need for any special patient isolation procedures to be introduced for radiation protection purposes. Further aspects of patient management, including discharge from hospital and post mortem autopsy, will also be addressed.

Radioprotection associé au traitement radiothérapique des tumeurs hépatiques par ^{90}Y

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^{90}Y est émetteur beta pur à vie courte ($t_{1/2}$ = 64 heures), que l'on a commencé récemment à utiliser dans le traitement radiothérapique des tumeurs primaires et métastatiques du foie. La procédure consiste en l'introduction d'une cathétère dans l'artère hépatique, sous contrôle fluoroscopique, suivie par l'injection de 100 à 300 mCi d'^{90}Y contenu dans les microsphères de verre. Ces sphères, d'un diamètre de 20 microns, sont bloquées par les vaisseaux capillaires dans les lésions hépatiques. On présente ici les aspects de protection radiologique associés à cette procédure, qui est normalement effectuée dans le secteur angiographie du département de radiographie. Dans des conditions post-traitement normales, il n'y a virtuellement pas de risque de contamination radioactive (feces, urine, sueur, etc.. . .) en provenance du patient. Des mesures par chambre d'ionisation et TLD ont été conduites pour déterminer les débits de doses par bremstrahlung et les doses intégrées à proximité de patients, pendant plusieurs jours suivants le traitement. Les débits de dose et doses intégrées sont très faibles. Les doses intégrées sur deux jours à deux mètres des patients sont inférieures à 10 mrads. Ces résultats indiquent clairement qu'il n'est pas nécessaire, pour les besoins de la radioprotection, d'isoler les patients pour appliquer cette procédure. D'autres aspects de l'administration des patients, y compris leur décharge de l'hôpital et l'autopsie, sont aussi examinés.

Integrated TLD Measurements of Radiation Dose Due to Bremsstrahlung in the Vicinity of Yttrium-90 Patients

			Net Radiation Dose (millirads)						
Patient	**Y-90 Activity Injected**	**Hours Monitored**	**Under Mattress**	**Head of Bed**	**Foot of Bed**	**Bedside Table**	**Wall 1.3M from Bed Midline**	**Wall 1.0 M from Bed Midline**	**Adjacent Bed**
1.	50 mCi	48	21	4	0	N/A	1	3	1
2.	60 mCi	75	58	12	2	N/A	4	3	2
3.	70 mCi	72	110	22	4	16	7	16	N/A
4.	102 mCi	93	123	14	5	N/A	N/A	5	1
5.	110 mCi	68	109	15	2	14	7	10	N/A
6.	120 mCi	48	68	7	3	13	6	6	N/A
7.	193 mCi	94	241	18	4	N/A	N/A	9	4

CONVERSATION RECORD

TYPE:
Outgoing Telephone
Incoming Telephone x
Meeting

NAME OF PERSON CONTACTED:	ORGANIZATION:	TIME:	DATE:
Ann Warbick Cerone	MDS Nordion	2:45 pm	2/1/00

SUBJECT:
Adequacy of MDS Nordion's response

SUMMARY:
Ms. Cerone called me to inquire whether their response, dated January 14, 2000, was sufficient for NRC's deficiency questions. I responded to her stating that it appeared to be based on an acceptance review except that the drawings, i.e. Attachments 1-8 were marked as proprietary. I also told her that NRC needs only Attachment 8 for completing the safety evaluation. She said that she will write a letter and withdraw Attachments 1-8 and in the letter she will provide a non-proprietary copy of Attachment 8 for NRC.

ACTION REQUIRED:
NRC to continue the safety evaluation with the drawing to be sent by MDS Nordion.

PLACE THIS RECORD IN:
Registration File NR-220-D-113-S
QA File
Incident File
General File SSD 00-04

PERSON DOCUMENTING THE CONVERSATION:	SIGNATURE:	DATE:
John Jankovich	John P Jankovich	2/1/00