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Radionuclides in Human Breast Cancer

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13. ABSTRACT (Maximum 200 Words) This study has been designed to evaluation the spatial and temporal distribution as well as the radiation dosimetry of intratumoral injection of proprietary radiopharmaceuticals Ga-67 and Ga-68 Galium Iron Macroaggregates (GIMA). Our team has adopted a 2-prong approach for this study. While the refinement of the human protocol is ongoing, we continue on the basic preparative studies to investigate the imaging methods as well as other radiopharmaceuticals and strategies for locoregional treatment. Our preliminary findings have led to presentation of 5 abstracts and filing of one non-provisional patent application. We are awaiting the final approval of the human protocol and will proceed with the human study once DOD approval of the human protocol is obtained. The integration of the 2-prong will likely lead to invaluable information about locoregional treatment of solid tumors and development of new treatment strategies.				
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Introduction

The efforts of our laboratory in this project have proceeded in a two-prong approach. We continue to refine the human protocol (the IRB approved version of 6/2004 is enclosed in the Appendix section) to conform to the US Army IRB requirements. This is still an ongoing process. In the meantime, we conducted basic research studies to support future clinical applications. The basic research work includes preparation of different radiopharmaceuticals, imaging methods (ultrasound, MRI, PET and scintigraphy) for in vivo visualization of these radiopharmaceuticals, radiation dosimetry simulation, as well as toxicity and efficacy studies of intratumoral injection in the suppression of tumor growth in animals. While the refinement of the human protocol is still ongoing, the basic research efforts has lead to the publication of 5 abstracts (enclosed in the Appendix section) and the submission of a non-provisional patent application (US Patent Application Serial No.10/724,027) to the US Patent and Trademark Office. When the feasibility of using Gallium Iron Macroaggregates (GIMA) in human breast cancer is confirmed by the clinical studies, the results of our basic research will further guide the optimal choice of radiopharmaceuticals and strategies for the locoregional treatment of solid tumors.

Body

- 1) Recruitment of patients- Because of the ongoing refinement of our IRB-approved protocol to conform to the DOD requirements, no patients has been recruited. However, we had worked with the collaborating breast surgeons, MRI radiologists and ultrasound radiologists to establish the logistics of the imaging work flow and recruitment. These procedures are enumerated in the Protocol Appendices K to M (enclosed in this report as Appendix section I, II and III) of the IRB approved human protocol (Appendix IV) and Informed consent forms (Appendix V).
- 2) Establishing MR imaging scheme for measurement of Iron contents- Although no study has been performed on human subjects. We have performed animal (rats) experiments and confirm that the routine clinical protocol of T2-weighted GRE sequence is able to demonstrate the iron content after interstitial injection. (Abstract #1 in Appendix).
- 3) Ultrasound scheme- Although no human study has been performed, our rat experiments has demonstrated the feasibility of routine clinical ultrasound instrument in the detection of GIMA particles after intratumoral injection (Abstract #1 in Appendix). After the human protocol is approved by DOD and human studies are conducted, such feasibility is likely to be confirmed also in humans.
- 4) PET/scintigraphy for spatial and temporal changes- repeated animal experiments using Ga-67 GIMA have shown persistent retention of GIMA in the injection site. However, because of the small size of a rat and the lower resolution of positrons (Ga-68) with PET, possible spatial change has not been evaluated. Such observation will be made with the human PET studies.
- 5) Construction of radiation absorbed doses for tumors- has not been accomplished because there is no human data yet. However, we have performed Monte Carlo simulation of different radionuclides with therapeutic potentials and also project the

radiation dosimetry after injection of GIMA into breast cancer, prostate cancer or liver cancer. (Abstract #2). Furthermore, we have performed tumor suppression experiments on rats with selected radiopharmaceuticals including Ga-67 GIMA, Y-90 labeled Iron Macroaggregates (YIMA) and In-111 labeled Iron Macroaggregates InIMA, which were prepared similarly to GIMA (Abstract #3), in contrast to Y-90 chloride, In-111 chloride and Ga-67 citrate. The abilities of GIMA and YIMA to suppress tumor growth in vivo are confirmed. Together with results from earlier animal experiments, these findings were compiled and a non-provisional patent application was filed on the use of particulate radiopharmaceuticals for the treatment of cancers (Appendix VI). Surprising results were found with In-111 chloride (3 mCi in 0.2-0.5 ml) and Y-90 chloride (0.1- 1 mCi in 0.2-0.5 ml) which also suppress tumor growth (Abstract #4). With biodistribution studies, we also found favorably lower radiation dosimetry estimates to red marrow from Y-90 chloride than previously reported in the literature (Abstract #5).

Key Research Accomplishments

- ❑ Confirmation of the feasibility of MRI and ultrasound in the detection of interstitially injected GIMA in rats
- ❑ Preparation of radiopharmaceuticals with therapeutic potentials
- ❑ Demonstration of efficacy of intratumoral GIMA, YIMA or Y-90 chloride in the suppression of tumor growth in rats
- ❑ Human radiation dosimetry estimation of GIMA from intratumoral injection in breast cancer, prostate cancer or liver.
- ❑ Human radiation dosimetry estimation of In-111 chloride or Y-90 chloride from rat biodistribution studies.

Reportable Outcomes

Presentations:

June 2004- Annual Meeting of the Society of Nuclear Medicine, Philadelphia, PA.

Wong, F. C. LOCOREGIONAL ABLATION OF RAT BREAST CANCER USING Y-90 Cl OR IN-111 Cl. J. Nucl. Med. 45(5 Suppl.): 334P, 2004.

Wong, F. C., Smrkovski, O. A., Chow, L., Y. Wang, L. and Sparks, R. B. LOWER RADIATION DOSIMETRIC ESTIMATES FROM BIODISTRIBUTION STUDIES OF PARENTERAL ADMINISTRATION (IM OR IV) OF Y-90 CHLORIDE. J. Nucl. Med. 45 (5 Suppl.):435P, 2004.

September 2004, Annual Meeting of European Association of Nuclear Medicine, Helsinki, Finland.

Wong, F. C. and Sparks R. B. Simulated Dosimetry Profiles of Locoregional Radionuclide Therapies using Radioactive Gallium Iron macroaggregates (GIMA). Eur. J. Nucl. Med. Imaging, 31(2 Suppl.): S293, 2004.

Wong, F. C. and Wang, S. Locoregional ablation of rat breast cancer using Ga-67 Iron macroaggregates (GIMA) and Y-90 Iron Macroaggregates (YIMA). Eur. J. Nucl. Med. Imaging, 31(2 Suppl.):S297, 2004.

Wong, F. C. and Wang, S. Paramagnetic Radiopharmaceuticals of Iron and Gadolinium Macroaggregates. Eur. J. Nucl. Med. Imaging, 31(2 Suppl.): S387, 2004.

Patent Applications:

11/2003 US Patent Application Serial No.10/724,027 F. Wong and Shuang Wang. Radiopharmaceuticals and Radioactive Microspheres for Locoregional Ablation of Abnormal Tissues.

Conclusions

We are proceeding with our 2-prong approach with different degree of success. The development of the human protocol for the conformance with DOD requirements is still ongoing. Our preparatory studies have shown interesting and rewarding findings that will provide invaluable information for the design of radiopharmaceuticals and optimal choice of locoregional strategies for the treatment of solid tumors. Once our human study confirms the feasibility of locoregional radionuclide treatment in the breast, similar strategies can be designed for other radiopharmaceuticals and for other solid tumors.

References

Abstract #1

Wong, F. C. and Wang, S. Locoregional ablation of rat breast cancer using Ga-67 Iron macroaggregates (GIMA) and Y-90 Iron Macroaggregates (YIMA). Eur. J. Nucl. Med. Imaging, 31(2 Suppl.):S297, 2004.

Abstract #2

Wong, F. C. and Sparks R. B. Simulated Dosimetry Profiles of Locoregional Radionuclide Therapies using Radioactive Gallium Iron macroaggregates (GIMA). Eur. J. Nucl. Med. Imaging, 31(2 Suppl.): S293, 2004.

Abstract #3

Wong, F. C. and Wang, S. Paramagnetic Radiopharmaceuticals of Iron and Gadolinium Macroaggregates. Eur. J. Nucl. Med. Imaging, 31(2 Suppl.):S387, 2004.

Abstract #4

Wong, F. C. LOCOREGIONAL ABLATION OF RAT BREAST CANCER USING Y-90 Cl OR IN-111 Cl. J. Nucl. Med. 45(5 Suppl.): 334P, 2004.

Abstract #5

Wong, F. C., Smrkovski, O. A., Chow, L., Y. Wang, L. and Sparks, R. B. LOWER RADIATION DOSIMETRIC ESTIMATES FROM BIODISTRIBUTION STUDIES OF PARENTERAL ADMINISTRATION (IM OR IV) OF Y-90 CHLORIDE. J. Nucl. Med. 45 (5 Suppl.):435P, 2004.

Appendix I.

Appendix – K.

Appendix Subtitle: Screenign Record

Name/MRN: _____

Patient Identified BY: _____ **on** _____.

Eligibility Criteria

Eligible Patients:

Patients must have signed the informed consent.

Patients must be 18 years of age or older

Patients must have breast cancer diagnosed by histopathology but no surgical resection of the tumor.

Patients should have received no previous focal external beam radiation therapy to the thorax.

Patients who have not had chemotherapy for the breast cancer; hormonal therapy alone will be eligible.

Patients with adequate platelets white cells :

Granulocytes $\geq$ 1000 cells/mcl

Platelets $\geq$ 40,000/mcl

Patients with Zubrod performance scale of 2 or below.

Patients with breast tumor >2 cm compressed thickness on mammogram but no tumor necrosis on MRI

Patients must have scheduled surgical resection (mastectomy or conservation surgery) within 2 weeks

Ineligible Patients

Patients of child-bearing age who have positive pregnancy test or are lactating.

Patients with septicemia, severe infection or acute hepatitis.

Patients who had radiation therapy or chemotherapy of the breast cancer

Patients who had residual radiation from previous radionuclide administration, from the day of injection:

F-18 agents of more than 10 mCi within 2 days for the Ga-68 GIMA and Ga-67 GIMA groups;

In-111, Ga-67 or I-131 agents of more than 1 mCi within 14 days for the Ga-67 GIMA groups.

Patients who cannot undergo MRI procedures- nonvisualization of tumor on MRI or incompatible implants

Patients with claustrophobia cannot be entered for the Ga-67 GIMA groups

Entry into Ga-68 GIMA will be acceptable with only one session of conscious sedation.

Patients who have scheduled surgical resection in less than 7 days are not eligible to for Ga-67 GIMA

Informed Consent Form delivered and explained to patient by: _____ **on** _____.

Informed Consent Form obtained and countersigned by: _____ **on** _____.

Appendix II

Appendix – L.

Appendix Subtitle: Ga-68 GIMA Patient handling Record

	<u>DAY OF INJECTION</u>		
<u>Timeline</u>	<u>Preparation</u>	<u>Procedures</u>	<u>verified by</u>
	(20 minutes before injection)	Patient Arrives in MRI	
		Patient Injected with:	
	done prone with	mCi Ga68 (GIMA)	
	slight compression	q.s. to 1.0 ml with sterile NS	
	in MRI	By: _____	
	(performed by MRI tech)	Immediate MRI	
	(immediately after MRI)	Observe for adverse reactions, e.g, pain	
	(immediately after MRI)	Ultrasound	
		By: _____	
	(~ 1hr post injection)	Patient Arrives in PET/CT	
	(check patient positioning)	Serial 3D PET/CT started	
		WB PET/CT ~5-bed positions	
		no extremities/ no brain	
		5 minute Serial Chest PET/CT Scan	
	(~ 2-3 Hr post injection)	Follow-up MRI	
	(immediately after MRI)	Follow-up Ultrasound	
		By: _____	
comments:			

Appendix III

Appendix – M.

Appendix Subtitle: Ga67 GIMA Patient Handling Record

Time/Day	Preparation	Procedure	verified by
	in Nuclear Medicine	WB Transmission (prior to injection)	
	in Nuclear Medicine	Obtain baseline blood sample #1	
	(give patient urine container # 1	Collect baseline urine container # 1	
	(20 minutes before injection)	Patient Arrives in MRI	
	done prone with	mCi Ga67 (GIMA)	
	slight compression	q.s. to 1.0 ml with sterile NS	
	in MRI	By: _____	
	(performed by MRI tech)	Immediate MRI	
	(immediately after MRI)	Observe for adverse reaction,e.g. pain	
	(immediately after MRI)	Ultrasound by _____.	
	(~ 2 hrs post injection)	Patient Arrives in Nuclear Medicine	
	(check patient positioning)	WB Imaging- 2 hrs PI	
	immediately after WB	Spot Image done over chest	
	~2 hrs post injection	Collect urine container # 2	
	~2 hrs post injection	Obtain blood sample # 2	
	(check patient positioning)	WB Imaging- ~4 hrs PI	
	immediately after WB	Spot Image done over chest	
	(performed by MRI tech)	Followup MRI	
	(immediately after MRI)	Followup Ultrasound by _____.	
	~4 hrs post injection	Collect urine container # 3	
	~4 hrs post injection	Obtain blood sample # 3	
	(check patient positioning)	WB Imaging- ~24 hrs PI	
	immediately after WB	Spot Image done over chest	
	(performed by MRI tech)	Followup MRI	
	(immediately after MRI)	Followup Ultrasound by _____.	
	~24 hrs post injection	Collect urine container # 4	
	~24 hrs post injection	Obtain blood sample # 4	
	(check patient positioning)	WB Imaging- ~Day 2, 3 or 4	
	immediately after WB	Spot Image done over chest	
	(performed by MRI tech)	Followup MRI	
	(immediately after MRI)	Followup Ultrasound by _____.	
	Day 2, 3 or 4	Collect urine container # 5	
	Day 2, 3 or 4	Obtain blood sample # 5	

Appendix IV

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Protocol Page

Radiation Dosimetry of Intra-tumoral Injection of Radionuclides in Human
Breast Cancer
ID03-0070

Core Protocol Information

Short Title	Intratumoral Injection of Radionuclides into Human Breast Cancer
Study Chair:	Edmund Kim
Additional Contact:	Franklin Wong
Department:	Nuclear Medicine
Phone:	713-794-1052
Unit:	59
Full Title:	Radiation Dosimetry of Intra-tumoral Injection of Radionuclides in Human Breast Cancer
Protocol Type:	Standard Protocol
Protocol Phase:	N/A
Version Status:	Activated 07/27/2004
Version:	06
Document Status:	Saved as "Final"
Submitted by:	Franklin Wong--7/12/2004 4:04:14 PM
OPR Action:	Accepted by: Marion Olson -- 7/19/2004 2:37:07 PM

The Objectives are:

1. Use MRI to measure the spatial and temporal profiles of GIMA after intratumoral injection into breast cancer
2. Use Positron Emission Tomography (PET) for Ga-68 GIMA and high resolution gamma scintigraphy for Ga-67 GIMA to measure the spatial and temporal profiles of the radioactivity of GIMA after intratumoral injection into breast cancer;
3. Use the imaging data from MRI and nuclear imaging to calculate whole-body, organ, and locoregional radiation dosimetry to evaluate safety and efficacy factors for intratumoral GIMA.

The Hypotheses are:

1. After intratumoral injection, GIMA will be dispersed but remain contained in the tumor.
2. The radiation absorbed doses will be high within the tumor but low in the body and surrounding organs.

Locoregional Radiation Therapy of Breast Cancer - a beginning

Multiple trials of breast conservation in patients treated with and without whole breast radiation have found that the majority (> 90%) of local recurrences occur at the site of surgical resection [1]. Clinical trials have confirmed the usefulness of sealed radionuclides as internal radiation sources for locoregional adjuvant treatment of breast cancer, as demonstrated by the recent FDA approval of MammoSite using Iridium-192 [2]. Therefore, conventional radiation treatment to the whole breast following breast conserving surgery may not be a necessary approach for the majority of women. More directed local treatment with radiotherapy appears to be safe and effective treatment. Conventional brachytherapy involves the implanting of sealed radiation sources implanted into the post-surgical field for several weeks [3, 4]. Recent clinical trials have reported favorable outcomes treating brain and breast cancer patients using a single implanted catheter filled with Iodine-125 Iotrex and Iridium-192 seeds irradiating the tissues around the post-surgical cavity (by Proxima Therapeutics, Inc.). This approach has recently gained FDA approval (GlialSite for brain tumor and MammoSite for breast cancer [1, 5, 6, 7]). Locoregional radionuclide therapy offer several desirable features: predictable dosimetry, the capability of being monitored, and short duration. Ablating breast tumors using intratumoral injection of radionuclides without has not been explored. This is due to the lack of requisite information on radionuclide dispersion and on radiation dosimetry in the tumor and surrounding tissues to establish efficacy and safety. This proposed

study aims to explore the feasibility of using intratumoral injection of unsealed radionuclides as internal radiation sources.

Breast Lymphoscintigraphy - an opportunity to study radionuclides in human tissues

Breast lymphoscintigraphy is a nuclear medicine procedure that is increasingly important in the identification of sentinel lymph node(s). Typically, aliquot(s) of about 1cc containing 0.5 mCi of Technetium-99m (Tc-99m) labeled sulfur colloid (SC) is injected percutaneously into the tumor or breast tissues around the tumor. Smaller sizes (<0.22 micron) of SC allow better lymphatic drainage and therefore better visualization of the sentinel lymph node(s). Only a small fraction (<1%) [8, 9] of the SC injected ever drains via the lymphatics to allow visualization of the sentinel lymph node(s). Conversely, particles of larger sizes (>0.22 micron) or direct intratumoral (IT) injection of SC into the breast tumor reveals even less lymphatic drainage. Although unsealed, radionuclides injected into the tumor or surrounding tissues are indeed subject to spatial sequestration. The injection site appears spherical and unchanged (for days) on scintigrams. Although difficult to quantify, ultrasound guidance during selected breast lymphoscintigraphy shows that injections of SC into the breast tissue result in a larger dispersed volume which has not been adequately assessed. Radiation dosimetry of breast lymphoscintigraphy have shown variations up to ten-fold [10, 11, 12], partly because of the imprecision in determining the volume of the dispersed injectate. An injection of 0.5 mCi Tc99m SC delivers about 40 cGy to the injection site and 4 cGy to the sentinel lymph node. When standard guidelines are observed, there is good margin for radiation safety and the radiation absorbed dose to the sentinel lymph node is about one tenth that of the injection site [13]. The Medical Internal Radionuclide Dosimetry (MIRD) schemes require accurate determination of volume and residence time of dispersed radionuclides [14]. A recent report directly measured the injectate volume using the full-width half maximum (FWHM) of the injection site from the scintigram. The accuracy of this volume estimate was limited by the system resolution of 2 cm [12]. The search for an accurate measurement of the dispersed injectate volume for dosimetry has been futile because, besides the radioactivity, there is no other physical signal from the injected radionuclide for external imaging.

A paramagnetic radiopharmaceutical Gallium-Iron Macroaggregate (GIMA) has been identified to provide both radioactive and paramagnetic signals for external measurement. This study is designed to evaluate the volume of dispersion and radiation dosimetry of GIMA after intratumoral injection into untreated human breast tumor.

Radionuclide Dosimetry of Unsealed Sources- Simulated Radiation doses to tumor and surrounding tissues

Earlier general internal dosimetry schemes including MIRDOSE3 (an established Medical Internal Radiation Dosimetry program) do not provide depth dosimetry to account for surrounding tissues. Earlier reports of simulation are limited to specific radionuclides in specific configurations [15, 16]. In our study, Monte Carlo simulation for Y-90 Zevalin was applied and found helpful in defining regions of toxicity [17]. A simulation project using sphere and shell models with common core volumes of 0.4, 2, 10, 50 and 250 cc is continuing and we reported radiation dosimetry in the core and 30 concentric layers from 19 radionuclides [18]. As predicted before, the radiation absorbed doses to the sentinel lymph nodes will be about one tenth of those to the injection sites in the tumor. The extremes of heterogeneous distribution of radionuclides in the lesion were reported using shell models assuming that all the radionuclide was confined to the first layer around the central cavity. There was little dosimetry difference from the sphere models (<10%) in tissues beyond 1 cm. These sphere [18] and shell models [19] provide estimates of dosimetry ranges. Although the exact radiation dosimetry has yet to be determined, the radiation doses to the tumor can be estimated from the published biological half-life of 30 hours [20]. The 3 groups (0.25 mCi Ga-67 GIMA, 0.5 mCi Ga-67 GIMA and 0.5 mCi Ga-68 GIMA) of patients will receive estimated doses of 315, 632 and 463 cGy respectively in the injection site, with a 10% isodose range of 0.02 cm, 0.02 cm and 0.20 cm from the injection site edge respectively. Based on preclinical studies suggesting a total of 2% leakage of radiogallium in the form of free Ga(+3), the MIRDOSE3 models predict low radiation absorbed doses to the vital organs in units of cGy/mCi:

Simulated Dosimetr	Ga-68 GIMA	0.5 mCi Ga-68 GIMA	Ga-67 GIMA	0.2 mCi Ga-67 GIMA
		For this study		for this study
Organ	rad/mCi	Total rads	rad/mCi	Total rads
Adrenals	0.0130	0.0065	0.1200	0.0240
Brain	0.0025	0.0013	0.0140	0.0028
Breast w/Injectate	1.0000	0.5000	22.0000	4.4000
Breast wo/injectate	0.0550	0.0275	0.5900	0.1180
Gallbladder Wall	0.0100	0.0050	0.0940	0.0188
LLI Wall	0.0030	0.0015	0.0290	0.0058
Small Intestine	0.0091	0.0046	0.0270	0.0054
Stomach	0.0140	0.0070	0.1500	0.0300
ULI Wall	0.0084	0.0042	0.0450	0.0090
Heart Wall	0.0560	0.0280	0.5900	0.1180
Kidneys	0.0072	0.0036	0.0590	0.0118
Liver	0.0170	0.0085	0.1700	0.0340
Lungs	0.0400	0.0200	0.4500	0.0900
Muscle	0.0110	0.0055	0.1000	0.0200
Ovaries	0.0026	0.0013	0.0150	0.0030
Pancreas	0.0140	0.0070	0.1400	0.0280
Red Marrow	0.0140	0.0070	0.1200	0.0240
Bone Surfaces	0.0120	0.0060	0.1700	0.0340
Skin	0.0170	0.0085	0.1600	0.0320
Spleen	0.0130	0.0065	0.1100	0.0220
Testes	0.0011	0.0006	0.0053	0.0011
Thymus	0.0530	0.0265	0.5800	0.1160
Thyroid	0.0090	0.0045	0.0790	0.0158
Urin Bladder Wall	0.0026	0.0013	0.0140	0.0028
Uterus	0.0028	0.0014	0.0170	0.0034
Total Body	0.0600	0.0300	0.3200	0.0640
EFF DOSE EQUIV	1.2000	0.6000	5.1000	1.0200
EFF DOSE	0.4200	0.2100	1.9000	0.3800

Using human breast tumor as a model system, dosimetric measurement will be achieved by acquiring the spatial and temporal distribution of injected GIMA, measured from MRI and nuclear imaging. Ga-68 GIMA (with a physical half-life of 1.1 hours) is used to take advantage of the higher resolution and sensitivity of PET to measure the short-term spatial distribution of GIMA; while Ga-67 GIMA (physical half-life of 78 hours) is used to measure the prolonged distribution of radioactivity using a gamma camera. Confirmation of the sequestration and derivation of radiation dosimetry will permit variations to achieve high radiation dose for therapeutic effects. For instance, larger amounts of radioactivities may be achieved by using larger volumes of GIMA while maintaining the Ga/Fe ratio; alternatively, larger radioactivities may be delivered by increasing the Ga/Fe ratio while maintaining the volume of the injectate. Results from this dosimetric study will provide bases for the design of future phase I and II clinical trials to use this class of radiopharmaceuticals to treat selected subgroups of patients with breast cancers and to correlate with biologic markers.

A known radiopharmaceutical Ga-68 /Fe macroaggregates (GIMA) [20] that may provide paramagnetic signals for volume measurement by MR imaging and simultaneously emit gamma rays for nuclear imaging was identified. It has a biologic half-life of 30 hours, a physical half-life of 1.2 hours and measures 10-30 micron in size. It was used in human lung perfusion imaging in the 1970's until the advent of the current imaging agent of Tc-99m -macroalbumin aggregates. It was produced in a carrier-added (additional nonradioactive gallium) preparation (0.12 Ci/mole) containing large amounts of additional nonradioactive gallium which in turn caused dose-limiting toxicity [20]. Following similar steps while deleting the toxic nonradioactive gallium (carrier), our laboratory has managed to produce carrier-free GIMA (with Ga-68 and Ga-67, respectively) of good stability (>98% after incubation in PBS for 24 hours) and confirmed the large sizes (99%>0.5 microns). Additionally, we have demonstrated decreases in Gradient Echo (GRE) signals on MRI with increasing Fe contents in the concentration range intended for intratumoral injection. Ga-68 GIMA is a positron emitter with a physical half-life of 1.1 hours with which the short-term organ distribution will be monitored using PET to exploit the high sensitivity and good spatial resolution (advantages over gamma-camera). Ga-67 GIMA is a gamma-ray emitter with a physical half-life of 78 hours during which the long-term organ distribution of GIMA can be monitored using gamma-cameras.

3.1 Supplier/How Supplied

3.1.1 Carrier-free Gallium-68 GIMA will be prepared according to the method of Colombetti [20] with the exception that no non-radioactive gallium (carrier) will be added. The 1-hour short-lived isotope Ga-68 will be obtained from a Ga-68 generator (Du Pont Radiopharmaceuticals, N, Billerica, MA). The product is a colloid suspended in saline. Aseptic procedures will be followed and pyrogenicity test will be performed and negativity will be confirmed before injection. Waterproof gloves will be worn by the personnel during preparation procedures. All vials will be brought to room temperature immediately prior to use. Part of the contents in the vials will be tested for the evaluation of pyrogenicity using the LAL assay (Whittaker Bioproducts, Walkersville, MD) which will last approximately 30 minutes. The synthesis and testing procedures typically last 80 minutes. Therefore, about three-fold more radioactivity will be prepared for each vial. The suspended colloid is available in screw-cap vials with radioactivity ranging from 0.1 to 2 mCi per vial. The total iron content is approximately 2 milligrams. The radioactivity purity is greater than 99% at the time of calibration. The sterility of the products will be tested and monitored for 10 days for aerobic and anaerobic pathogens using BD Bactec Plus/F and Thioglycolate cultures (Becton and Dickinson, Sparks, MD), as a

standard testing procedure of radiopharmaceuticals of short half-lives.

- 3.1.2 The South Texas Nuclear Pharmacy has agreed to provide carrier-free Ga67-GIMA in pyrogen-free (LAL test-negative) conditions and monitor sterility tests for each dose preparation for 10 days.

3.2 Determination of radioactivity of GIMA.

The radioactivity of either Ga-68 and Ga-67 will be measured by a Capintec dose calibrator and the volume will be noted.

3.3 Storage and Disposal

Unopened vials of Ga-68 GIMA and Ga-67 GIMA will be stored at room temperature and shielded from sunlight behind lead blocks.

3.4 Toxicity.

From the published results of human lung scanning, no adverse effects have been attributed to GIMA. Published toxicity of gallium compound has been correlated with the nonradioactive free gallium (carrier) with a limiting dose of 1mg, corresponding to the about 0.1 mCi of the low-specificity GIMA. The high specific activity GIMA prepared by our method contains no nonradioactive gallium and the physical amount of gallium (Ga-68) is one-billionth that of the earlier preparation [20] and is therefore well below the toxicity threshold. In fact, cancer patients injected with larger systemic doses up to 10 mCi carrier-free Ga-67 (as used in routine tumor localization imaging) do not have signs of toxicity.

All Study patients must meet the eligibility criteria:

4.1 Eligible Patients

- 4.1.1 Patients must have signed the informed consent.
- 4.1.2 Patients must be 18 years of age or older
- 4.1.3 Patients must have breast cancer diagnosed by histopathology but no surgical resection of the tumor.
- 4.1.4 Patients should have received no previous focal external beam radiation therapy to the thorax.
- 4.1.5 Patients who have not received systemic or cytotoxic chemotherapy for the breast cancer under study. Patient under hormonal therapy alone will be eligible.
- 4.1.6 Patients with adequate platelets to avoid excessive bleeding and adequate white cells to avoid infection.
 - Granulocytes $\geq$ 1000 cells/mcl
 - Platelets $\geq$ 40,000/mcl
- 4.1.7 Patients with Zubrod performance scale of 2 or below.

- 4.1.8 Patients with breast tumor > 2 cm compressed thickness on mammogram but no tumor necrosis by MRI.
- 4.1.9 Patients must have scheduled surgical resection (either mastectomy or conservation surgery) of the breast tumor within 2 weeks after injection.

4.2 Ineligible Patients

- 4.2.1 Patients of child-bearing age who have positive pregnancy test or are lactating.
- 4.2.2 Patients with septicemia, severe infection or acute hepatitis.
- 4.2.3 Patients who had radiation therapy or chemotherapy of the breast cancer prior to the planned surgery.
- 4.2.4 Patients who had residual radiation from previous radionuclide administration, from the day of injection:
 - F-18 agents of more than 10 mCi within 2 days for the Ga-68 GIMA and Ga-67 GIMA groups;
 - In-111, Ga-67 or I-131 agents of more than 1 mCi within 14 days for the Ga-67 GIMA groups.
- 4.2.5 Patients who cannot undergo MRI procedures (including nonvisualization of tumor on MRI and implants incompatible with MRI)
- 4.2.6 Patients with claustrophobia cannot be entered for the Ga-67 GIMA groups because of the requirements of repeated MRI requiring repeated conscious sedation. Entry into Ga-68 GIMA will be acceptable with only one session of conscious sedation.
- 4.2.7 Patients who have scheduled surgical resection of the breast tumor in less than 7 days are not eligible to enter the Ga-67 GIMA groups

Since breast cancer is predominantly a disease of the adults and some teenage pediatric patients and GIMA is expected to stay within the tumor, no dose adjustment is made for younger patients because of statistical requirements of uniformity for small sample sizes.

5.1 Human Study:

Patients will be recruited from female breast cancer patients scheduled for surgery at least one-week from the planned day of injection. One of the inclusion criteria will be a tumor size of > 2cm in diameter but no tumor necrosis as determined by MRI. No spillage outside of the tumor is expected from an injection of 1 cc. A total of 10 patients in 2 groups of 5 patients each will be studied. The MRI and nuclear imaging studies will follow routine clinical procedure.

The first group of 5 patients will receive 0.5 mCi of Ga-68 GIMA (in 1 cc saline) intratumorally under MRI guidance and imaged with MRI and then undergo PET/CT studies at 1 hour after injection on the first day. The second groups will receive 0.2 mCi intratumoral

injections of Ga-67 GIMA (in 1cc saline) under MRI guidance and then undergo whole-body scintigraphy, MRI and ultrasound at 2, 4, 24 hours and one of the 2nd, 3rd or 4th day after injection. Blood sample collection will take place during each of the scintigraphy session. Although the exact radiation dosimetry has yet to be determined, the radiation doses to the tumor can be estimated from the published biological half-life of 30 hours [20]. These 2 groups of patients will receive estimated doses of 463 cGy and 262 cGy respectively in the tumor, with a 10% isodose range of 0.20 cm and 0.02 cm from the injection site edge respectively.

5.1.1 Patient Entry Requirements

Patients entered into this patient treatment study must meet eligibility requirements and sign the informed consent form. Each patient will be given a standard medical examination including a breast MRI with a medical history and laboratory work to determine eligibility. Patients will be accrued from the breast oncology clinics. When a patient with a breast cancer larger than 2 cm and who needs to undergo surgery is identified, the patient will be interviewed and provided information about this study. Signed informed consent will be obtained by Dr. Edmund Kim or other physician investigators (except Dr. Franklin Wong because of potential conflict of interest) no earlier than the next day after the initial interview to provide adequate time for the patient to consider participation.

5.2 MRI and Injection

The patients will be scanned using a GE Signa Lx 1.5 Tesla MRI scanner equipped with a high performance gradient system (amplitude = 22mT/m; slew rate = 120 T/m/s). A phased-array bilateral breast RF coil will be used to maximize the signal-to-noise ratio. A breast positioning system with two compression plates and Vitamin E markers will be used to hold the breast in a reproducible position. Image slice thickness will be approximately 6mm and the scan will be positioned to also include the axilla as much as possible.

Before entry into the study, patients will have been asked about metallic implants such as pacemakers and other devices as well as history of claustrophobia. Patient with these conditions will have been excluded as determined by the MRI radiologist collaborators. Specific and easily accessible tumors will be preferred over other locations. An MR-compatible 20-gauge needle of 7 cm in length will be used. If sedation is required and indicated, oral dose of 1 mg of Ativan or 5 mg of valium will be administered as per established procedures in the MRI suite.

The breast tumor will first be localized using a fast gradient echo T1-weighted 3D pulse sequence in the sagittal plane. An MR-

compatible disposable sterile needle will be placed intra-tumorally. Areas of necrosis, if any (developed after the pre-injection MRI), will be avoided. An MR scan will be performed to ensure the proper location of the needle. Prior to injection, a high-resolution baseline image will be obtained using a gradient echo (GRE) pulse sequence with parameters selected to be sensitive to T2*. Injection may be preceded with surface or subcutaneous local anesthesia at the needle entrance through the surface. The GIMA will be injected in one single intratumoral injection into the tumor over 1 minute. The needles will then be slowly removed. This procedure is similar to routine breast lymphoscintigraphy. Immediately after injection, images (without breast compression) from multi-phase T2*-weighted MRI will be acquired using the same pulse sequence in quick successions up to 1 hour. All subsequent MRI images will be without breast compression. The volume of the injectate will be determined from manual segmentation.

5.3 Nuclear imaging using PET/CT and High Resolution Scintigraphy

The earlier biodistribution of GIMA sequestration in the tumor and lymph nodes will be studied with Ga-68 GIMA using PET in the first group of 5 patients. Accurate localization and quantitation of radioactivity will be derived from the superior accuracy and resolution of PET. However, delayed PET studies will not be useful because Ga-68 decays rapidly (1.1 hour half-life). The second groups of patients will receive 0.2 mCi of Ga-67 GIMA to assess the prolonged phase (up to 5 days) of radioactivity distribution using whole-body gamma camera scanning.

After MR guided injection and imaging, the patient will be sent to the Nuclear Medicine/PET Clinic. The radioactivity residence time in the tumor and lymph nodes will be derived from serial scintigrams or PET scans. For patients injected with Ga-67 GIMA, scintigrams will be acquired in a Siemens dual-head ECAM gamma camera equipped with ultra-high resolution collimators. This combination will be able to achieve a system resolution of 7mm FWHM (tested with Tc-99m at a distance of 10 cm). One transmission scan will be performed before injection. Then, whole-body and planar imaging will continue at 2, 4, 24 hours and one of the 2nd, 3th or 4th day after injection. Patients injected with Ga-68 GIMA will undergo PET scans with attenuation correction using a high resolution Seimens HR Plus or a GE DST PET/CT scanner with spatial resolution of 6 mm covering the thorax. Images will be reconstructed in 2D/3D mode and the Ga-68 voxel concentration will be measured in the tumor and in the lymph node and be correlated with volumes from anatomic imaging including MRI and CT.

5.3.1 Urine and Blood Collection.

For the Ga-67 GIMA group, patients will be asked to provide urine samples at the following time intervals: before injection and during scintigraphy sessions at 2, 4, 24 hours and one of the 2nd, 3rd or 4th day after injection. Patients will be instructed and provided containers to collect all urine output up to the last day of imaging and urine samples will be collected during the scintigraphy sessions. Urine samples will have volume, time of excretion, and radioiodine content measured. All these patients will be asked to provide blood samples (3-4 cc each) at nuclear imaging sessions to characterize the systemic Ga-67 clearance and whole-body and organ radiation dosimetry. Blood samples will be collected by a physician, nurse or nuclear medicine technologist.

5.3.2 Ultrasonography

The injectate volumes will be monitored using ultrasonography using parameters for routine breast imaging, following each MRI session.

5.4 Dosimetry modeling of beta and gamma emissions from radionuclides

There are three components necessary for the estimation of absorbed doses to tissues surrounding the injected activity: 1) The energy deposited in the surrounding tissues will be determined using radiation transport analysis [21], 2) the geometry of the activity distribution (source region) will be determined using MR image data, and 3) the total number of radioactive transitions that occur in the region will be determined using data from the scintigram. Both beta and gamma emissions will be evaluated. The total radiation absorbed doses will be derived for the tumor and surrounding tissues.

The volumetric data measured from MRI will be used to derive the S-values of the tumors using voxel-based simulation [22] to calculate the radiation absorbed doses to the injection sites and the surrounding tissues. Radiation dose rates, or S-values, will be compared with those from the sphere [18] and shell models [19] to evaluate the effects of potentially heterogeneously distributed injectate in the tumor. Such comparison will establish the boundaries of the models and aid choices of dosimetric methods in future studies.

5.5 Pathologic and Autoradiographic Evaluation

Histopathologic data will be collected from the surgical specimen obtained during the scheduled tumor resection (about 7-14 days from injection). If present, the histologic changes from radiation effects [23, 24] in and around the tumor/lymph nodes will be correlated with predicted and measured dosimetry. Selected histopathologic slices, as revealed from the reddish-brown appearance of GIMA, from patients injected with Ga-67 GIMA will be temporarily secured for autoradiography (overnight) to visualize geographic distribution. The

fraction of injected radioactivity in the tumor, lymph nodes and injection sites will be determined, without physical damage to the specimens. The histologic changes and GIMA distribution from autoradiography will be used to correlate with MRI-derived volumetric data and with radioactivity data from nuclear imaging.

5.6 Potential Radiation Effects and Radiation Safety to the personnel

Because of the rapid decay of Ga-68 GIMA with half-life of 1.1 hours, negligible residual radioactivity (0.2 nano Ci) is expected 1 day after injection. Therefore, the planned surgery can be performed without health risk to the personnel. The surgical specimens will not undergo autoradiography although histopathologic correlations will be performed. With a biologic half-life of 30 hours and effective half-life of 21 hours, the residual Ga-67 GIMA will be less than 2% of the original dose after the 5 days of imaging (or 6 effective lives). At 7 days after injection, there will be essentially negligible residual amount (2 micro Ci, in total) of Ga-67 and health risk is minimal to health personnel, as long as general body-fluid precaution is followed including washing hands.

Prior to the imaging procedures, subjects will be questioned to obtain a medical history, and given a complete physical examination including a mammogram, breast MRI and laboratory tests including CBC to determine eligibility. Patients who have not previously received a breast MRI (with contrast if necessary) will have one performed (at the cost of the study) prior to entry into the study to evaluate the tumor size and assure absence of tumor necrosis. Women with child-bearing potential will receive a pregnancy test.

For the groups injected with Ga-67 GIMA, blood and urine samples will be taken from the patients at nuclear imaging time to measure radiogallium clearance and retention up to 5 days.

8.1 Toxicity

The radiation absorbed doses to the body and organs are low for both the low doses (0.5 mCi, maximum) of Ga-67 and Ga-68, compared with the routine dose of 8 mCi of Ga-67 citrate for tumor localization studies. The residual of 1 mg of Fe in the tissue is also not expected to present significant toxicity, considering the routine intramuscular injection of up to 1000 mg of iron sulfate for the treatment of anemia.

8.2 End-points of Study

End-point will be defined as grade III/IV toxicity (NCI criteria) in 2 or more of the 5 patients in a particular dose level.

- 9.1 All patients will be followed with reasonable efforts until 1 month after injection. Any patient initially accepted into the study, but who subsequently is determined to be ineligible for radionuclide evaluation will be removed from the study. The reason and time of removal will be documented.
- 9.2 The development of unacceptable toxicity is defined as unpredictable, irreversible or grade 4 toxicity.
- 9.3 Non-compliance by patient with protocol requirements.
- 9.4 Patients have the right to withdraw from the study at any time without consequence. If a patient withdraws from the study, reasonable attempts will be made to document the reason for withdrawal.
- 9.5 Any patient can be removed at the discretion of the investigator or sponsor.

This is a study of biodistribution. Two groups of 5 patients each will be studied with 0.2 mCi Ga-67 GIMA and 0.5 mCi Ga-68 GIMA respectively. Therefore, a total of 10 patients will be entered into the study. Only descriptive statistics (mean, variance, ratios and diagrams) will be applied to analyse the results of dispersed volumes by MRI and ultrasound, tumor and organ percentage of injected doses, dosimetry, potential toxicity and histologic changes.

- 11.1 Any life-threatening and/or unexpected and serious (grade 3 or 4) adverse reaction will be reported immediately to the study chairman who, in turn, must notify the Surveillance Committee.
 - 11.2 All patients experiencing an adverse reaction must have an adverse reaction form completed.
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Appendix V

THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Informed Consent

**INFORMED CONSENT/AUTHORIZATION FOR
PARTICIPATION IN RESEARCH**

**Radiation Dosimetry of Intra-tumoral Injection of Radionuclides
in Human Breast Cancer
ID03-0070**

Subtitle: Intratumoral Injection of Gallium-67 GIMA for Gamma Camera Imaging and
Magnetic Resonance Imaging

1.

Participant's Name

I.D. Number

You are being asked to take part in this clinical research study at The University of Texas M.D. Anderson Cancer Center (hereinafter referred to as "UTMDACC" or "the institution"). This research study is strictly voluntary. This consent form explains why we are performing this research study and what your role will be if you choose to participate. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to participate in the study. This study complies with all laws and regulations that apply.

You are being asked to take part in this study because you have breast cancer and you have a surgery scheduled to remove the cancer.

DESCRIPTION OF RESEARCH

2. PURPOSE OF STUDY

The goal of this clinical research study is to learn how special radioactive molecules called gallium-iron macroaggregates (GIMA) distribute (travel and spread) in the body after they are injected into breast cancer tissue.

3. DESCRIPTION OF RESEARCH

For the current diagnostic procedure called [lymphoscintigraphy](#), small radioactive particles (called colloids) are injected into a lymph node. Then, a special nuclear medicine scanner is used to watch these particles slowly distribute in the body. Researchers noticed the larger the molecule, the slower the particles move in the body. In fact, some of the larger colloid molecules seem to stay at the site of injection with very little movement. Since the amount of radiation on these colloids is very low, they cannot be used to treat cancer. New molecules have been developed called GIMA. These GIMA molecules have been designed to act like the colloid molecules (very slow-moving). However, the GIMA molecules were made to carry larger radioactive particles. Since these molecules are very slow-moving, they can be injected directly into a tumor without spreading out very far from the site of injection. In this way, radiation can be delivered directly to the tumor tissue without spreading to normal tissue.

For this study, small particles of radiation (Ga-67) will be attached to GIMA molecules. These molecules will then be injected into the breast cancer tumor. Special scanners will be used (gamma camera and MRI) to "see" how far the molecules move away from the injection site. If it is found that the molecules do not move very far, in the future, more radiation particles can be attached to the GIMA molecules. These GIMA molecules can then be used to treat cancer with radiation. The radiation level in GIMA (but not its size) can be measured from outside of the body by a gamma camera. The amount of iron in GIMA can be measured from outside of the body by a MRI scanner. The distribution of iron in GIMA can be used to determine the size of the GIMA collection by the appearance of darkening in the images around the injection site. It will be injected by a MRI-compatible needle to avoid potential injury during MRI. The small amounts of iron (one thousandth of a gram) in the GIMA injection will not be sufficient to cause physical movement of the particles because the particles are firmly dispersed within the tumor tissues. Ultrasound measurement is non-invasive and may provide similar size information and may in fact prove to be a more convenient method to monitor the size of GIMA in the future. Combining the radiation level and size measurements will allow researchers to [determine how](#) much radiation is delivered to the tumor and to other organs (if any).

Participants will receive a GIMA with a particle of radiation attached (Ga-67) that gives off a lower amount of radiation (0.2 mCi). The amount of radiation you will receive from the GIMA molecules is very low, about the same as a routine nuclear medicine scan.

The GIMA will be injected directly into the tumor tissue with the help of a MRI scanner. The MRI scanner will be used to make sure the needle is inserted directly into the tumor. Also, MRI scans will be done within one hour after the injection. An ultrasound examination of the injection site will also be performed to confirm the location of the GIMA particles

You will undergo nuclear imaging scans in the nuclear medicine clinic at 1, 2, and 4 hours after the injection as well as once a day for the next 4 days. You will also have MRI scans and ultrasound for the first 4 days after the injection. You will be asked to have blood (1 teaspoon) and urine samples collected during each imaging session.

Participants will have their regularly scheduled surgery. The tissue that is collected during the procedure will be studied to see the effect of the treatment on the tissue. Part of the tissue collected will be retained for analysis of the small amount of radioactivity left.

This is an investigational study. The research human use of radioactive Ga-67 GIMA has been approved by the UTMDACC Radiation Drug Research Committee which has been authorized by the FDA. The GIMA, nuclear imaging scans, ultrasound examinations and MRI scans performed for this study will be provided free of charge. Because participation in the Ga-67 GIMA group requires additional trips to UTMDACC over 5 days, you may be partially reimbursed for lodging expenses. If you live more than 50 miles from UTMDACC, and choose to stay in a local hotel during the study, you may be partially reimbursed up to 4 nights (up to \$70 per night). Up to 5 participants will take part in this Ga-67 GIMA portion of the research and up to a total of 10 participants will take part in this study. All will be enrolled at UTMDACC.

This protocol is partially funded by a research grant from United States Army Medical Research and Materiel Command. It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research. Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this study..

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS

While on this study, you are at risk for the side effects listed in this form. You should discuss these with the study doctor or your regular doctor. The known side effects are listed in this form, but they will vary from person to person. Many side effects go away shortly after the study drug is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent and may even cause death.

Giving GIMA through the needle into the breast cancer tumor may result in pain at the injection site and or infection. GIMA have radiation particles attached to them. Radiation may increase the chance of developing new cancer. The radiation may also alter the cells in the tumor causing changes for the future planning of further treatment.

MRI (Magnetic Resonance Imaging) uses a large magnet instead of x-rays to take pictures of the inside of your body. People who have metal in their bodies (pacemakers, neurostimulators, certain clips, or staples from prior surgery) may not receive a MRI. The magnetic field used in MRI scanning may harm such people or cause problems with devices such as pacemakers. Part or all of the body will be passed into a long, narrow tube (scanner) which is open at both ends. The scanner has an intercom, which will allow you to speak to the doctors and staff during the procedure. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. In addition, you may feel light vibrations throughout your body. Some people, especially those who have a tendency to feel uncomfortable in small or closed spaces, may feel "closed in" and become anxious while in the scanner. If you feel ill or anxious during scanning, doctors and the MRI staff will give comfort or the scanning will be stopped.

Ultrasound examination involves no ionizing radiation and is a safe routine procedure to evaluate breast tissues. In this study, it is used to confirm and follow the gross distribution of GIMA particles; while MRI is used to follow the refined disibution of GIMA.

Gamma camera scan is a medical technique that externally monitors the radioactivity in body and will be used to track the movement of the Ga-67 GIMA through the body. The gamma camera can take pictures of Ga-67 GIMA and "see" where it is in the body. By watching how Ga-67 GIMA travels through the body and studying where Ga-67 GIMA collects, researchers can learn if any radiation is deposited in certain organs in the body. Some people may feel "closed in" while lying in the scanner. However, the scanner is open at both ends and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during

scanning, doctors and/or technicians will give comfort or the scanning will be stopped.

For this study, the Ga-67 GIMA is radioactive substances of low radiation levels. The total amount of radiation you receive from this study is about the same as 1-2 chest x-rays.

You may experience pain, bleeding, and/or bruising from the blood draws. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn

Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy for regulatory compliance and quality (301-619-21650 (non-duty hours call 301-619-2165 **and** send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S.Army Medical Research and Materiel Command, ATTN: MPMC-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

This research study may involve unpredictable risks to the participants.

5. POTENTIAL BENEFITS

If this research study shows that GIMA stays at the injection site, future cancer therapies may be developed. This information may be of benefit to future patients. There are no benefits for you in this study.

6. ALTERNATE PROCEDURES OR TREATMENTS

You may choose not to take part in this study.

I understand that the following statements about this study are true:

7. According to the institutional conflict of interest policy, the principal investigator of this study and my primary physician cannot have a financial interest in any aspect of this research. However, in instances of medical emergency, it is possible that I may be cared for by a physician and/or administrator who has some form of financial interest in the sponsor of this study.

As of 06/10/2003, the following investigators on this study have disclosed an equity or stock option interest in the sponsor of this study: Through the University of Texas M. D. Anderson Cancer Center, Dr. Franklin C. Wong, a collaborator of this protocol has filed a patent application to the U.S. Patent and Trademark Office on radionulcide cancer therapies including the method of producing carrier-free GIMA. For these reasons, there is potential conflict of financial interest (intellectual properties) in this study involving Dr. Franklin C. Wong, The University of Texas, and UTMDACC. Dr. Franklin C. Wong is also the principal investigator of a U.S. Army Breast Cancer Research Grant supporting this study. Dr. E. Edmund Kim is the principal investigator who will supervise this study in UTMDACC. Either Dr. E. Edmund Kim or Dr. Gary Whitman will perform the injection of Ga-67 GIMA while you are in the MRI scanner.

The University of Texas M.D. Anderson Cancer Center has a financial interest in the sponsor of this study.

The University of Texas System has a financial interest in the sponsor of this study.

8. If I want to receive updated information regarding the financial interests of any physician and/or administrator at UTMDACC who has cared for me, I may call the Conflict of Interest Coordinator at (713) 792-3220. Upon request, I will be given access to information disclosing the identity of all physicians and/or administrators who have a financial interest in the sponsor of this study.
9. My participation is voluntary.
10. I may ask any questions I have about this study, including financial considerations, of my treating physician. I may contact the principal investigator for this study Dr. Edmund Kim at 713-794-1052 or the Chairman of the institution's Surveillance Committee at 713-792-2933 with any questions that have to do with this study.
11. I may withdraw at any time without any penalty or loss of benefits. I should first discuss leaving the study with my physician. Should I withdraw from this study, I may still be treated at UTMDACC.
12. I understand that the study may be changed or stopped at any time by my doctor, the principal investigator, the study sponsor, or the Surveillance Committee of UTMDACC.

13. I will be informed of any new findings that might affect my willingness to continue participating in the study.
14. The institution will take appropriate steps to keep my personal information private. However, there is no guarantee of absolute privacy. The Food and Drug Administration ("FDA"), and/or United States Army Medical Research and Material Command might review my record to collect data or to see that the research is being done safely and correctly. Under certain circumstances, the FDA could be required to reveal the names of participants.
15. If I suffer injury as a direct result of participation in this study, the institution will provide reasonable medical care. I understand that I will not receive reimbursement of expenses or financial compensation from the institution, the sponsor, the investigators or the United States Army Medical Research and Material Command for this injury. If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, (insert name and telephone number of principal investigator). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U. S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221. for this injury. I may also contact the Chairman of UTMDACC's Surveillance Committee at 713-792-2933 with questions about study related injuries.
16. Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (HMO, Health Insurance company, etc.), will be my responsibility.
17. I recognize that there are no plans to provide any compensation to me for any patents or discoveries that may result from my participation in this research.

Authorization for Use and Disclosure of Protected Health Information

- A. During the course of this study, the research team at UTMDACC will be collecting information about you that they may share with the FDA and/or United States Army Medical Research and Material Command. This information may include your treatment schedule and the results of any tests, therapies, or procedures that you undergo for this study. The purpose of collecting and sharing this information is to learn about how the treatment affects your disease and any side effects you experience as a result of your treatment.

Your doctor and the research team may share study information with certain individuals. These individuals may include representatives of the FDA and/or the above listed sponsor, clinical study monitors who verify the accuracy of the information, individuals with medical backgrounds who determine the effect that the treatment has on your disease, and/or individuals who put all the study information together in report form. The UTMDACC research team may provide this information to the FDA and/or the above listed sponsor at any time.

- B. There is no expiration date for the use of this information as stated in this authorization. You may withdraw your authorization to share this information at any time in writing. More information on how to do this can be found in the UTMDACC Notice of Privacy Practices (NPP). You may contact the Office of Protocol Research at 713-792-2933 with questions about how to find the NPP.
- C. If you refuse to provide your authorization to disclose this protected health information, you will not be able to participate in the research project.
- D. I understand that my personal health information will be protected according to state and federal law. However, there is no guarantee that my information will remain confidential, and may be re-disclosed at some point.

CONSENT/AUTHORIZATION

Having read and understood the above, and having had the chance to ask questions about this study and reflect and consult with others, I give _____ permission to enroll me on this study. I have been given a copy of this consent.

SIGNATURE OF PARTICIPANT

DATE

WITNESS OTHER THAN PHYSICIAN OR INVESTIGATOR

DATE

SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP

DATE

I have discussed this clinical research study with the participant and/or his or her authorized representative, using a language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SIGNATURE OF STUDY DOCTOR OR PERSON OBTAINING
CONSENT

DATE

Translator

I have translated the above informed consent into
_____ for this

participant.
Language)

(Name of

NAME OF TRANSLATOR

SIGNATURE OF TRANSLATOR

DATE



Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Radiation Dosimetry of Intra-tumoral Injection of Radionuclides
in Human Breast Cancer
ID03-0070

Subtitle: Intratumoral Injection of Gallium-68 GIMA for Imaging by Positron Emission Tomography and Magnetic Resonance Imaging

1. _____
Participant's Name I.D. Number

You are being asked to take part in this clinical research study at The University of Texas M.D. Anderson Cancer Center (hereinafter referred to as "UTMDACC" or "the institution"). This research study is strictly voluntary. This consent form explains why we are performing this research study and what your role will be if you choose to participate. This form also describes the possible risks connected with being in this study. After reviewing this information with the person responsible for your enrollment, you should know enough to be able to make an informed decision on whether you want to participate in the study. This study complies with all laws and regulations that apply.

You are being asked to take part in this study because you have breast cancer and you have a surgery scheduled to remove the cancer.

DESCRIPTION OF RESEARCH

2. PURPOSE OF STUDY:

The goal of this clinical research study is to learn how special radioactive molecules called gallium-iron macroaggregates (GIMA) distribute (travel and spread) in the body after they are injected into breast cancer tissue.

3. DESCRIPTION OF RESEARCH:

For the current diagnostic procedure called [lymphoscintigraphy](#), small radioactive particles (called colloids) are injected into a lymph node. Then, a special nuclear medicine scanner is used to watch these particles slowly distribute in the body. Researchers noticed the larger the molecule, the slower the particles move in the body. In fact, some of the larger colloid molecules seem to stay at the site of injection with very little movement. Since the amount of radiation on these colloids is very low, they cannot be used to treat cancer. New molecules have been developed called GIMA. These GIMA molecules have been designed to act like the colloid molecules (very slow moving). However, the GIMA molecules were made to carry larger radioactive particles. Since these molecules are very slow moving, they can be injected directly into a tumor without spreading out very far from the site of injection. In this way, radiation can be delivered directly to the tumor tissue without spreading to normal tissue.

For this study, small particles of radiation (Ga-68) will be attached to GIMA molecules. These molecules will then be injected into the breast cancer tumor. Special scanners will be used (PET and MRI) to "see" how far the molecules move away from the injection site. If it is found that the molecules do not move very far, in the future, more radiation particles can be attached to the GIMA molecules. These GIMA molecules can then be used to treat cancer with radiation. The radiation level in GIMA (but not its size) can be measured from outside of the body by scanners such as a PET scanner. The amount of iron in GIMA can be measured from outside of the body by a MRI scanner. The distribution of iron in GIMA can be used to determine the size of the GIMA collection by the appearance of darkening in the images around the injection site. It will be injected by a MRI-compatible needle to avoid potential injury during MRI. The small amounts of iron (one thousandth of a gram) in the GIMA injection will not be sufficient to cause physical movement of the particles because the particles are firmly dispersed within the tumor tissues. Ultrasound measurement is non-invasive and may provide similar size information and may in fact prove to be a more convenient method to monitor the size of GIMA in the future. Combining the radiation level and size measurements will allow researchers to [determine how](#) much radiation is delivered to the tumor and to other organs (if any).

Participants in this group will receive a GIMA with Ga-68 attached at a radiation dose of 0.50 mCi. The amount of radiation you will receive from the GIMA molecules is very low, about the same as a routine nuclear medicine scan (1-2 chest X-rays).

The GIMA will be injected directly into the tumor tissue with the help of a MRI scanner. The MRI scanner will be used to make sure the needle is inserted directly into the tumor. Also, MRI scans and ultrasound examination will be done within one hour after the injection and also after the 1-hour PET scanning which will take place after the initial MRI and ultrasound imaging. In other words, the sequence of event will be: an initial MRI for the injection of Ga-68 GIMA, a MRI and ultrasound to measure the particle size distribution, PET scanning to measure Ga-68 radioactivity distribution followed by repeated MRI and ultrasound to measure the particles. These procedures are expected to last about 3 hours totally.

Participants in all groups will have their regularly scheduled surgery. The tissue that is collected during the procedure will be studied to see the effect of the treatment on the tissue.

This is an investigational study. The human research use of radioactive Ga-68 GIMA has been approved by the UTMDACC Radiation Drug Research Committee which has been authorized by the FDA. The Ga-68 GIMA, PET scans, ultrasound examinations and MRI scans performed for this study will be provided free of charge. Five participants will take part in this group. All will be enrolled at UTMDACC.

This protocol is partially funded by a research grant from United States Army Medical Research and Materiel Command. It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research. Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this study..

4. RISKS, SIDE EFFECTS, AND DISCOMFORTS TO PARTICIPANTS:

While on this study, you are at risk for the side effects listed in this form. You should discuss these with the study doctor or your regular doctor. The known side effects are listed in this form, but they will vary from person to person. Many side effects go away shortly after the

study drug is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent and may even cause death.

Giving Ga-68 GIMA through the needle into the breast cancer tumor may result in pain at the injection site and or infection. Ga-68 GIMA have radiation particles attached to them. Radiation may increase the chance of developing new cancer. The radiation may also alter the cells in the tumor causing changes for the future planning of further treatment.

MRI (Magnetic Resonance Imaging) uses a large magnet instead of x-rays to take pictures of the inside of your body. People who have metal in their bodies (pacemakers, neurostimulators, certain clips, or staples from prior surgery) may not receive a MRI. The magnetic field used in MRI scanning may harm such people or cause problems with devices such as pacemakers. Part or all of the body will be passed into a long, narrow tube (scanner) which is open at both ends. The scanner has an intercom, which will allow you to speak to the doctors and staff during the procedure. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. In addition, you may feel light vibrations throughout your body. Some people, especially those who have a tendency to feel uncomfortable in small or closed spaces, may feel "closed in" and become anxious while in the scanner. If you feel ill or anxious during scanning, doctors and the MRI staff will give comfort or the scanning will be stopped.

Ultrasound examination involves no ionizing radiation and is a safe routine procedure to evaluate breast tissues. In this study, it is used to confirm and follow the gross distribution of GIMA particles; while MRI is used to follow the refined distribution of GIMA.

A PET (Positron Emission Tomography) scan is a medical technique that monitors the activity in the brain and other organs and will be used to track the movement of the Ga-68 GIMA through the body. The PET scanner can take pictures of Ga-68 GIMA and "see" where it is in the body. By watching how Ga-68 GIMA travels through the body and studying where Ga-68 GIMA collects, researchers can learn if any radiation is deposited in certain organs in the body. Some people may feel "closed in" while lying in the scanner. However, the scanner is open at both ends and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during scanning, doctors and/or technicians will give comfort or the scanning will be stopped.

For this study, the Ga-68 GIMA is radioactive substance of low radiation levels. The Ga-68 GIMA PET scan procedure also exposes

your body to low-level of radiation. The total radiation you receive from these procedures is about the same as 1-2 chest x-rays.

Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC Deputy for regulatory compliance and quality (301-619-21650 (non-duty hours call 301-619-2165 **and** send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S.Army Medical Research and Materiel Command, ATTN: MPMC-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

This research study may involve unpredictable risks to the participants.

5. POTENTIAL BENEFITS:

If this research study shows that GIMA stays at the injection site, future cancer therapies may be developed. This information may be of benefit to future patients. There are no benefits for you in this study.

6. ALTERNATE PROCEDURES OR TREATMENTS:

You may choose not to take part in this study.

I understand that the following statements about this study are true:

7. According to the institutional conflict of interest policy, the principal investigator of this study and my primary physician cannot have a financial interest in any aspect of this research. However, in instances of medical emergency, it is possible that I may be cared for by a physician and/or administrator who has some form of financial interest in the sponsor of this study.

As of 06/10/2003, the following investigators on this study have disclosed an equity or stock option interest in the sponsor of this study: Through the University of Texas M. D. Anderson Cancer Center, Dr. Franklin C. Wong, a collaborator of this protocol has filed a patent application to the U.S. Patent and Trademark Office on radionulcide cancer therapies including the method of producing carrier-free GIMA. For these reasons, there is potential conflict of financial interest (intellectual properties) of this study involving Dr. Franklin C. Wong, The University of Texas, and UTMDACC. Dr. Franklin C. Wong is also the principal investigator of a U.S. Army Breast Cancer Research Grant supporting this study. Dr. E. Edmund Kim is the principal investigator who will supervise this study in UTMDACC. Either Dr. E. Edmund Kim or Dr. Gary Whitman will perform the injection of Ga-68 GIMA while you are in the MRI scanner.

The University of Texas M.D. Anderson Cancer Center has a financial interest in the sponsor of this study.

The University of Texas System has a financial interest in the sponsor of this study.

8. If I want to receive updated information regarding the financial interests of any physician and/or administrator at UTMDACC who has cared for me, I may call the Conflict of Interest Coordinator at (713) 792-3220. Upon request, I will be given access to information disclosing the identity of all physicians and/or administrators who have a financial interest in the sponsor of this study.
9. My participation is voluntary.
10. I may ask any questions I have about this study, including financial considerations, of my treating physician. I may contact the principal investigator for this study Dr. Edmund Kim at 713-794-1052 or the Chairman of the institution's Surveillance Committee at 713-792-2933 with any questions that have to do with this study.
11. I may withdraw at any time without any penalty or loss of benefits. I should first discuss leaving the study with my physician. Should I withdraw from this study, I may still be treated at UTMDACC.
12. I understand that the study may be changed or stopped at any time by my doctor, the principal investigator, the study sponsor, or the Surveillance Committee of UTMDACC.

13. I will be informed of any new findings that might affect my willingness to continue participating in the study.
14. The institution will take appropriate steps to keep my personal information private. However, there is no guarantee of absolute privacy. The Food and Drug Administration ("FDA"), and/or United States Army Medical Research and Materiel Command might review my record to collect data or to see that the research is being done safely and correctly. Under certain circumstances, the FDA could be required to reveal the names of participants.
15. If I suffer injury as a direct result of participation in this study, the institution will provide reasonable medical care. I understand that I will not receive reimbursement of expenses or financial compensation from the institution, the sponsor, the investigators or the United States Army Medical Research and Materiel Command for this injury. If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, (insert name and telephone number of principal investigator). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U. S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221. for this injury. I may also contact the Chairman of UTMDACC's Surveillance Committee at 713-792-2933 with questions about study related injuries.
16. Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (HMO, Health Insurance company, etc.), will be my responsibility.
17. I recognize that there are no plans to provide any compensation to me for any patents or discoveries that may result from my participation in this research.

Authorization for Use and Disclosure of Protected Health Information

- A. During the course of this study, the research team at UTMDACC will be collecting information about you that they may share with the FDA and/or United States Army Medical Research and Material Command. This information may include your treatment schedule and the results of any tests, therapies, or procedures that you undergo for this study. The purpose of collecting and sharing this information is to learn about how the treatment affects your disease and any side effects you experience as a result of your treatment.

Your doctor and the research team may share study information with certain individuals. These individuals may include representatives of the FDA and/or the above listed sponsor, clinical study monitors who verify the accuracy of the information, individuals with medical backgrounds who determine the effect that the treatment has on your disease, and/or individuals who put all the study information together in report form. The UTMDACC research team may provide this information to the FDA and/or the above listed sponsor at any time. There is no expiration date for the use of this information as stated in this authorization.

- B. You may withdraw your authorization to share this information at any time in writing. More information on how to do this can be found in the UTMDACC Notice of Privacy Practices (NPP). You may contact the Office of Protocol Research at 713-792-2933 with questions about how to find the NPP.
- C. If you refuse to provide your authorization to disclose this protected health information, you will not be able to participate in the research project.
- D. I understand that my personal health information will be protected according to state and federal law. However, there is no guarantee that my information will remain confidential, and may be re-disclosed at some point.

CONSENT/AUTHORIZATION

Having read and understood the above, and having had the chance to ask questions about this study and reflect and consult with others, I give _____ permission to enroll me on this study. I have been given a copy of this consent.

SIGNATURE OF PARTICIPANT

DATE

WITNESS OTHER THAN PHYSICIAN OR INVESTIGATOR

DATE

SIGNATURE OF PERSON RESPONSIBLE & RELATIONSHIP

DATE

I have discussed this clinical research study with the participant and/or his or her authorized representative, using a language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

SIGNATURE OF STUDY DOCTOR OR PERSON OBTAINING
CONSENT

DATE

Translator

I have translated the above informed consent into
_____ for this

participant.
Language)

(Name of

NAME OF TRANSLATOR

SIGNATURE OF TRANSLATOR

DATE



Tissue Consent

Radiation Dosimetry of Intra-tumoral Injection of
Radionuclides in Human Breast Cancer
ID03-0070

INFORMED CONSENT AND AUTHORIZATION FOR COLLECTION OF TISSUE, BODILY FLUIDS, AND DATA FOR THE MEASUREMENT OF RADIATION DOSE FROM INTRATUMORAL INJECTION OF Ga-67 GIMA

You are being asked to take part in this study because you have schedule breast cancer surgery and elect to participate in the Ga-67 GIMA injection study group.

Participant's Name

I.D. Number

One of the major goals of The University of Texas M. D. Anderson Cancer Center (UTMDACC) is to learn as much as possible about cancer. By studying the disease, researchers and doctors may find ways to improve treatment and move closer to finding a cure for cancer. One of the ways UTMDACC can learn more about cancer is by studying tissue samples and bodily fluids (such as blood and urine). As part of your standard care, you may have these types of samples collected for tests. After these tests are completed, there may be leftover tissue and/or bodily fluids. UTMDACC would like your permission to collect and store these leftover samples for future research projects. If these samples cannot be used for research purposes, they will be discarded as they normally would be.

Another way researchers can learn about cancer is by studying patient information. By studying the information from your medical record and comparing it to information gathered from other patients with cancer, UTMDACC may find ways to improve patient care and move closer to finding a cure for cancer. Researchers would like your permission to store information about you. This information will be stored in secure databases and may be used for future research projects.

Before your information, tissue samples, and/or bodily fluids can be used for research, the people doing the research must get specific approval from the Institutional Review Board (IRB) of UTMDACC. The IRB is a committee made up of doctors, researchers, and members of the community. The IRB is responsible for protecting the participants involved in research studies and making sure all research is done in a safe and ethical manner. All research done at UTMDACC, including research involving your information, tissue samples, and/or bodily fluids from this bank, must first be approved by the IRB.

BENEFITS OF PARTICIPATION: Future research with your information, tissue samples, and/or bodily fluids may lead to new treatments for cancer and/or other diseases. While the research that may be done with your information, tissue samples, and/or bodily fluids is not designed to help you specifically, it may help people who have cancer and/or other diseases in the future.

RISKS OF PARTICIPATION: The main risk to you is accidental release of information. To protect your privacy, all tissue samples and data used for research are kept in secure and confidential tissue banks and databases.

YOUR CHOICE TO GIVE OR DENY CONSENT AND AUTHORIZATION WILL NOT AFFECT THE CARE YOU RECEIVE AS A PATIENT

CONSENT AND AUTHORIZATION FOR STORAGE OF TISSUE AND/OR BODILY FLUIDS:

If tissue and/or bodily fluids are taken for diagnostic tests and/or therapeutic treatments and are still available after those procedures are completed, researchers may wish to collect these samples and store them in a secure and confidential tissue bank. Before the tissue and/or bodily fluids in the tissue bank can be used for research, the people doing the research must get specific approval from the IRB. Reports about any research done with your sample(s) would **not** be given to you or your doctor, and these reports would **not** be put in your health records. In the future, people who do research with your sample(s) may need to know more information about your health. This information may be obtained from your medical record; however, this would **not** be done without specific approval from the IRB. Researchers responsible for this bank will make reasonable efforts to preserve your privacy; however, they cannot guarantee complete privacy.

Research with tissue and/or bodily fluids may result in the development of beneficial treatments, devices, new drugs, and/or patentable procedures, from which you will not receive any financial benefits or compensation.

The purpose of this consent and authorization is only for the collection and storage of tissue and/or bodily fluids. It is not to give permission for use of your tissue for future research. All future research with these samples must first be approved by the IRB.

Please select one:

YES, my tissue and/or bodily fluids **may** be collected and maintained in this tissue bank. _____ initials

NO, my tissue and/or bodily fluids **may not** be collected and maintained in this tissue bank. _____ initials

CONSENT AND AUTHORIZATION FOR BANKING OF INFORMATION:

UTMDACC can also learn about cancer by studying patient information. This information will be gathered from your UTMDACC medical record. Any information that is collected will be maintained by the MEASUREMENT OF RADIATION DOSE FROM INTRATUMORAL INJECTION OF Ga-67 GIMA in confidential and secure databases. Before this information can be used for research, the people doing the research must get specific approval from the IRB. Reports about any research done with your information would **not** be given to you or your doctor, and these reports would **not** be put in your health records. UTMDACC will make every effort to keep this information confidential.

The purpose of this consent and authorization is only for the collection and storage of information. It is not to give permission for use of your information for future research. All future research with this information must first be approved by the IRB.

Please select one:

YES, my information **may** be collected and maintained in this database.
_____ initials

NO, my information **may not** be collected and maintained in this database.
_____ initials

If you have any questions, please discuss this consent/authorization with your attending physician.

This form has been explained to my satisfaction, and I certify by my signature below that I understand and agree to its contents. This authorization has no expiration date and shall be considered in effect until I withdraw my authorization. I can withdraw this authorization at any time, though researchers responsible for this bank may have already used my information for research purposes. The written withdrawal of authorization may be submitted to: M. D. Anderson Cancer Center, Chief Compliance Officer, 1515 Holcombe Blvd. #537, Houston, TX 77030. A copy of the UTMDACC Notice of Privacy Practice is available from the Office of Protocol Research at 713-792-2933.

Signature of Patient / Other Person Legally Authorized to Sign on Date
Patient's Behalf

Printed Name of Patient / Other Person Legally Authorized to Sign on Date
Patient's Behalf

Signature of Witness Printed Name of Witness Date

This form has been translated to the patient / other legally responsible person by:

Signature of Translator Printed Name of Translator Date

Locoregional Ablation of rat breast cancer using Ga-67 Iron Macroaggregates (GIMA) and Y-90 I Macroaggregates (YIMA)

Franklin C. Wong and Shuang Wang

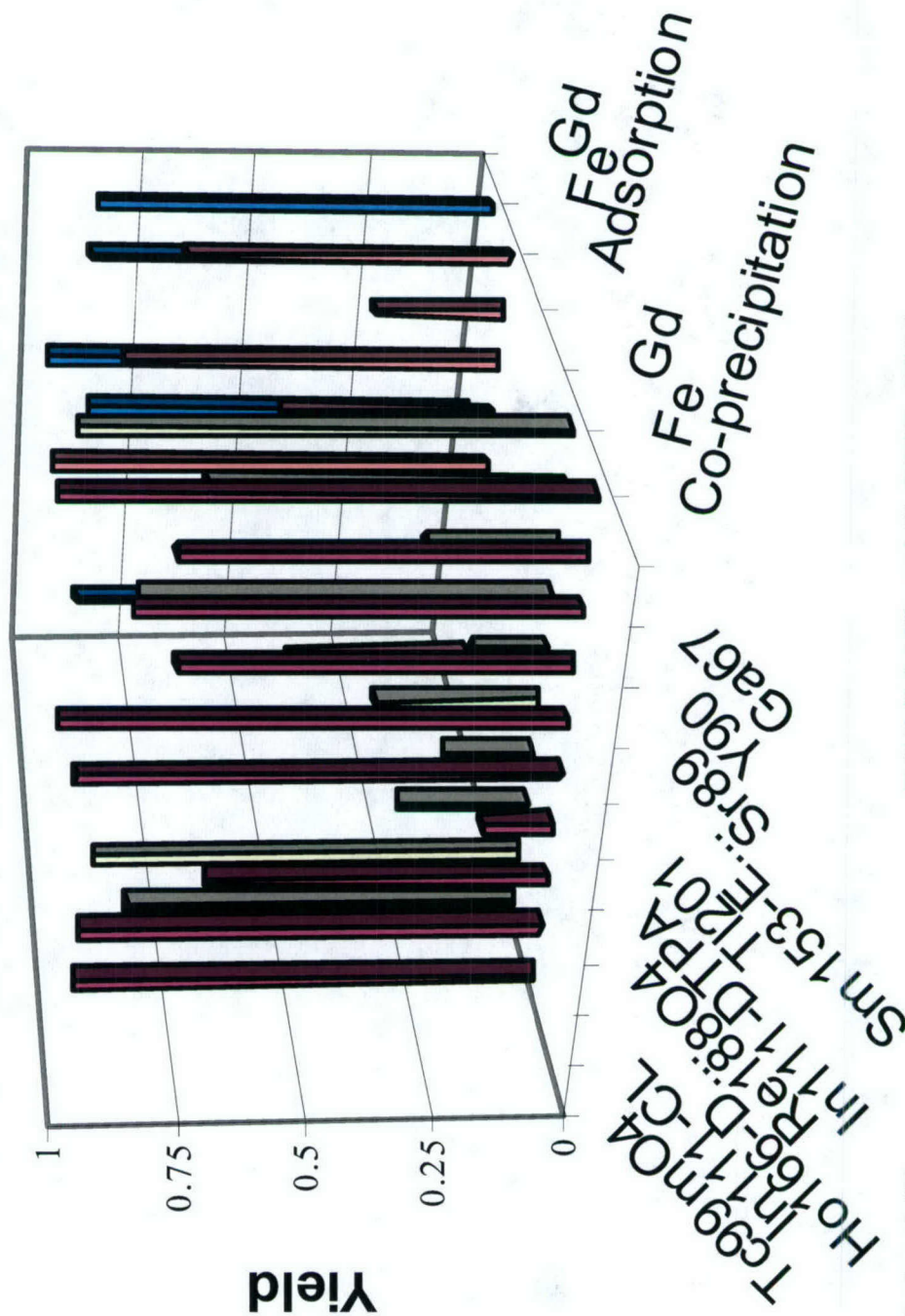
The University of Texas M. D. Anderson Cancer Center, Houston,
Texas, USA

*Acknowledgement: US DOD Army Breast Cancer Research
Grant #BC020808*

Introduction

- Interstitial particles are sequestered and cleared slowly by phagocytosis and lymphatics and may serve for locoregional ablation
- Treatment of solid tumors by intralesional injection of radiopharmaceuticals has not been fully explored
- Potential limitations include uncontrolled dispersion and lack of monitoring or dosimetry

Radiochemical yields of IMA and GdMA by co-precipitation and Adsorption. (P458)



Abstract #1

EJNMI 31(Suppl 2):S297, 2004

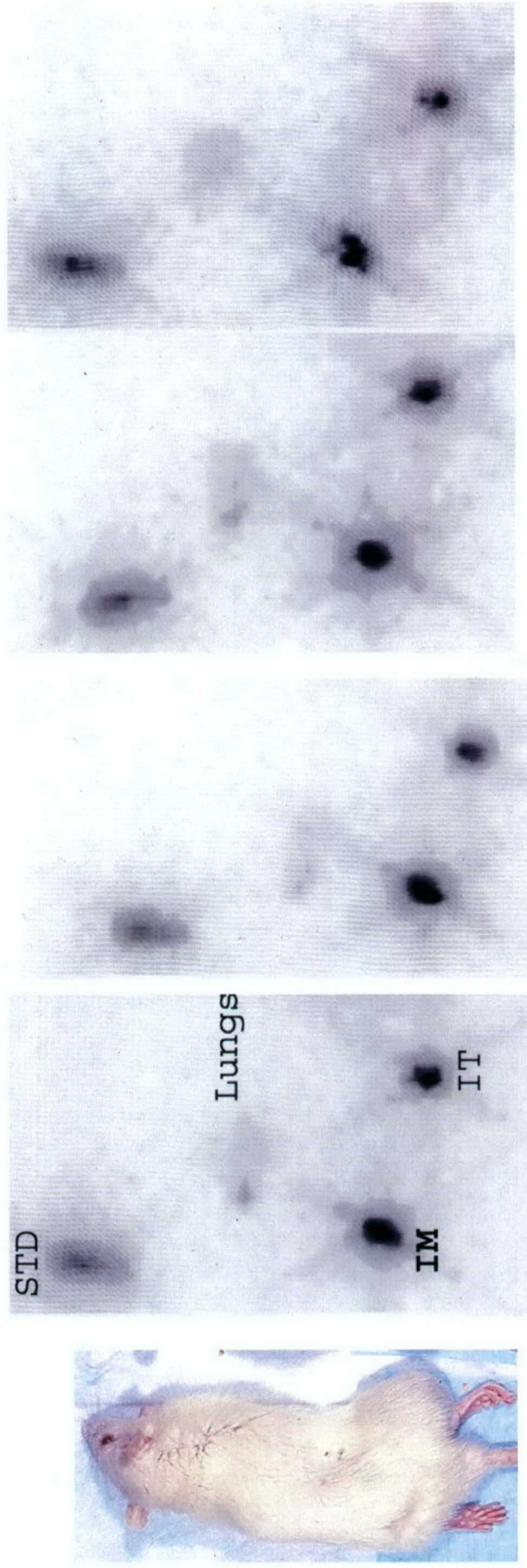
- GIMA and YIMA are particulate paramagnetic radiopharmaceuticals that we have synthesized
Wong, 31(suppl 2), S387, EJNMI, 2004.
- The radioactivity profile of GIMA can be monitored by scintigraphy
- The spatial distribution of IMA may be imaged by MRI with higher resolution.
- The heavy IMA particles ($D > 2.0$) may be monitored with ultrasounds

Radiation Dosimetry in Spheres

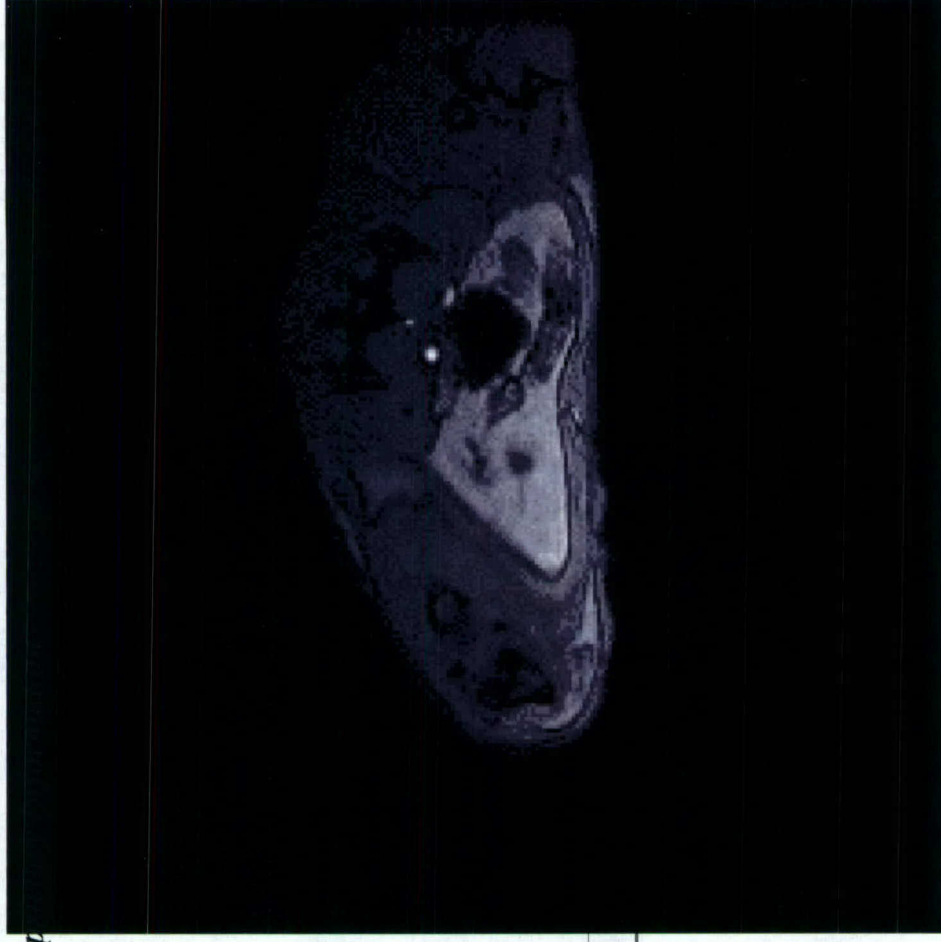
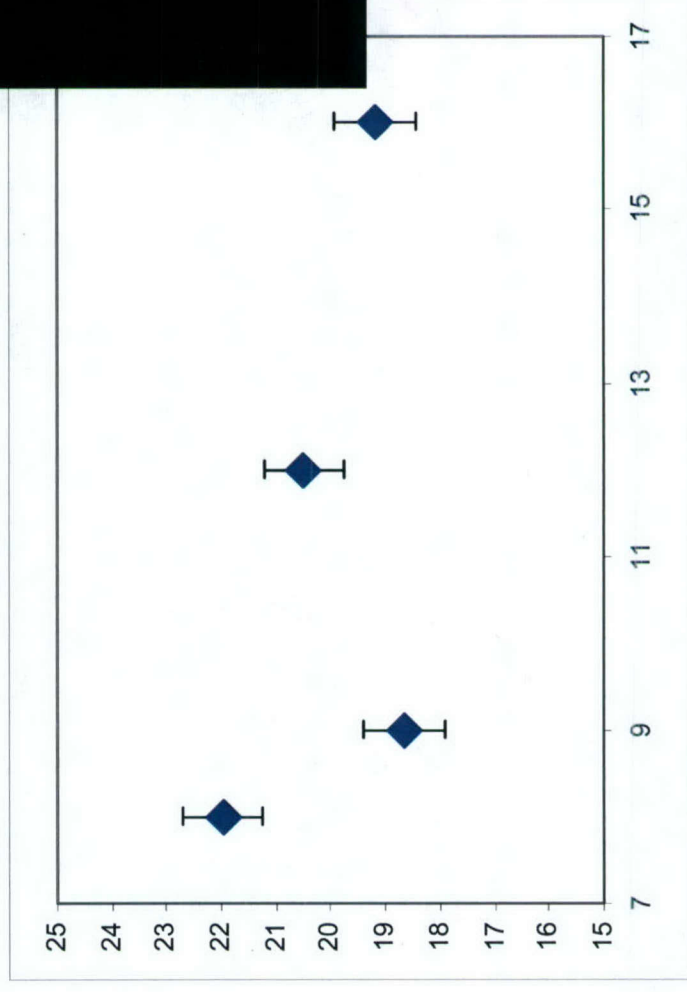
**Sphere
volume cc**

S- cGy/(mCi/cc)-Hr		Tc-99m	Ga-67	Y-90	P-32
	0.4	35.47	80.40	1127.98	971.66
	2.0	37.88	84.23	1431.67	1174.09
	10.0	41.80	89.11	1626.90	1275.30
	50.0	47.92	97.41	1735.36	1315.79
	250.0	60.62	110.69	1816.70	1366.40
10% Isodose range (cm)					
	0.4	0.02	0.02	0.19	0.15
	2.0	0.03	0.02	0.20	0.15
	10.0	0.15	0.04	0.21	0.15
	50.0	0.65	0.16	0.21	0.15
	250.0	1.80	0.95	0.22	0.17

Direct injection of Ga67 GIMA results in persistent deposition in tumor (IT) or muscles (IM).

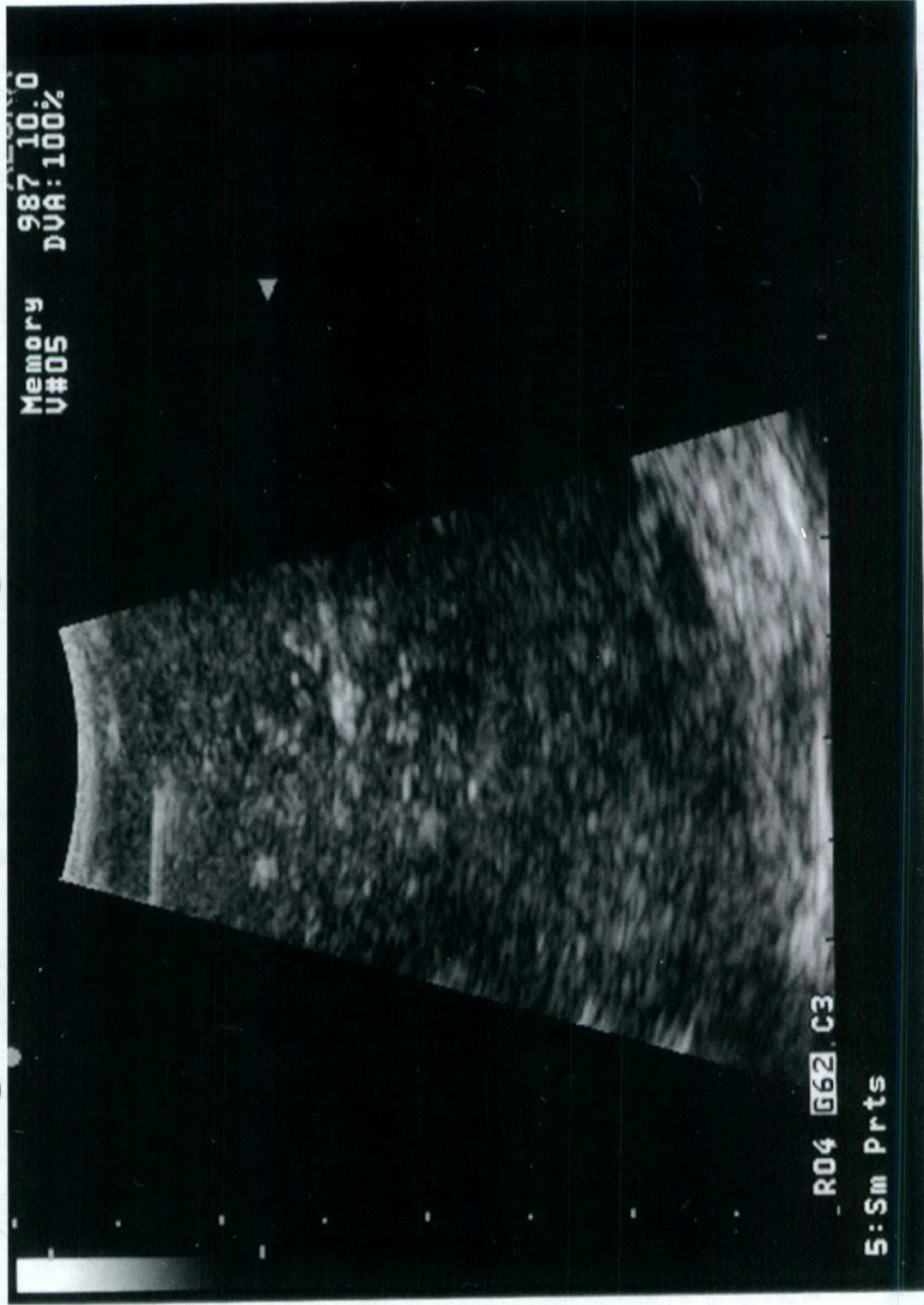


Rat MRI (GRE sequence) of IMA after IT Injection in the Right leg



Unpublished Proprietary Information

Sonographic Image of IT IMA



Abstract #1

EJNMI 31(Suppl 2):S297, 2004

Objectives

- To monitor sequestration of GIMA and YIMA
- To evaluate the efficacy of GIMA and YIMA
- To provide estimates of retention of Ga for human dosimetry of GIMA- Wong, 31(suppl 2), S283, *EJNMI*, 2004.

Methods

- Groups of triplicate female Fischer 344 rats were inoculated with 10^5 cells of 13762 rat mammary tumors in 0.2 ml saline into the right thigh muscle by a 22 gauge needle.
- At days 3, 0.2 ml of YIMA (0.1 - 1mCi) or GIMA (0.2 - 2 mCi) were injected in the tumor bed.
- Serial scintigrams were obtained up to 20 days
- Tumor size were measured up to 3cm when euthanization is required by the animal protocol.

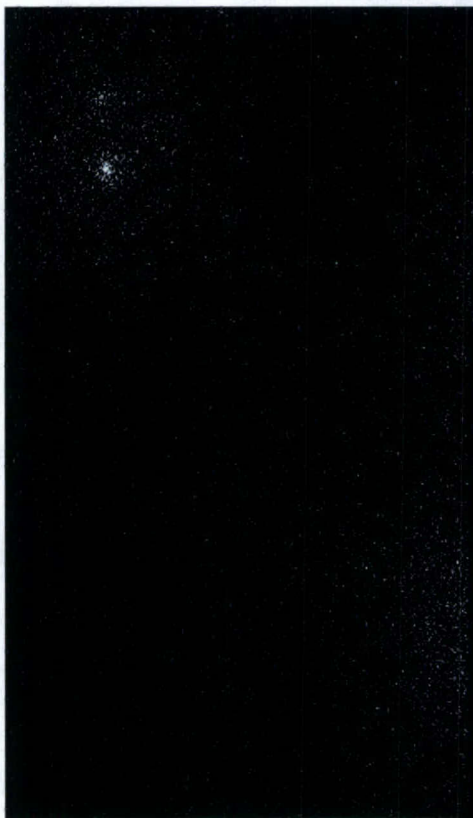
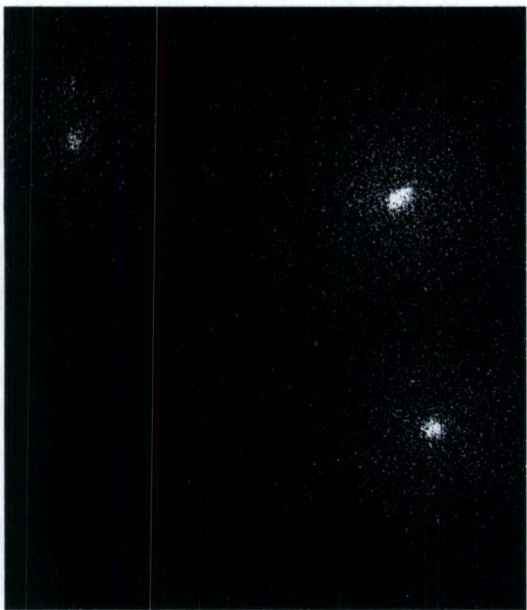
Unpublished Proprietary Information

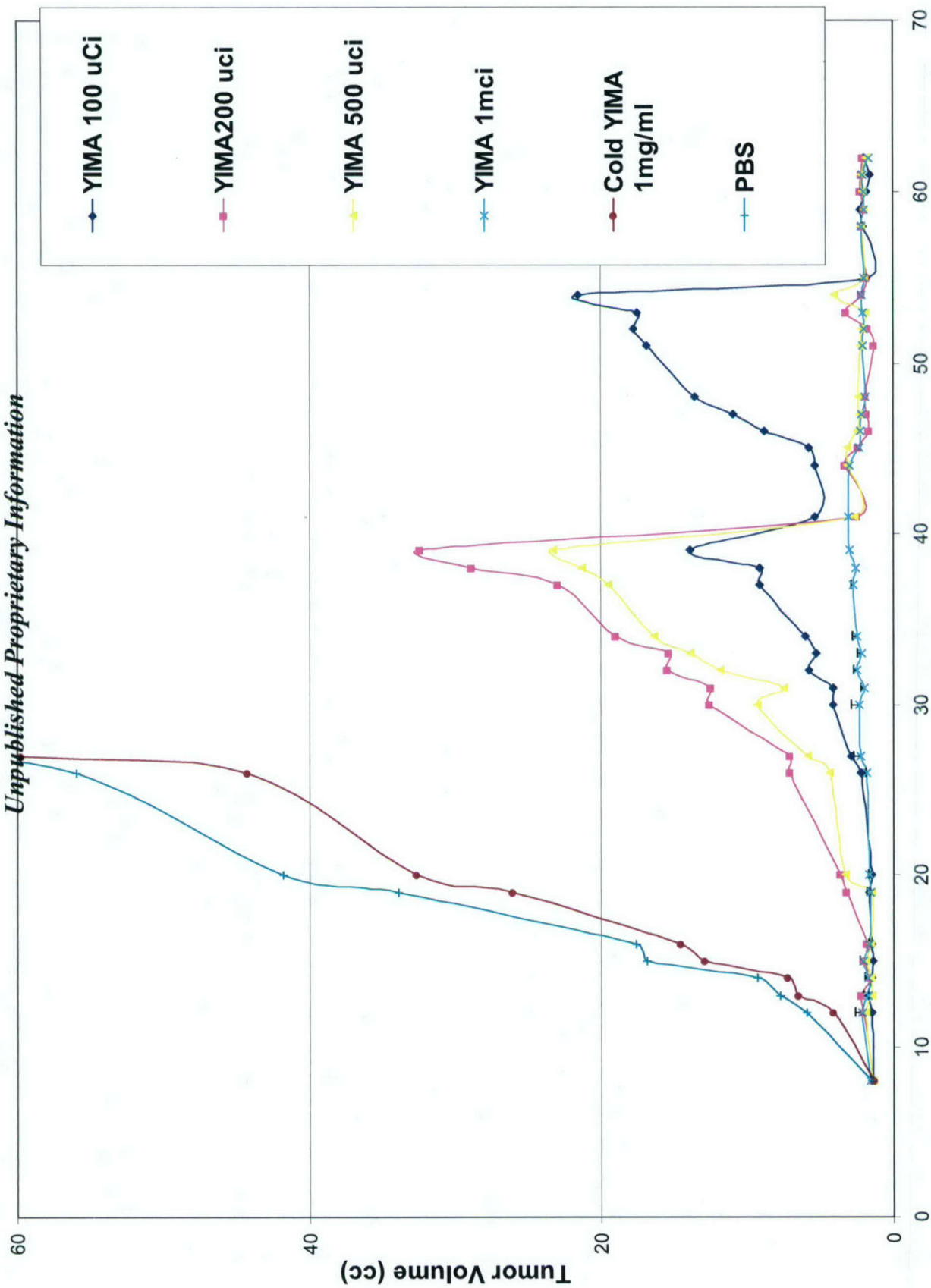
0.16H

YIMA

1.5H

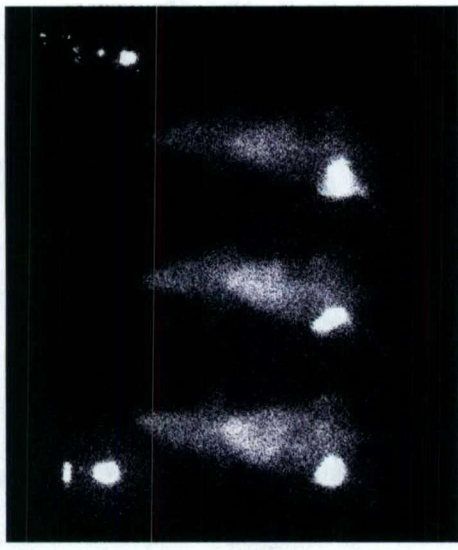
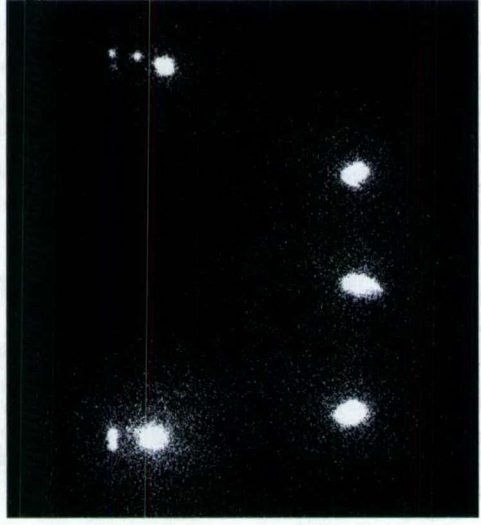
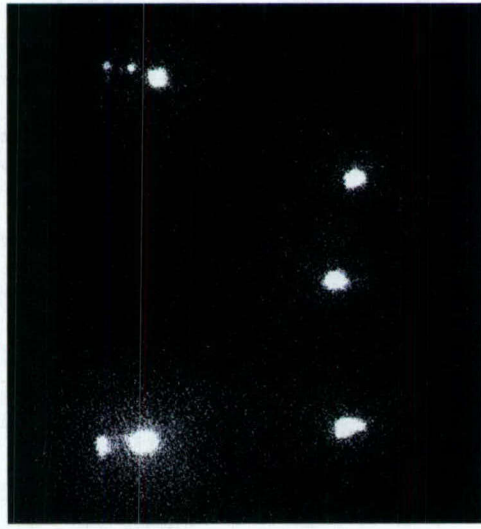
24H





EJNMI 31(Suppl 2):S297, 2004

Abstract #1



100uCi

GM200uCi

500uCi Ga

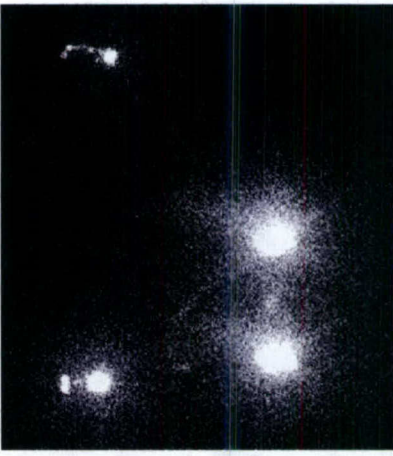
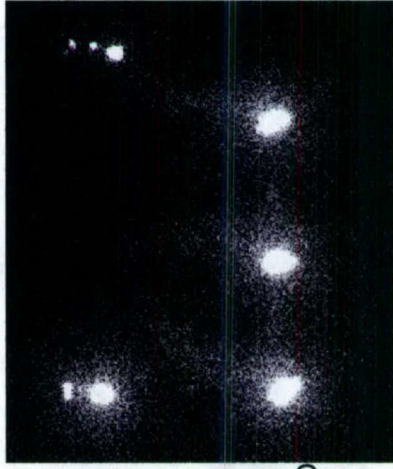
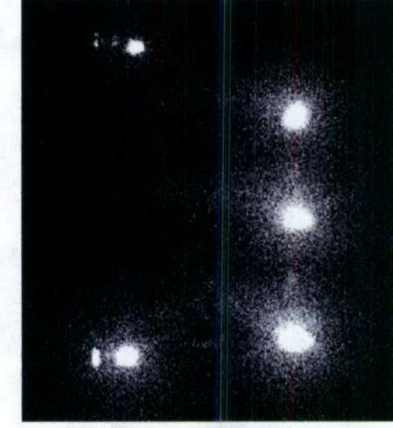
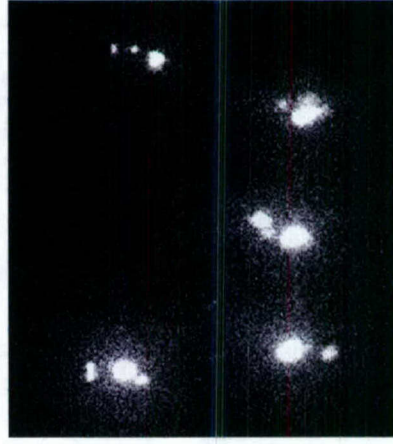
1Hr after IT injection of GIMA

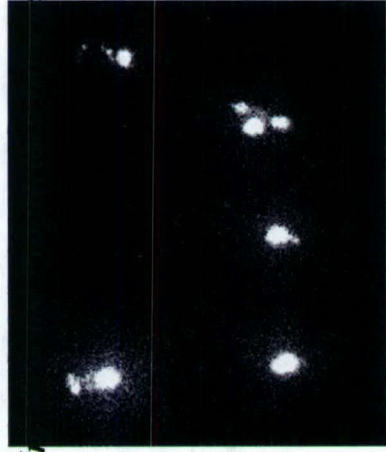
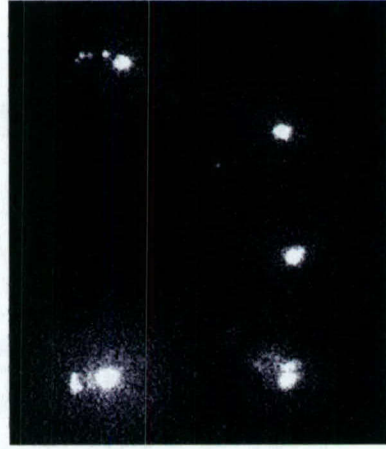
500uCi

1mCi

1mCi(adsorption)

2mCi





100uCi

200uCi

500uCi Ga

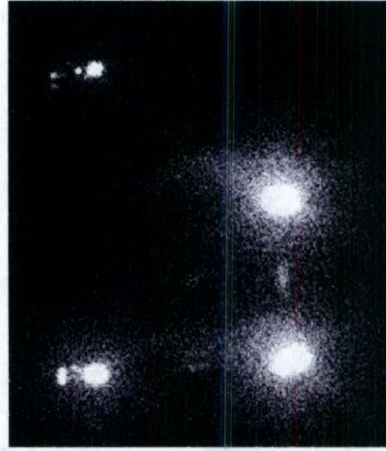
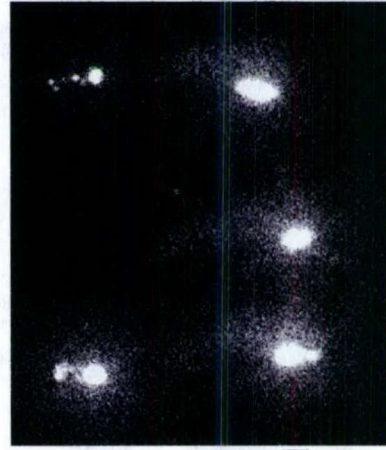
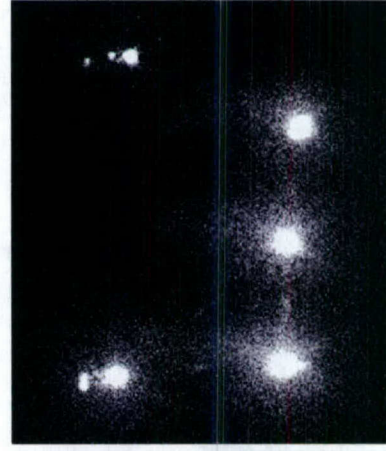
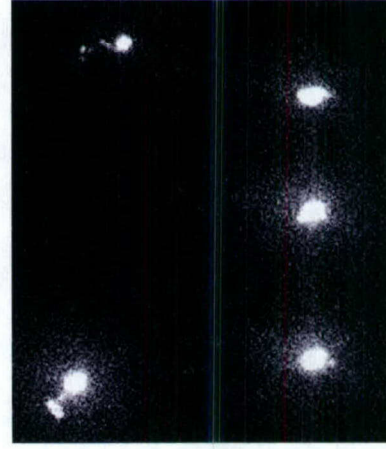
3Hr after IT GIMA

500uCi

1mCi

1mCi (adsorp)

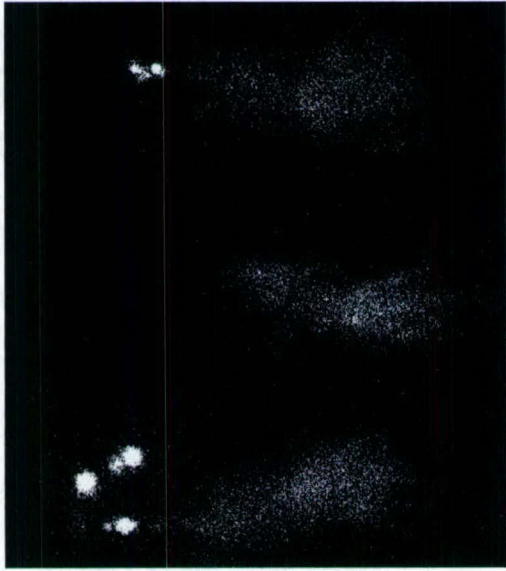
2mCi



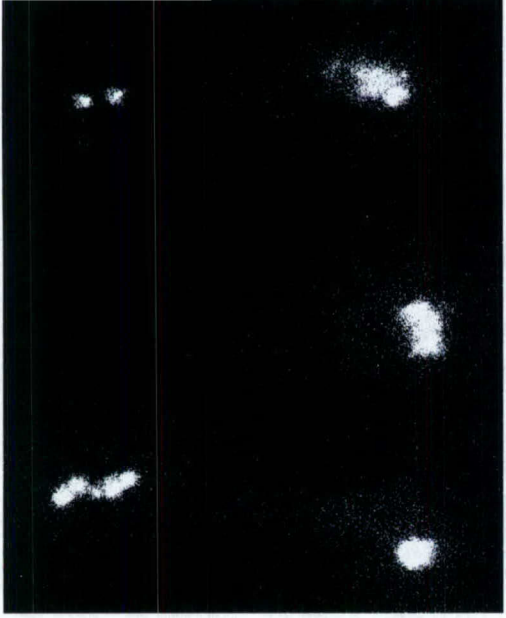
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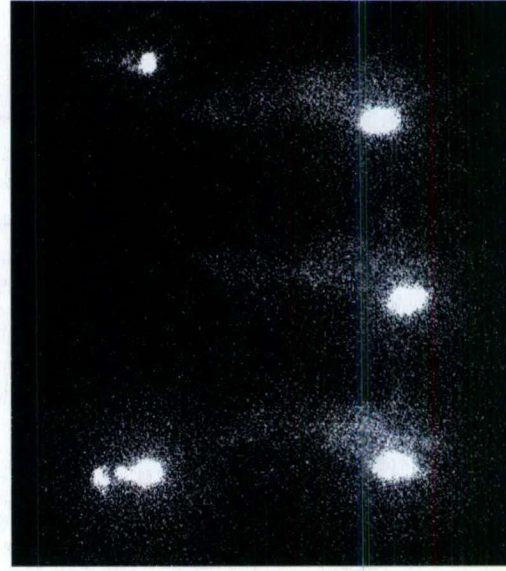
500uCi Ga



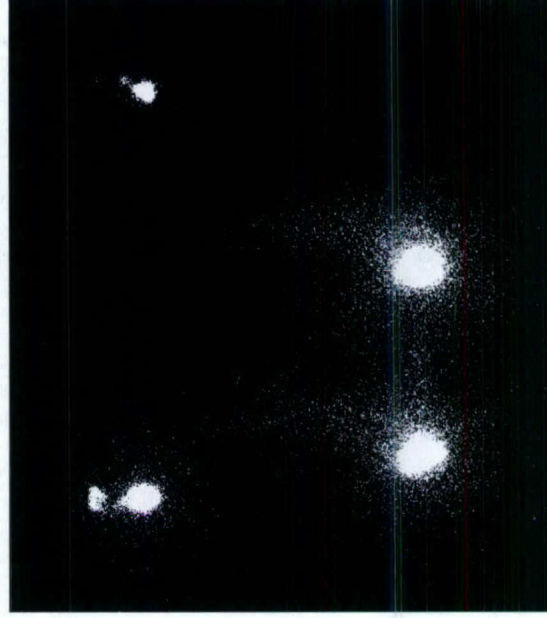
1mCi

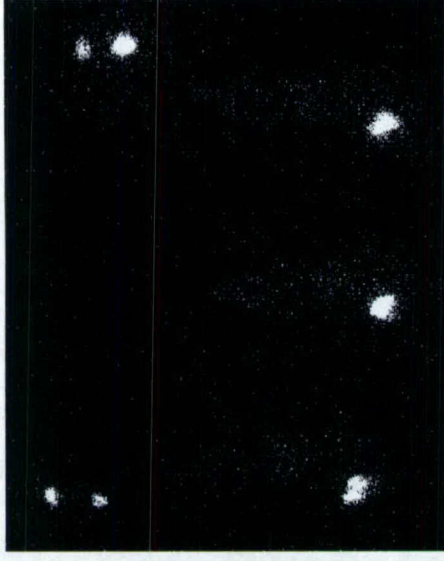
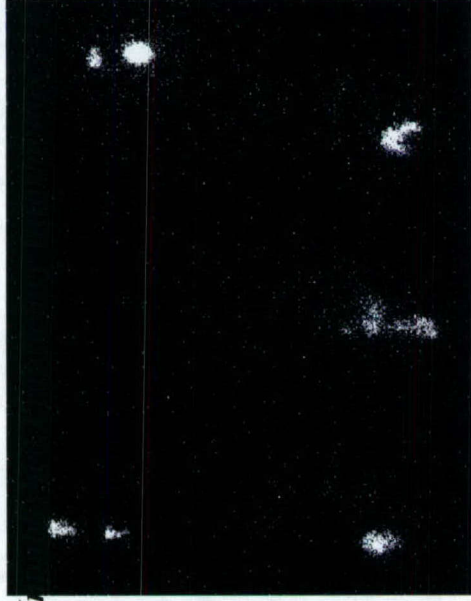
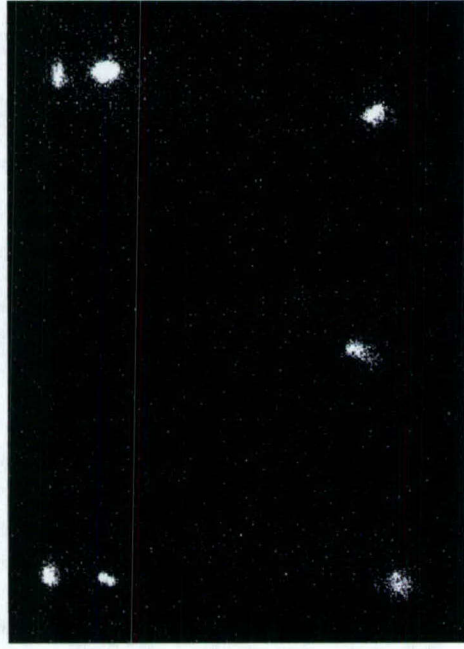
24Hr after IT GIMA

1mCi (adsorp)



2mCi





100uCi

200uCi

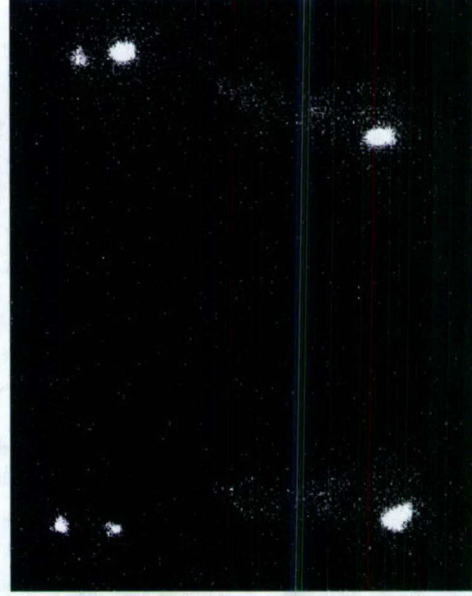
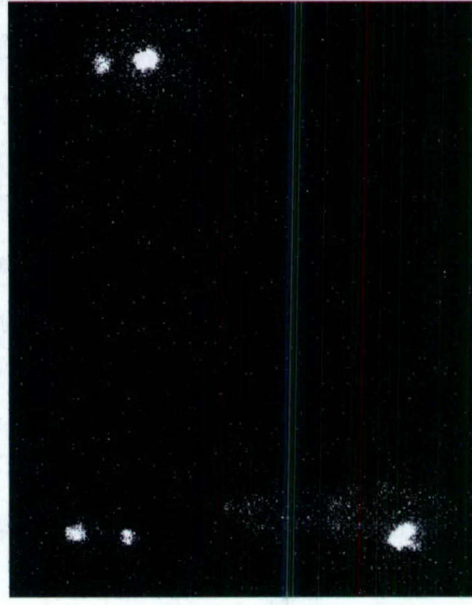
500uCi

Sequestration of GIMA at Day 14

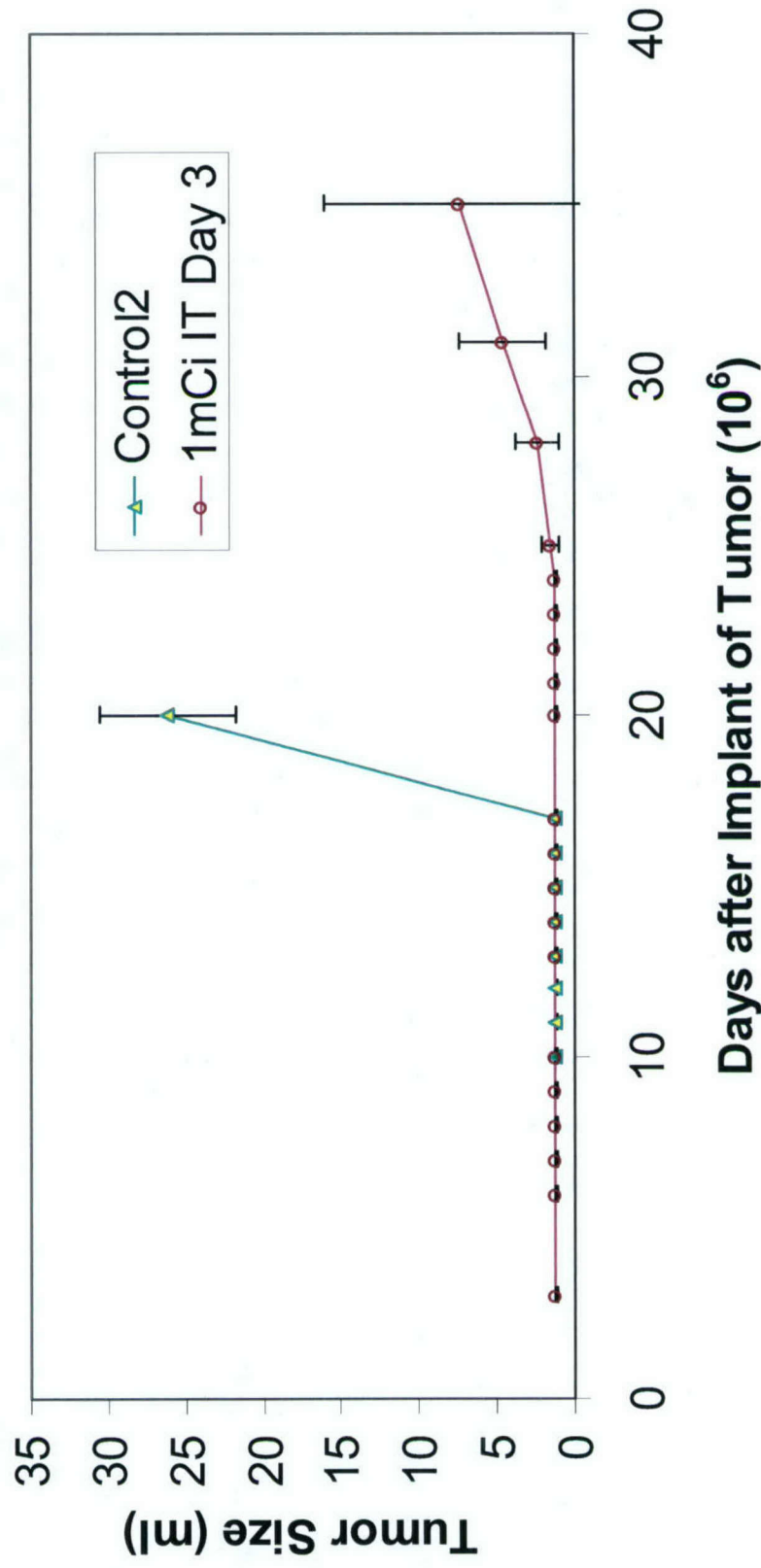
1mCi

1mC (adsorption)

2mCi



Results- Suppression of Tumor by IT GIMA



Abstract #1

EJNMI 31(Suppl 2):S297, 2004

Conclusion

- Both YIMA and GIMA are able to suppress tumor growth in this 13762 rat mammary tumor model
- Prolonged retention of GIMA and YIMA have been confirmed
- The leakage of Ga-67 from intratumoral GIMA is well below 2%.

Discussion

- This study confirms the correlation of radionuclide retention with the efficacy to suppress tumors
- The tumor model may be suitable for the evaluation of the effects of locoregional radionuclide therapy using other radiopharmaceuticals
- GMA distribution may be monitored with scintigraphy, MRI or ultrasonography

Unpublished Proprietary Information
**Simulated Dosimetry Profiles of
Locoregional Radionuclide Therapies
using Radioactive Gallium Iron
Macroaggregates (GIMA)**

Franklin C. Wong and Rick Sparks

**The University of Texas M. D. Anderson Cancer Center,
Houston, Texas, USA**

and

CDE Dosimetry Service, Knoxville, TN, USA

***Acknowledgement: US DOD Army Breast Cancer Research
Grant #BC020808***

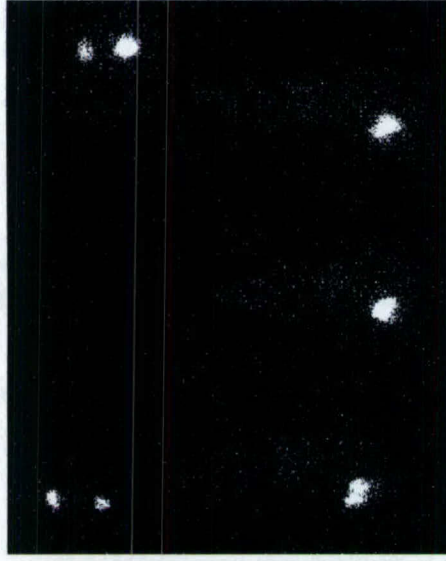
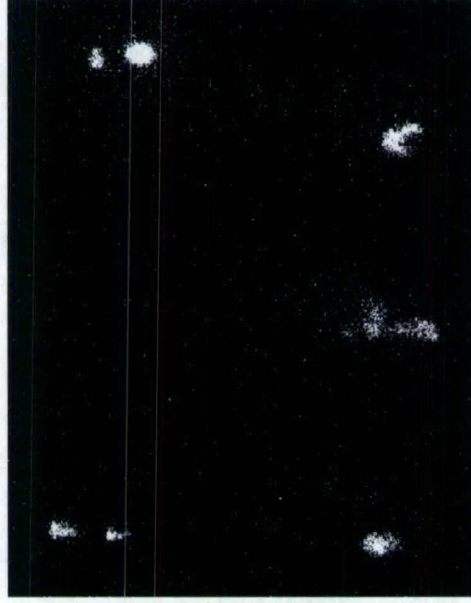
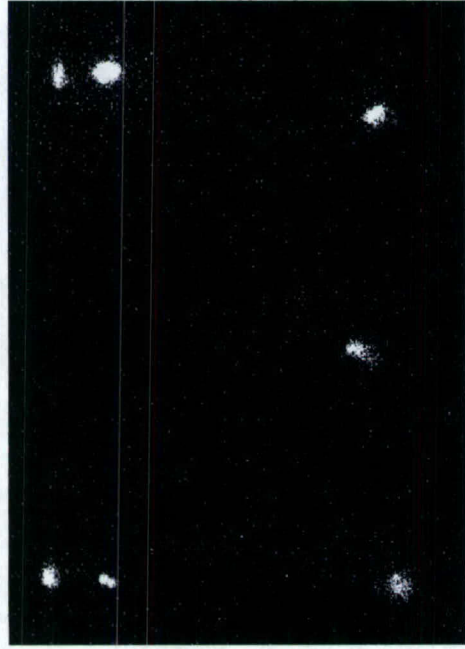
Abstract #2

EJNMI 31(suppl 2):S293, 2004

Introduction

- Locoregional therapies have pharmacokinetic advantages of maximum initial local exposure and low systemic toxicity after dilution
- Requisites for locoregional radionuclide therapies are safety and efficacy
- Monitoring by imaging is possible with radionuclides (and/or other imaging signals)
- Therapy should be guided by radiation dose estimates to the target and the rest of the body
- The key issue is the choice of therapeutic radiopharmaceuticals with optimal properties

- GIMA is a paramagnetic radiopharmaceutical that can be readily synthesized- Wong, 31(suppl 2), S387, *EJNMI*, 2004.
- In rat breast cancer models, Ga-67 GIMA consistently suppresses tumor growth- Wong, 31(Suppl. 2), S297, *EJNMI*, 2004.
- The decay profile of GIMA can be monitored by scintigraphy (< 2% leakage)
- The physical distribution of GIMA can be more precisely imaged by MRI.
- GIMA may be labeled with Ga-67 or Ga-68; the latter for monitoring with PET



100uCi

200uCi

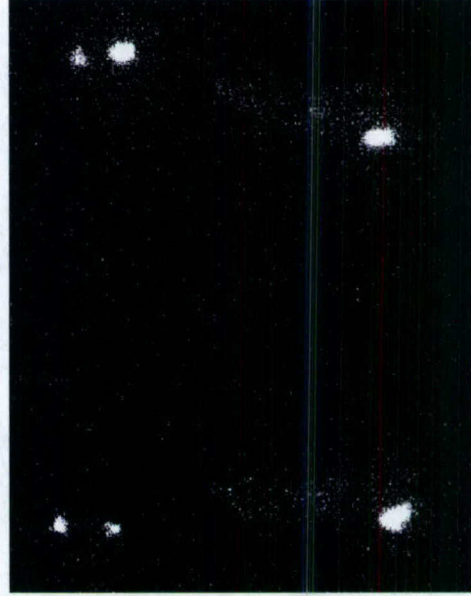
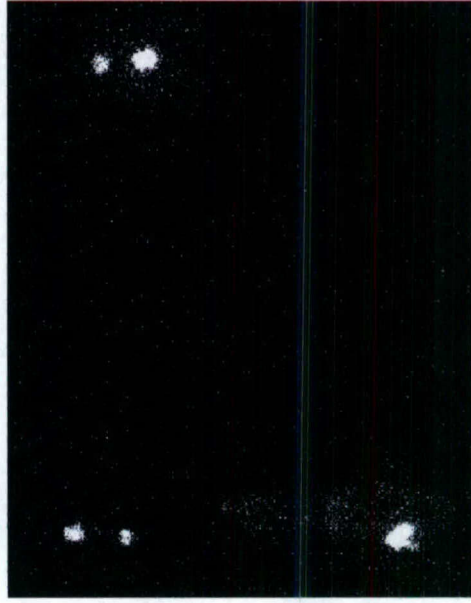
500uCi

Sequestration of GIMA at Day 14

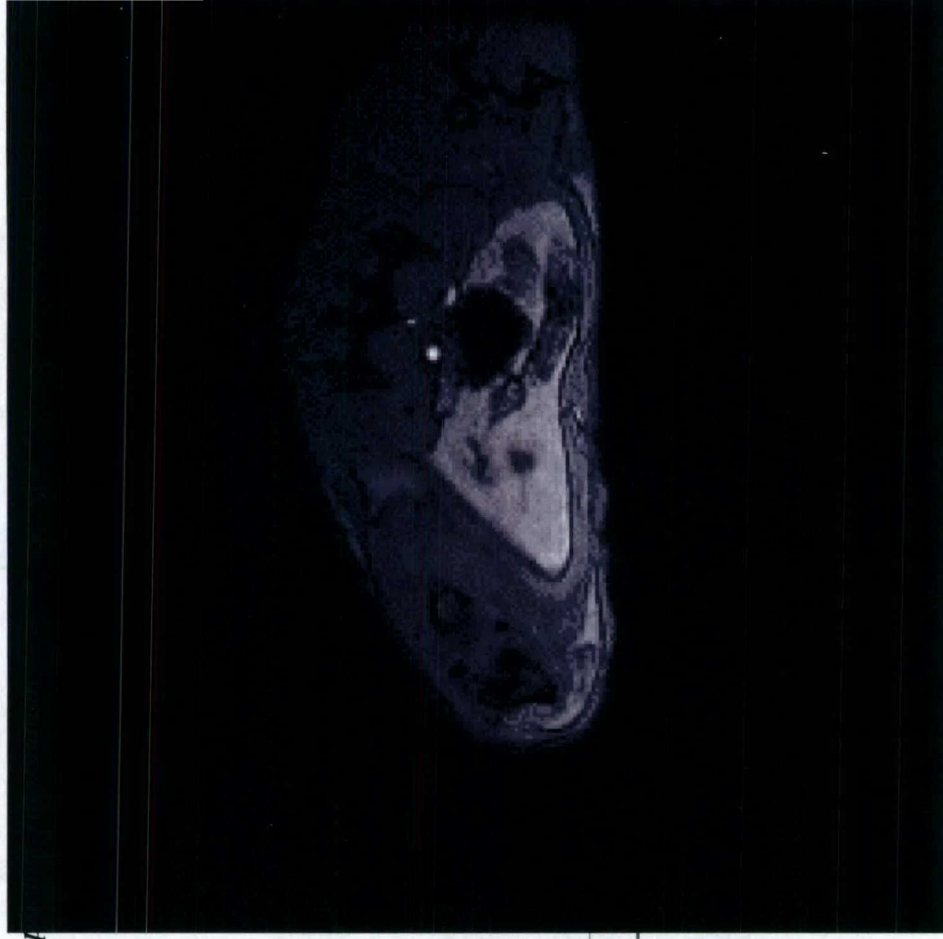
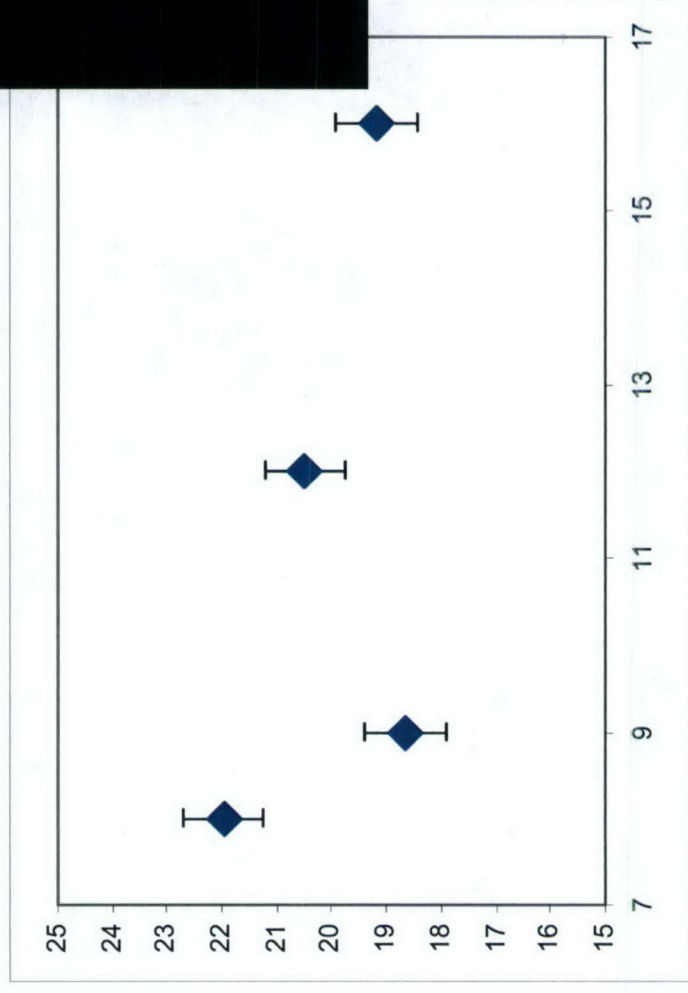
1mCi

1mCi (by adsorption)

2mCi



Rat MRI (GRE sequence) of IMA after IT Injection in the Right leg



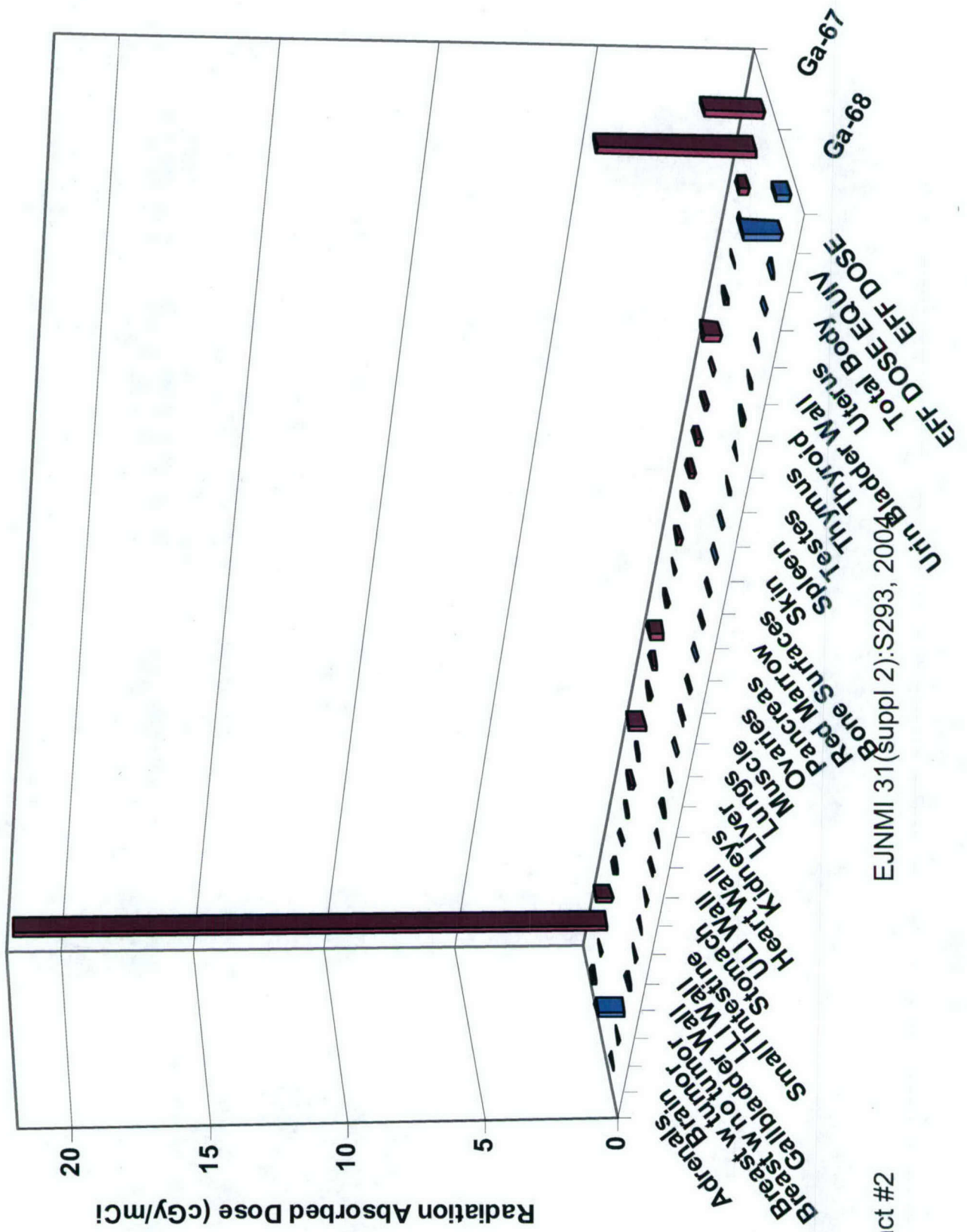
Objectives

- To simulate human organ dosimetry from locoregional injection of GIMA's labeled with Ga-67 or Ga-68.
- To derive the efficacy and safety profiles for injection into breast, prostate or liver.

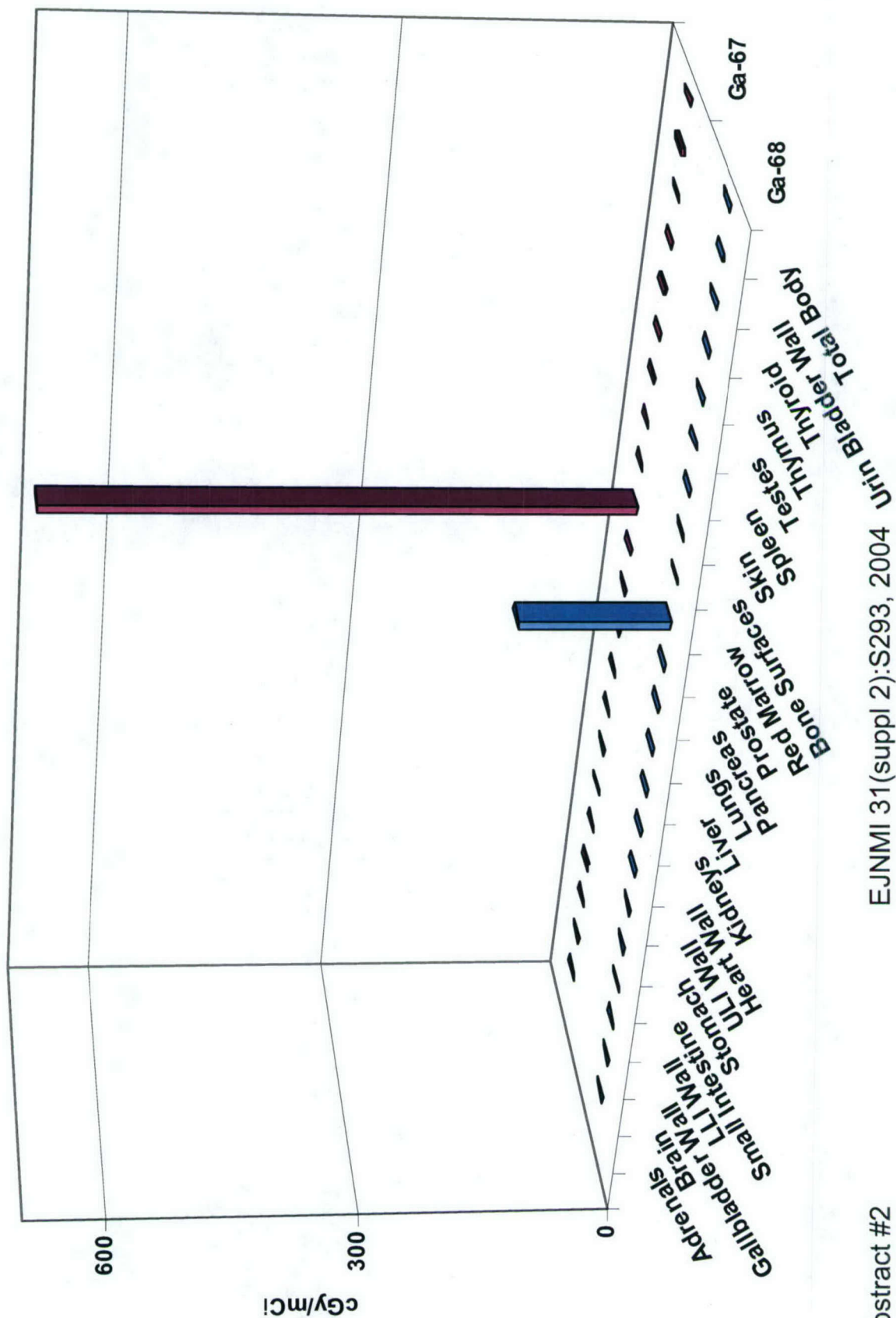
Methods

- Assuming 98% retention in the injection sites- breast, prostate or one of liver lobes (right lobe)
- Injectate volume of 2cc (intratumoral) in breast or prostate and 800 cc (intraarterial) in liver
- Absorbed dose estimates for organs were determined using the absorbed fractions for the reference adult male phantom developed by Cristy and Eckerman and using MIRDOSE 3.1.
- Depth radiation doses are derived from MCNP simulations considering all monoenergetic photons, electrons and positrons- *cf. Wong et al, JNM, 28(Supp), 2001*

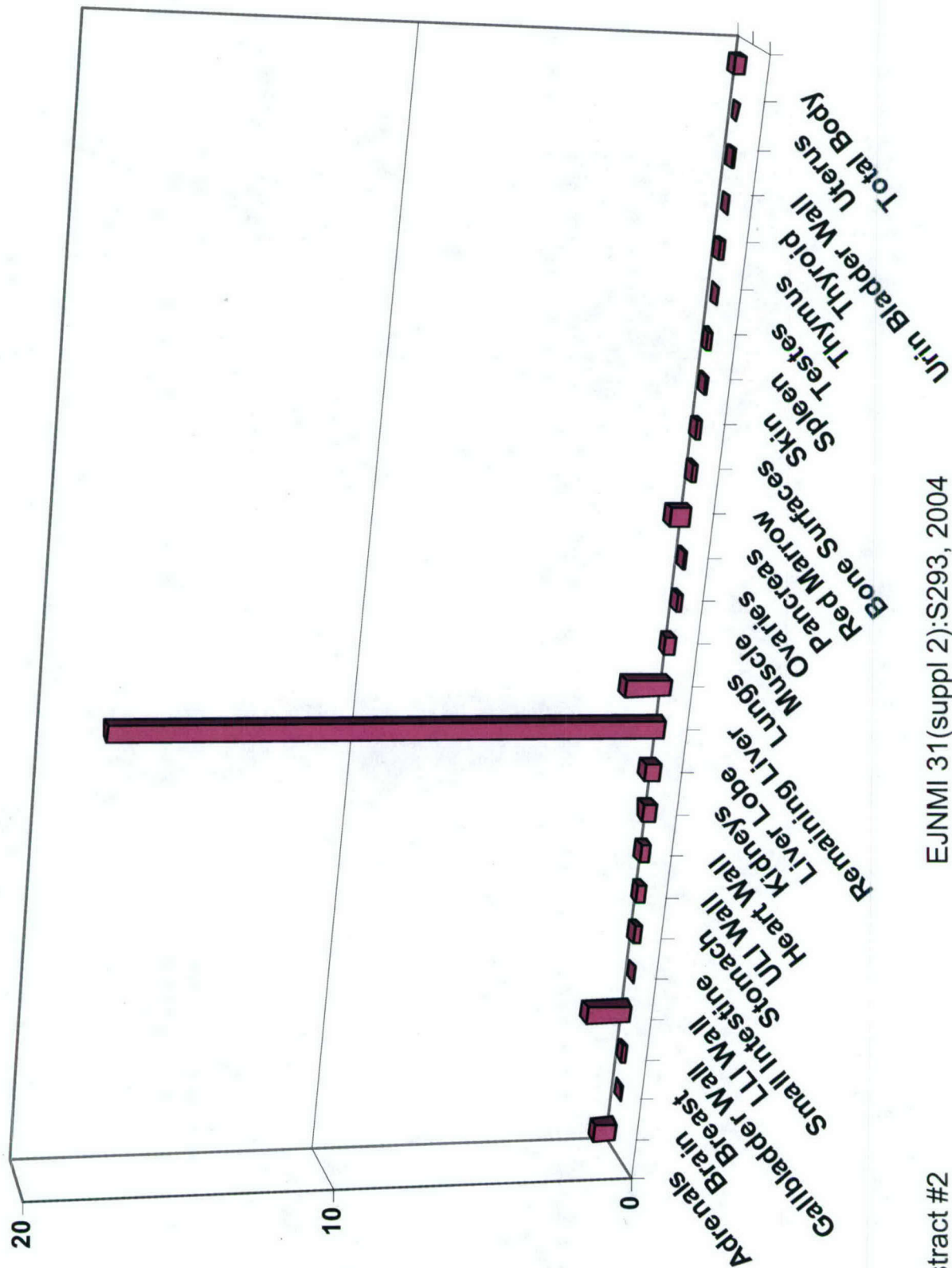
Simulated Radiation Dosimetry for Local Injection of GIMA in Breast



Simulate Radiation Dosimetry of Intratumoral Injection of GIMA in Prostate



Intraarterial Injection of ⁶⁷ Ga-67 GMA into the right lobe



Efficacy and Safety Profiles of GIMA

from simulated dosimetry

	Organ (cGy/mCi)		Marrow (cGy/mCi)		organ to marrow	
Injection model	Ga68	Ga67	Ga68	Ga67	Ga68	Ga67
breast tumor	991.76	4679.5	0.01	0.12	99176	38996
breast	1	22	0.01	0.12	100	183
prostate	170	690	0.02	0.12	8500	5750
liver		18		0.16		113

Depth Dosimetry from MNCP

	Sphere volume cc	Ga-68	Ga-67
S- cGy/(mCi/cc)-Hr			
	0.4	1014.63	80.40
	2.0	1234.29	84.23
	10.0	1389.72	89.11
	50.0	1524.39	97.41
	250.0	1676.83	110.69
10% Isodose range (cm)			
	0.4	0.13	0.02
	2.0	0.20	0.02
	10.0	0.20	0.04
	50.0	0.20	0.16
	250.0	0.25	0.95

Conclusion

- The findings of this study suggest both safety and efficacy of intratumoral injection of GIMA into human breast cancer and prostate cancer
- The radiation dosimetry profiles indicate safe (low-toxicity) use of GIMA in intra-arterial injection into the liver.

Discussion

- The current scheme is a plausible model for the planning of locoregional radionuclide therapy-choice of radiopharmaceuticals, followed by animal testing and human dosimetric estimates before clinical trials
- Current estimates depend on observation of 2% leakage. In our human trials, leakage will be measured and estimates will be adjusted
- work in progress: MRI for exact quantification of spatial and temporal dispersion; YIMA; other radiopharmaceuticals; and other cancers.

Paramagnetic Radiopharmaceuticals of Iron and Gadolinium Macroaggregates

Franklin C. Wong and Shuang Wang

The Univ. of Texas M. D. Anderson Cancer Center, Houston,
Texas, USA

*Acknowledgement: US DOD Army Breast Cancer Research
Grant #BC020808*

Introduction

- Intravenous In-111 and Ga-68 labeled macroaggregates were used in human lung imaging in the 70's, limited by toxicities related to nonradioactive In or Ga components (Stern et al, Nucleonics, 1966; Columbetti, JNM 1970)
- Particles injected interstitially are sequestered and cleared by phagocytosis which is a slow process. However the volume of the dispersed injectate is not known and cannot be determined by scintigraphy. Independent imaging signals are needed.
- Iron Macroaggregates (IMA) are large particles (18 um). When labeled with beta emitters, interstitial IMA may provide a means of locoregional ablation. The iron content will provide paramagnetic signals for magnetic imaging to determine the volume of the injectate and hence radiation dosimetry
- Radiolabeled gadolinium macroaggregates (GdMA) may serve similar purposes because of the strong paramagnetic signals

Objectives

- Synthesize IMA and GdMA by simple and reliable methods to produce no-carrier added products to avoid toxicity
- Evaluate products for stability over time
- Evaluate paramagnetic properties of IMA
- Visualization of IMA's

Methods- Production

- Co-precipitation: No carrier-added 0.01-0.05 mCi of Radioisotope (Ga-67, Y-90, Sr-89, Tl-201, Sm-153 EDTMP, Ho-166 DOTMP, Tc99mO4, Re-188O4, In-111 DTPA and In-111 Cl) are added to 1ml of FeCl3 or GdCl3 containing 1 mg of Fe or Gd before the pH is adjusted to 8-9 by NaOH or NH4OH
- Adsorption: selected radioisotope from above is are added to the solution after the pH is adjusted to 8-9
- Double labeling: 2 isotopes are mixed before adding FeCl3 or GdCl3 and alkalization
- Phytate: 2.5 mg of Phytic acid is added to the isotope before adding FeCl3 or GdCl3 and alkalization

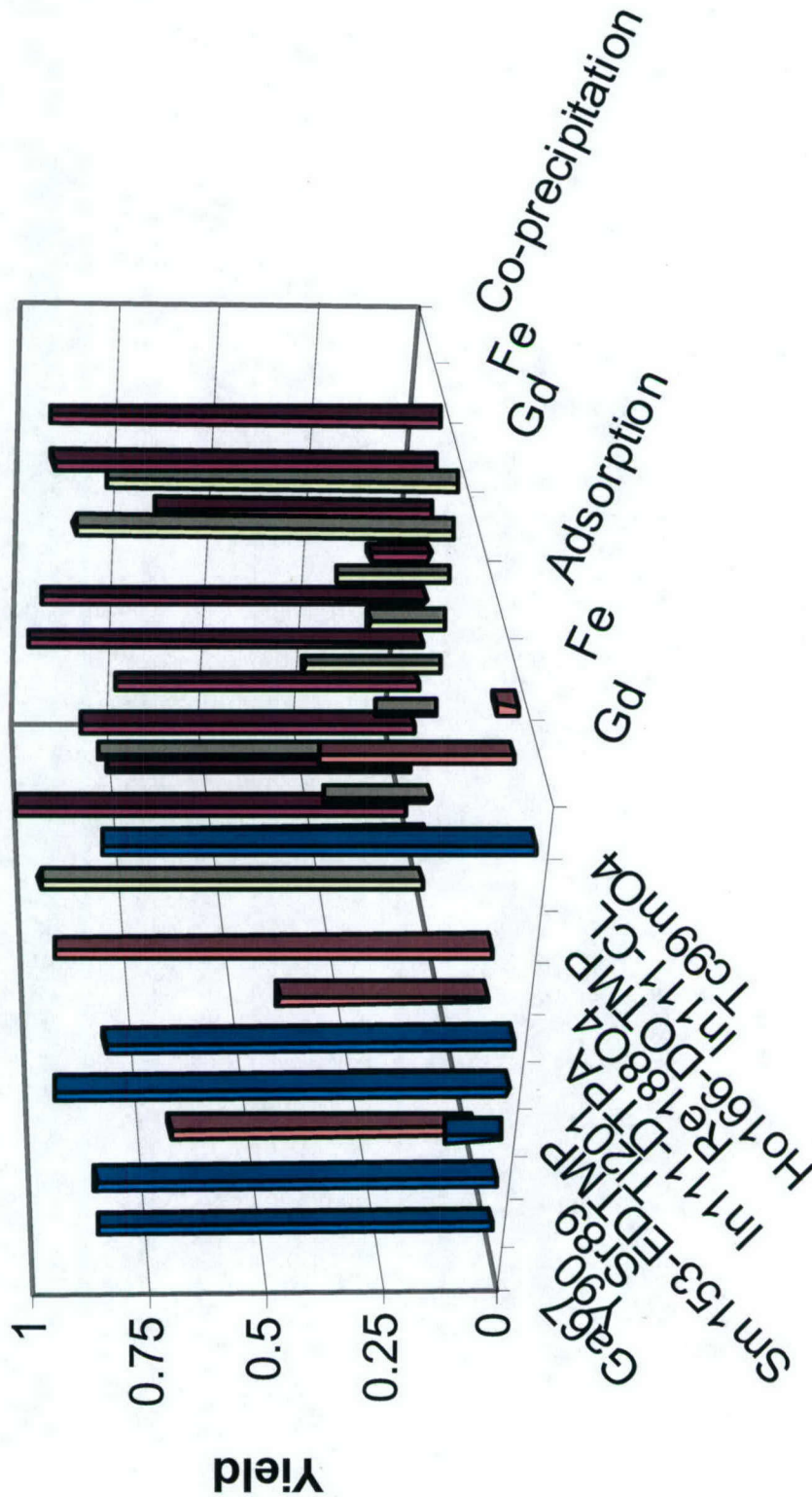
Methods- Testing

- After centrifugation at 3000 rpm for 5 mins, the precipitates are washed 3 times with phosphate buffered saline and tested for Radiochemical yield and stability.
- Ga-67 GIMA and Y-90 YIMA are upscaled for in vivo imaging and treatment studies
- 0.1- 2 mCi of GIMA are injected intramuscularly or intratumorally into rat breast cancer implants
- Serial scintigraphy of GIMA up to 30 days
- Phantoms containing GIMA (0.1 - 10 mM Fe) were imaged with MRI using FSE and GRE sequences

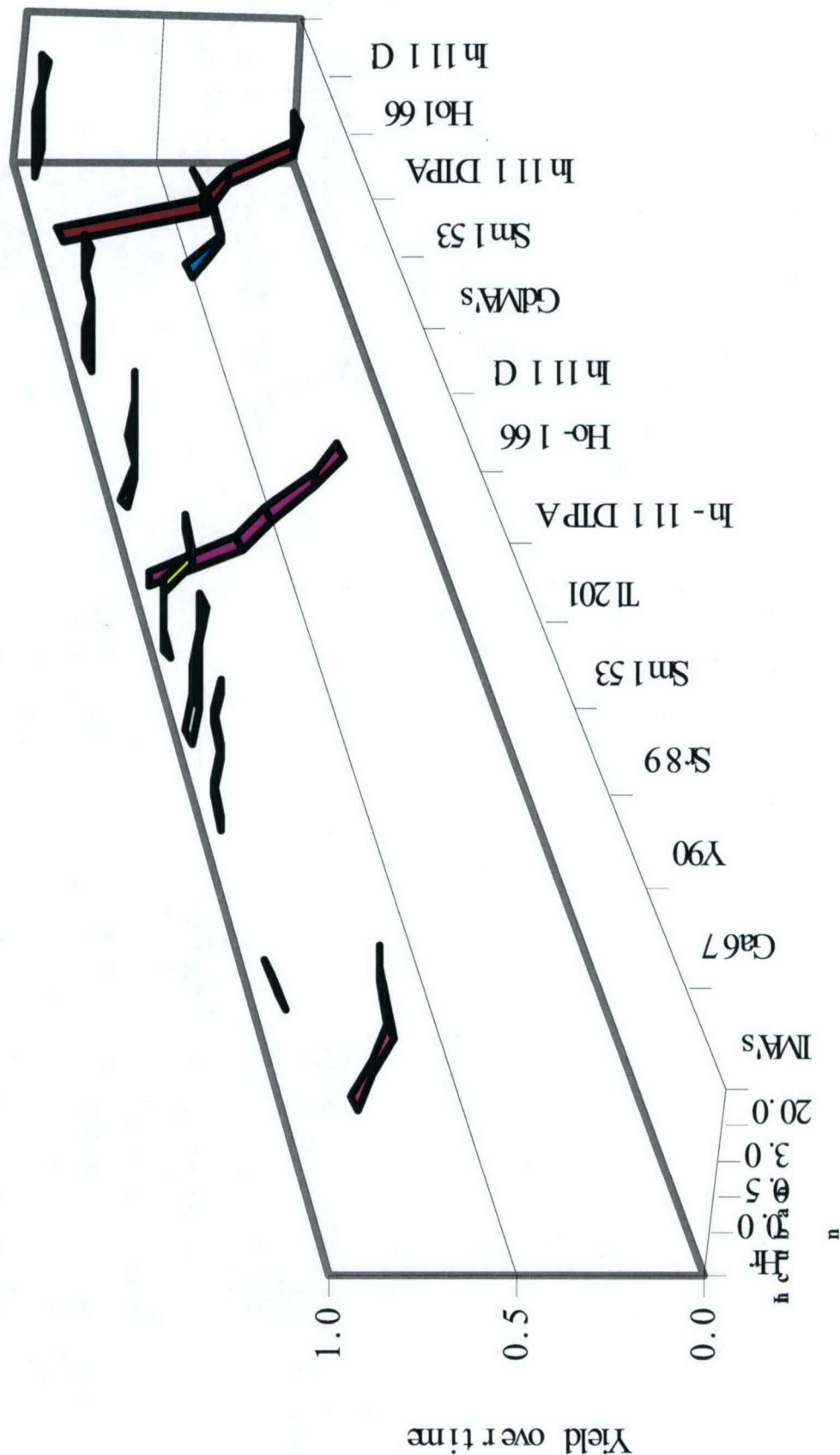
Abstract #3

EJNMI 31(suppl 2): S387, 2004.

Results – radiochemical yields of IMA and GdMA by Co-precipitation and Adsorption.



Results- Stability of IMA's and GdMA's



Results- Double-labeling of IMA and GdMA by In-111 and Y-90 with and without Phytate

Y90+In-111 double labeling- yield and stability

incubation in PBS	0h		3h		24h		48h		96h	
Yield	Y%	In%	Y%	In%	Y%	In%	Y%	In%	Y%	In%
IMA	62.5	88.2	55.0	91.3	51.7	84.7	43.0	83.0	45.7	85.9
GdMA	73.8	93.6	44.7	78.6	48.3	73.9	62.9	83.4	47.8	87.8

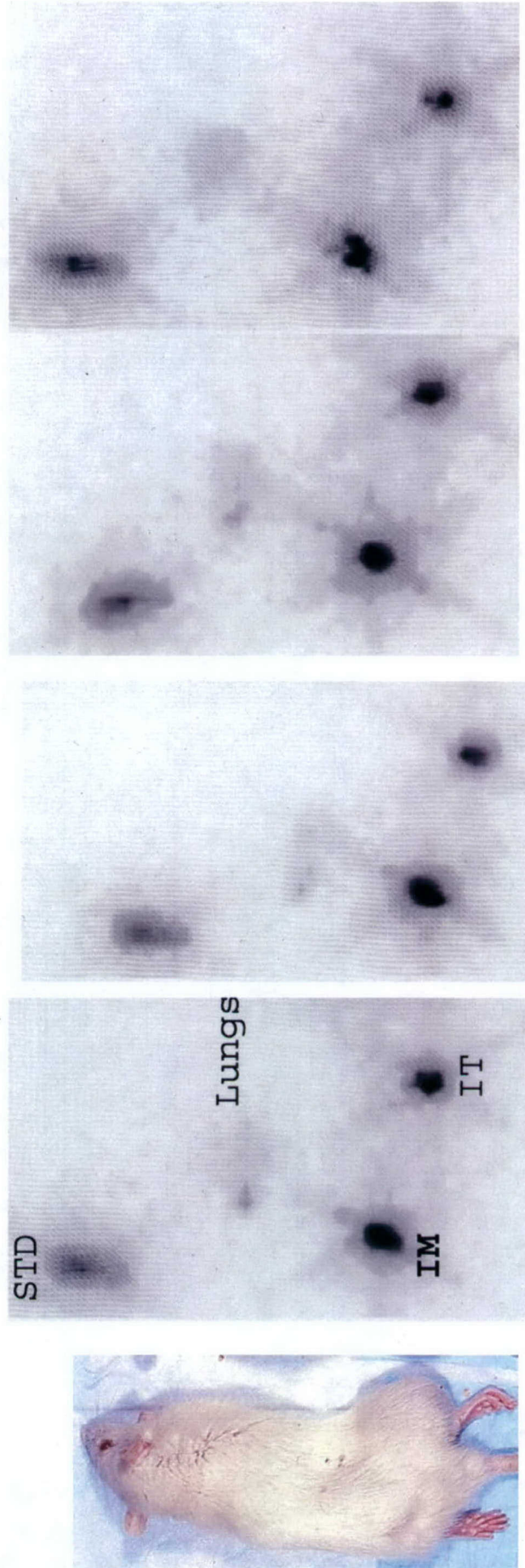
Y90+In-111 double labeling with Phytate- yield and stability

	0h		3h		24h		48h		96h	
Yield	Y%	In%	Y%	In%	Y%	In%	Y%	In%	Y%	In%
IMA phytate	19.1	49.2	33.3	49.2	20.4	54.9	34.6	53.4	21.7	50.8
GdMA phytate	30.3	90.2	35.8	83.5	27.7	82.6	45.2	82.1	26.9	81.6

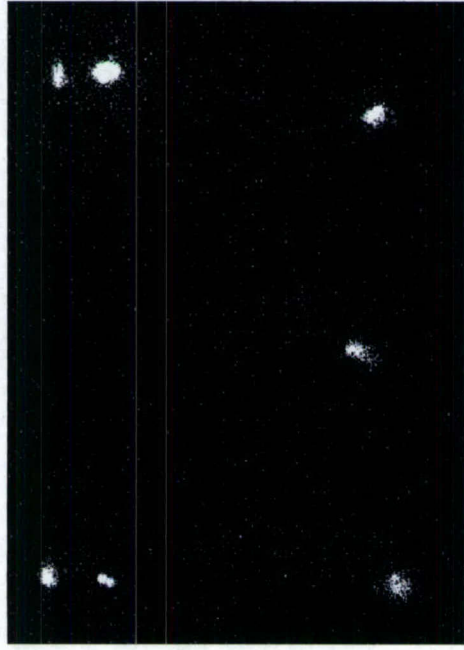
Abstract #3

EJNMI 31(suppl 2): S387, 2004.

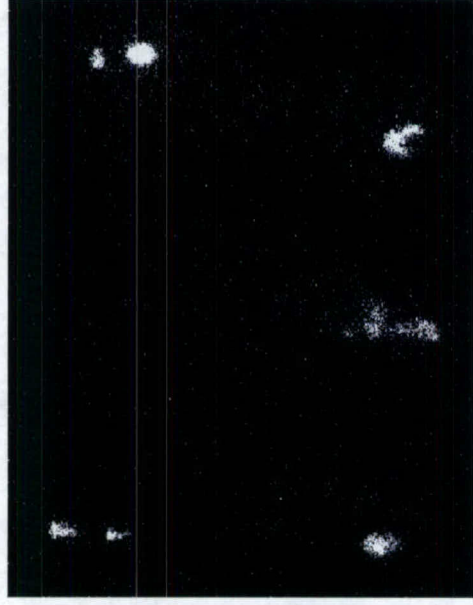
Direct injection of Ga67 GIMA results in persistent deposition in tumor (IT) or muscles (IM).



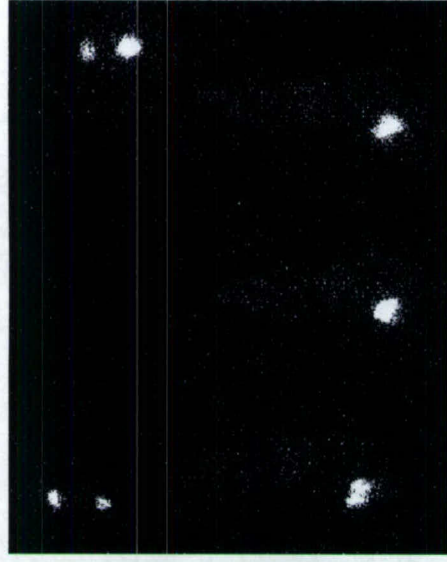
5 Min 1 Hr 2 Hr 18Hr



100uCi



200uCi

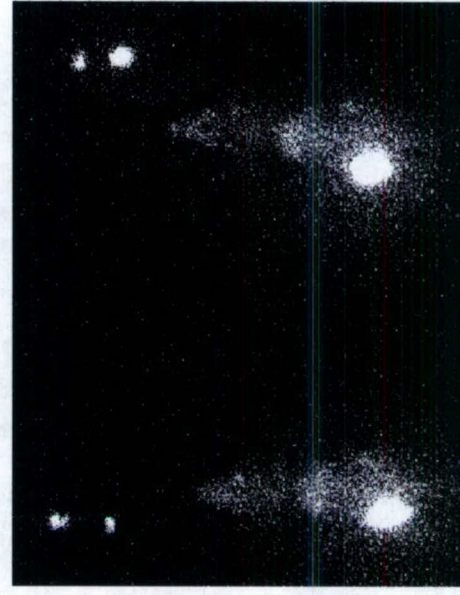
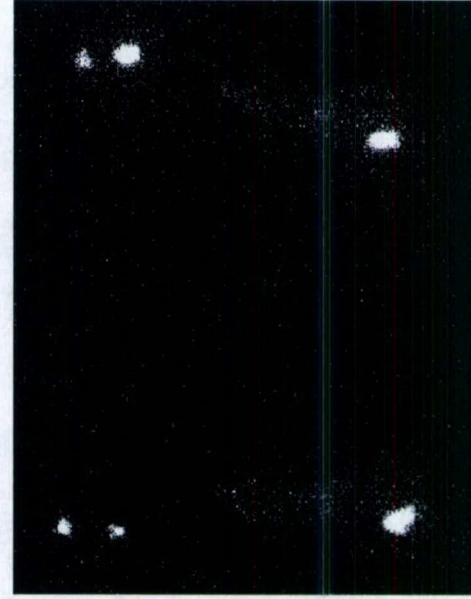
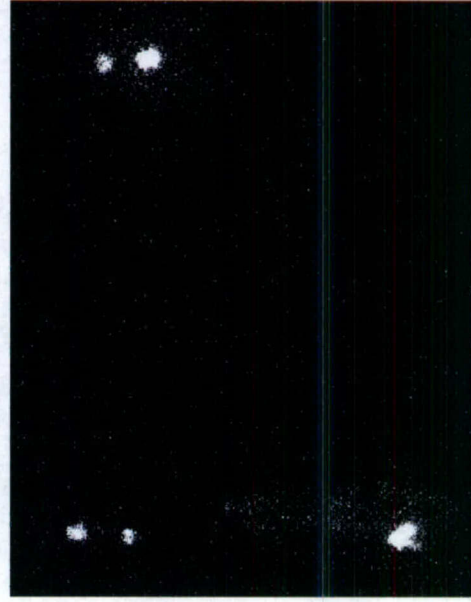


500uCi

Sequestration of GIMA at Day 14

1mCi

1mC (by adsorption)

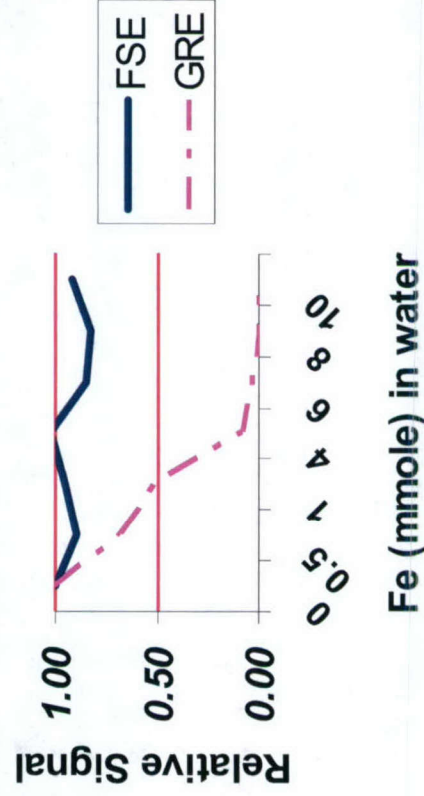


2mCi

Suppression of GRE signals on MRI is apparent by 1 mM of Fe in GIMA. With 10 mM Fe, GRE signals is no longer measurable



MRI signals of Fe Macroaggregates



Conclusion

- Selected combinations have high radiochemical yield and excellent stability
- Double labeling, i.e., labeling one isotope like Y-90 with In-111 is possible with IMA or GdMA, with or without phytate
- There is prolonged retention after local injection of GIMA
- GIMA is able to provide both scintigraphic and paramagnetic signals for monitoring and potentially for exact dosimetry

Discussion

- Adsorption renders products with slightly lower yield and lower stability. However, it enjoys major logistic advantage of producing the macroaggregates first (e.g., large batches)
- Double labeling may provide a means of visualizing pure beta emitters (e.g., Y-90) via gamma emitters in IMA or GdMA
- Scintigrams confirm prolonged in vivo sequestration of IMA after interstitial injection
- The magnetic properties of GIMA may provide estimates of dispersed volumes for dosimetry

Introduction

- Advantages of locoregional radionuclide therapy include higher local delivery and hence lower systemic toxicity.
- Current locoregional radiopharmaceuticals require complexe synthesis to achieve high local retention and low leakage
- Binding to interstitial proteins or components in the interstitium may serve as convenient and simple means to sequestrate free lanthanides including Ga-67, Y-90 or In-111 for locoregional irradiation

Aims of Study

- Evaluate efficacy of intratumoral injection of Tl-201Cl, Ga-67 citrate, Ga-68, Y-90 Cl or In-111 Cl in the suppression of tumor
- Image the whole-body distribution of these radionuclide to correlate with their efficacy

Methods

- Fisher 344 female rats (140-160 gm) are inoculated (IM) with 100,000 rat breast tumor 13762 cells in 0.1 cc saline in the right thigh.
- Intratumoral injection of Y-90 (0.1–1 mCi), In-111 Cl (0.2-3 mCi), Ga-67 citrate (0.4-1.2 mCi), Tl-201 Cl (1 mCi), Ga-68 Cl (2 mCi) or In-111 iron macroaggregates (1 mCi) in 0.2cc.
- Daily tumor size measurement until euthanasia (~30 cc) as required by the ACUF-protocol
- Scintigrams of In-111, Tl-201, Ga-67 groups using Siemens ~~M-Cam~~ up to 5 days

VA #11-000004
JAN 11 10 34 AM '04

Discussion (Cont'd)

- While this study explores the floor (efficacy) for intratumoral injection of Y-90 starting at 0.1 mCi, the ceiling (based on human radiation toxicity) has been estimated from a separate study: Abst #1357.
- Both efficacy and toxicity should be further explore between the floor and the ceiling for possibilities of using Y-90 Cl for locoregional therapy against tumors.
- **Acknowledgement:** MDACC NM research team;
US DQD Breast Cancer Research Grant BC020808
Abstract #4
Wong, F. JNM 45(5 supp), 334P, 2004

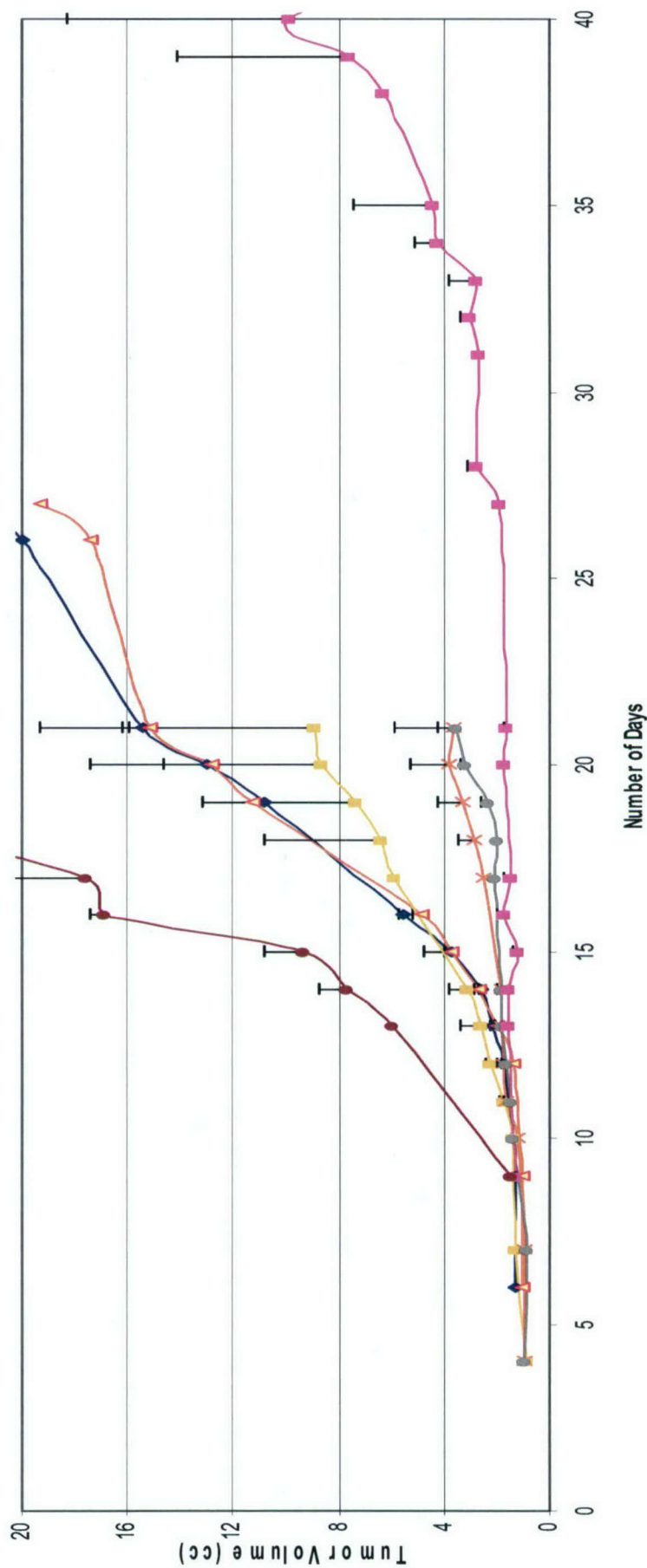
Results

- Dose-related tumor suppression is noted with Y-90 Cl and In-111 Cl (Figs. 1a and 1b)
- Persistent local sequestration of In-111 Cl is noted up to 5 days (Fig. 2)
- Little retention of Tl-201 Cl or Ga-67 citrate is noted after IT injection (Figs. 3 and 4)
- Image findings of radionuclide retention (Figs. 2, 3 and 4) correlates with tumor suppression (Figs. 1a and 1b).

Discussion

- Local sequestration of radionuclides after IT injection is confirmed with In-111 Cl and may explain its ability to suppress tumor. It may be inferred that the stronger beta emitter Y-90 Cl also suppresses tumor in similar fashions. The mechanism may be via interstitial protein binding.
- In addition to radionuclide retentions, considerations should also be given to dosimetric evaluations including the multiple emissions from the radionuclides and the geometric distribution of injectates and susceptibilities of tumor to radiations.

Fig. 1a Tumor Growth after IT treatment
with Tl-201, In-111 or Y-90 Cl



Abstract #

Fig. 1b. Tumor Growth after IT Injection

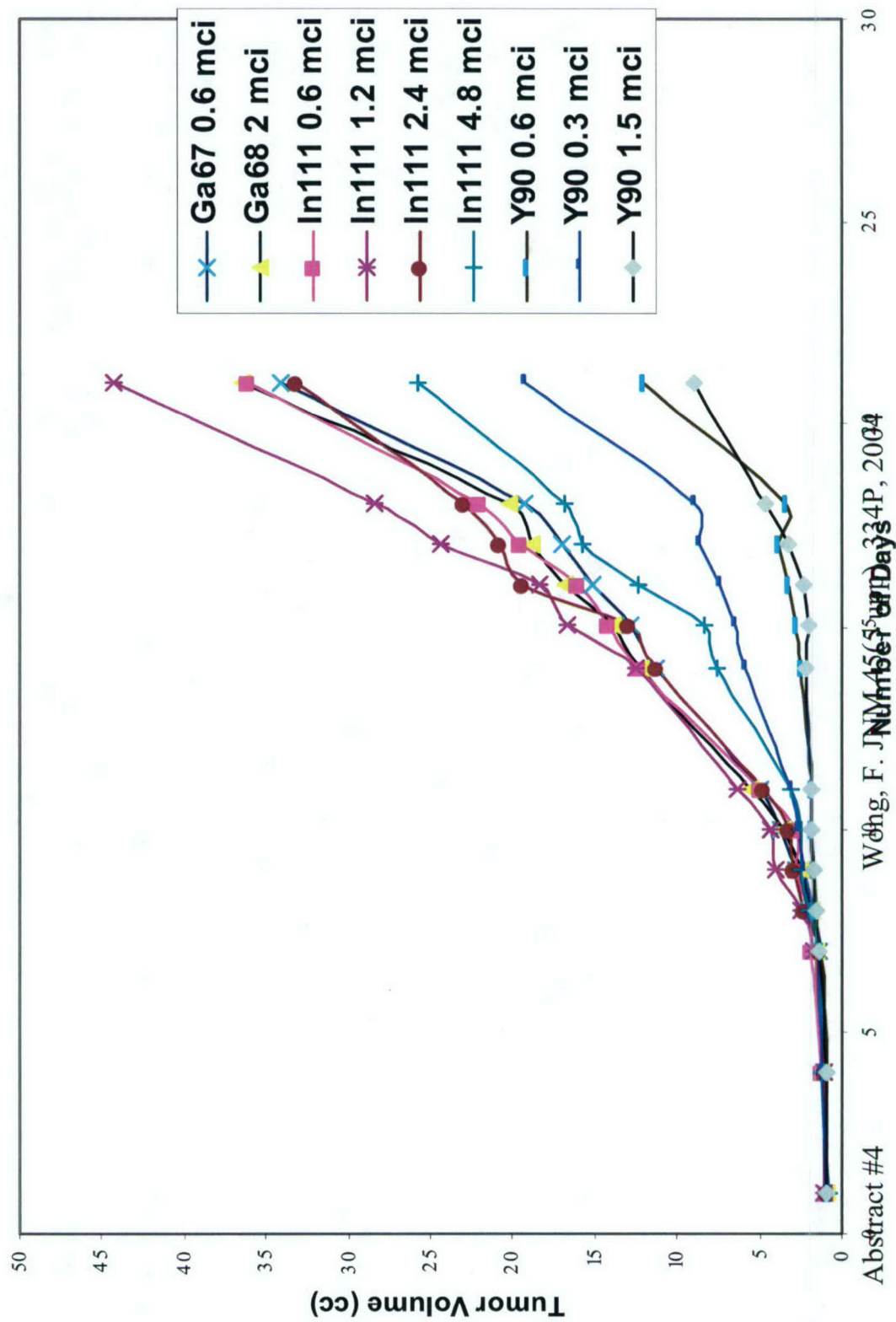


Fig. 2. Rat Scintigrams after ¹¹¹In injection of In-111 Cl

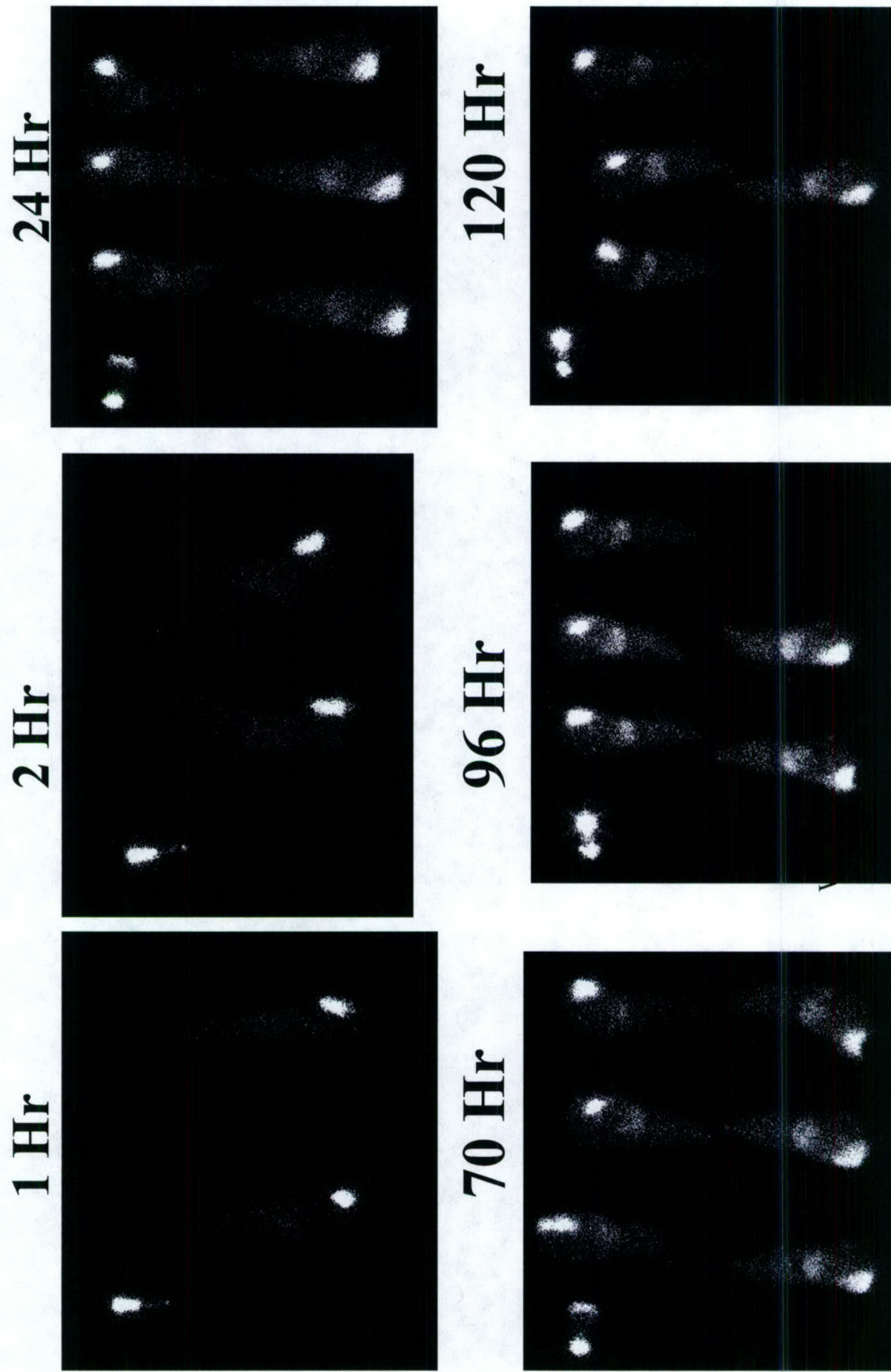
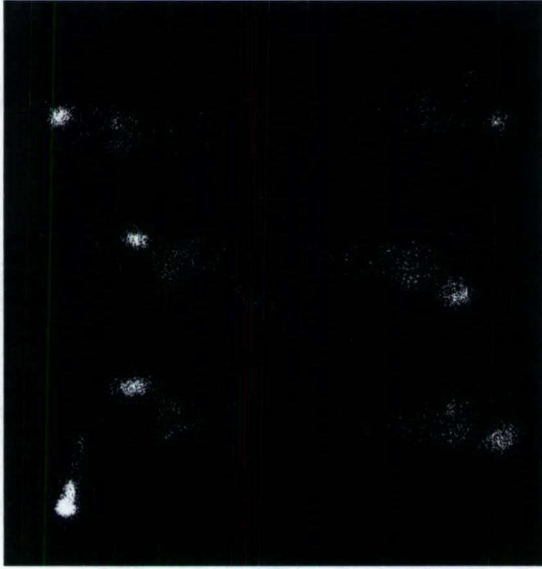


Fig. 3. *Unpublished Proprietary Information* Rat Scintigram after 0.6 mCi Tl-201 Cl, IT

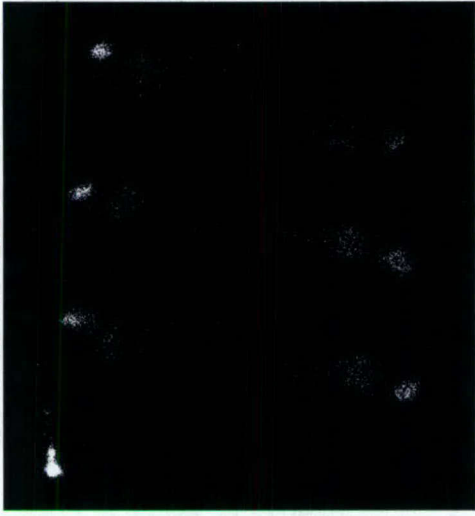
15 min



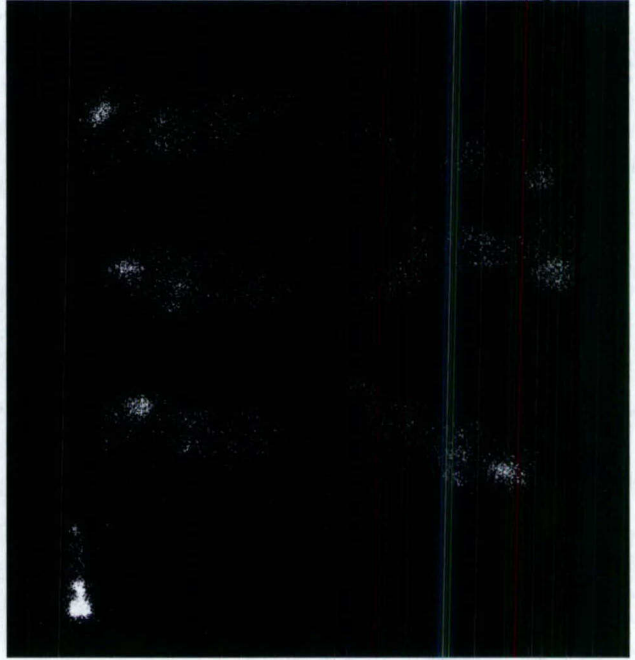
30 min



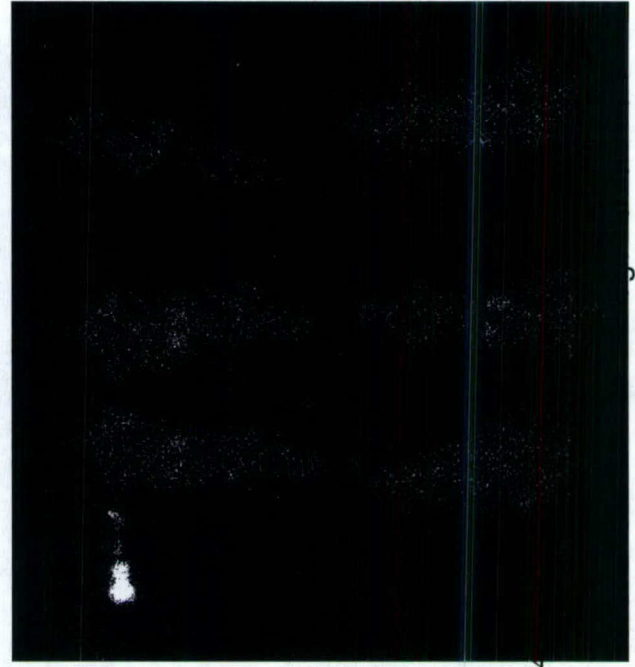
90 min



125 min



24 Hr



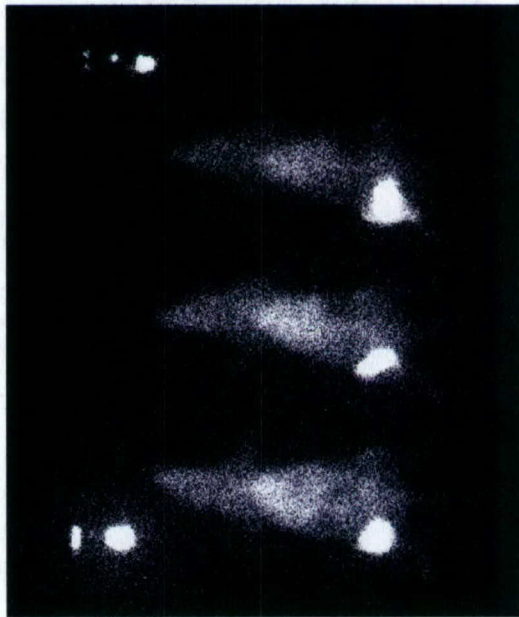
70Hr



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Fig. 4. Rat Scintigram after 0.6 mCi Ga-67, IT

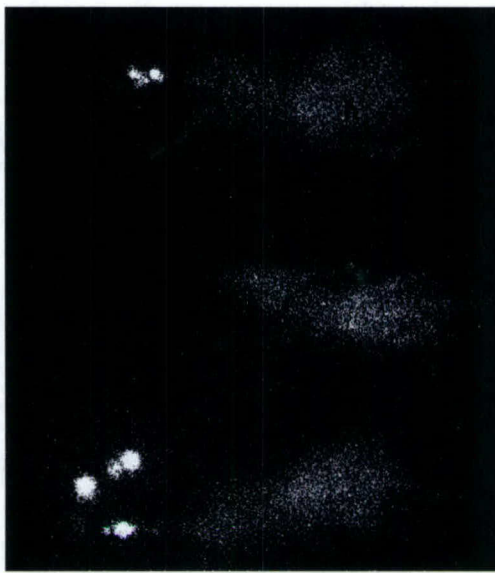
1Hr



3 Hr



24 Hr



Introduction

- There are increasing systemic and local application of Y-90 in radionuclide therapy. The toxic effects of free Y-90 is a concern.
 - Dosimetric estimates to red marrow vary
 - ICRP30: 15 cGy/mCi
 - Herzog (JNM, 1993): 3.74 cGy/mCi
 - Roche (EJNM, 1996): 9.25 cGy/mCi
- High body retention, >80%: Kutzner, 1983
- High skeletal uptake (IM Inj.): 50% at 4 days

Aims of Study

- Evaluate whole-body distribution of Y90 Cl after IV and IM injection
- Compare those of its surrogate In-111 Cl
- Construction of human radiation dosimetry to estimate damages from leakage of Y-90 or In-111 from radiopharmaceuticals after systemic or intrastitial administration.

Methods

- Organ harvesting and counting after IV or IM (right thigh) injection of 0.05 mCi of Y-90 or In-111 chloride in 0.1 ml saline.
- Biodistribution profiles up to 7 days.
- Human radiation dosimetry estimates from accepted anthropomorphic models.

Results

- For IM injection, there are higher fraction of injected doses (FID) in right thigh muscle than left; also up to 6 time higher FID in right femur than left femur (Figures 1 and 2).
- Total skeletal uptake is 16%, from IM Y-90
- For Y-90, kidneys/spleen have the highest doses; the critical organ is red marrow (Fig 3)
- IM and IV injection deliver similar radiation doses to the organs (Table 1)

Discussion

- The radiation absorbed doses to the red marrow are 4.8 and 5.0 cGy/mCi for IM or IV free Y-90; these estimates are lower than those of ICRP30 and between the two estimates from the same group using Y-86 citrate (Roche 1996; Herzog 1993)
- High whole-body retention and high skeletal uptakes are not confirmed.
- 5 cGy/mCi to the red marrow is still of concern because hematotoxicity starts at ~100 cGy
- ¹¹¹In is a good surrogate for Y-90 (Table 1)

Discussion (Cont'd)

- This study may establish the ceilings for locoregional radionuclide therapy using Y-90 Cl and In-111 Cl such as reported in Abst. #1055.
- More information on injectate distribution is needed to derive the dosimetry to tumors for correlation to efficacy.
- **Acknowledgement:** UT MDACC research team; US DOD Breast Cancer Research Grant BC020808

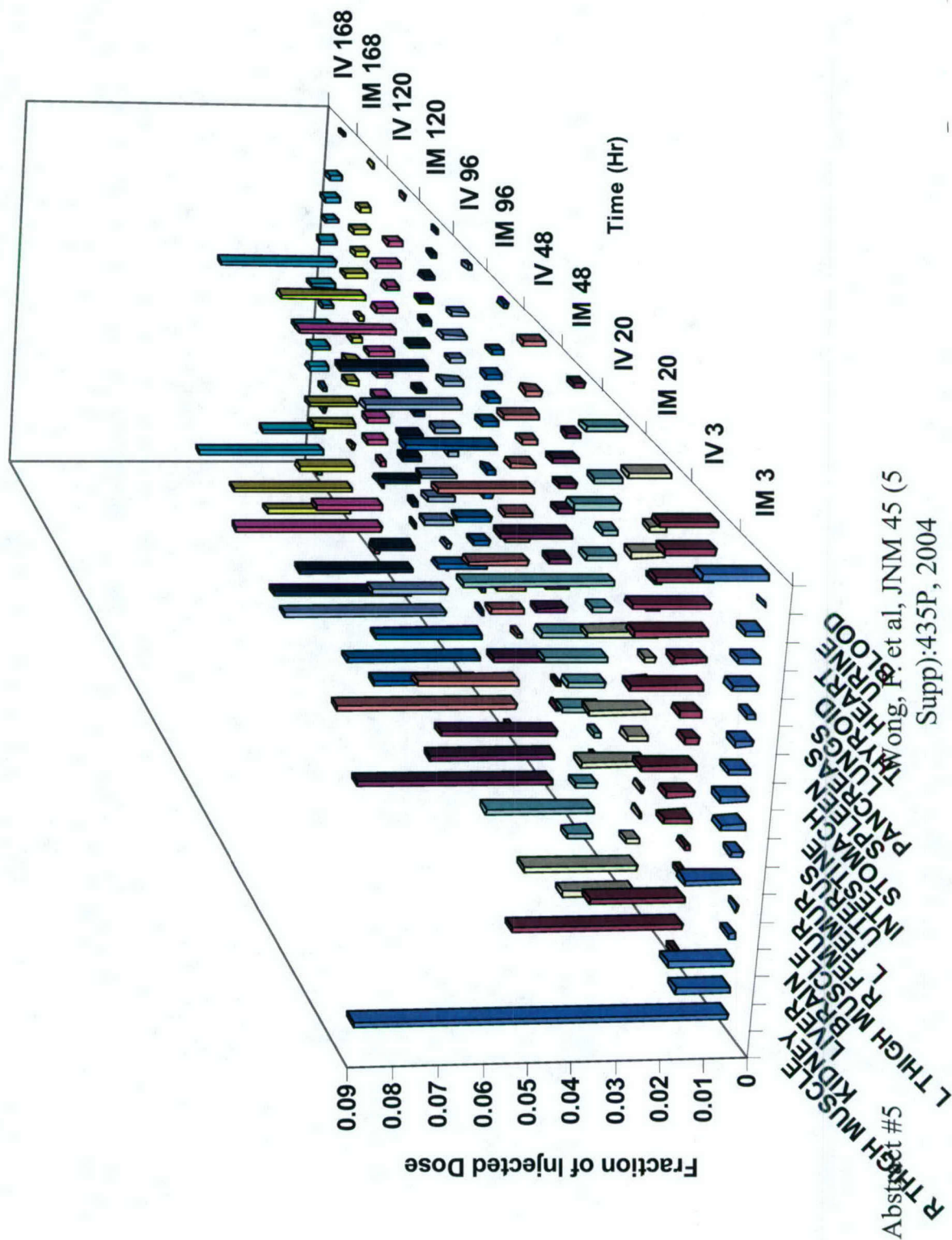
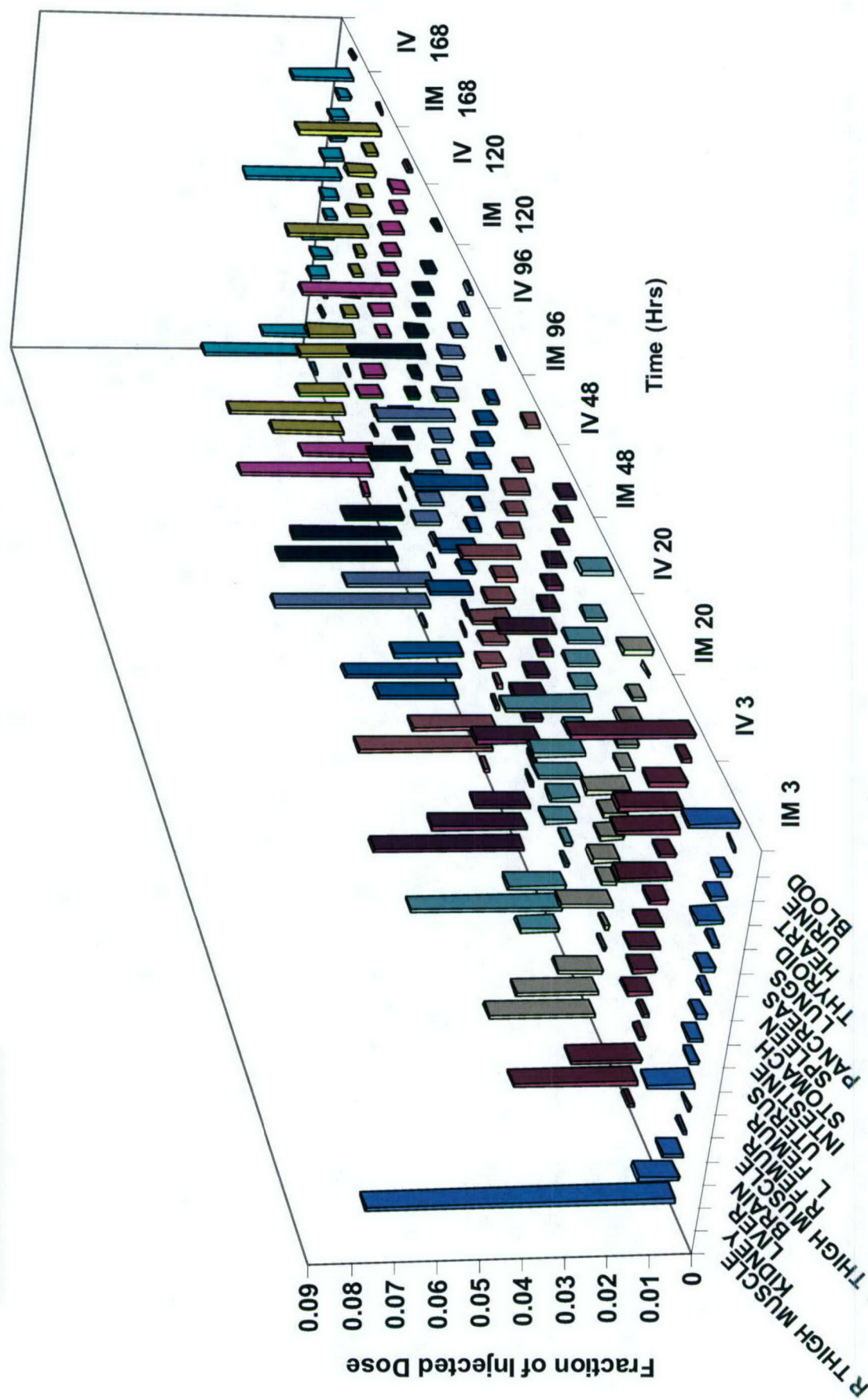
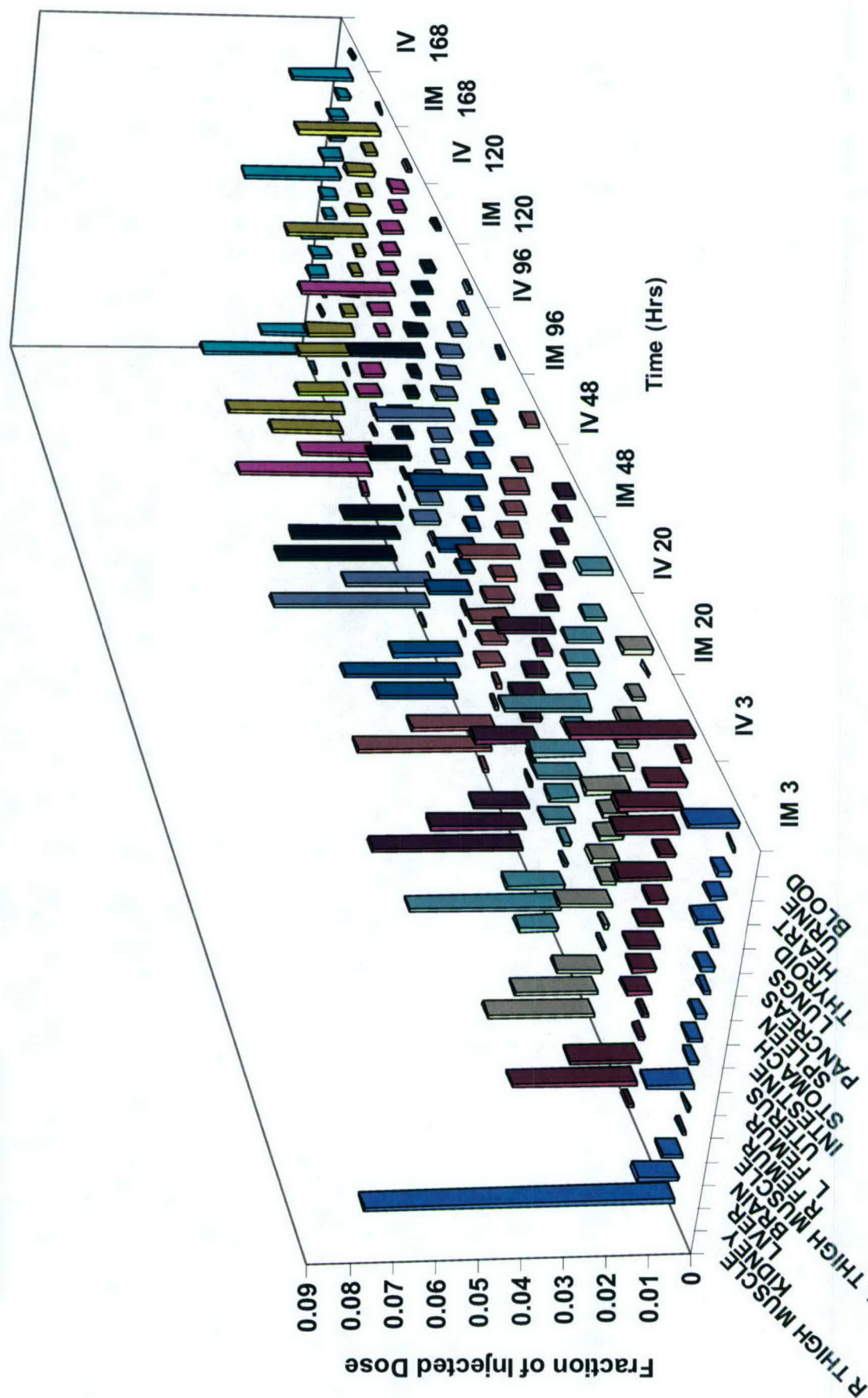


Figure 2. Biodistribution of In-111 Cl in Rats



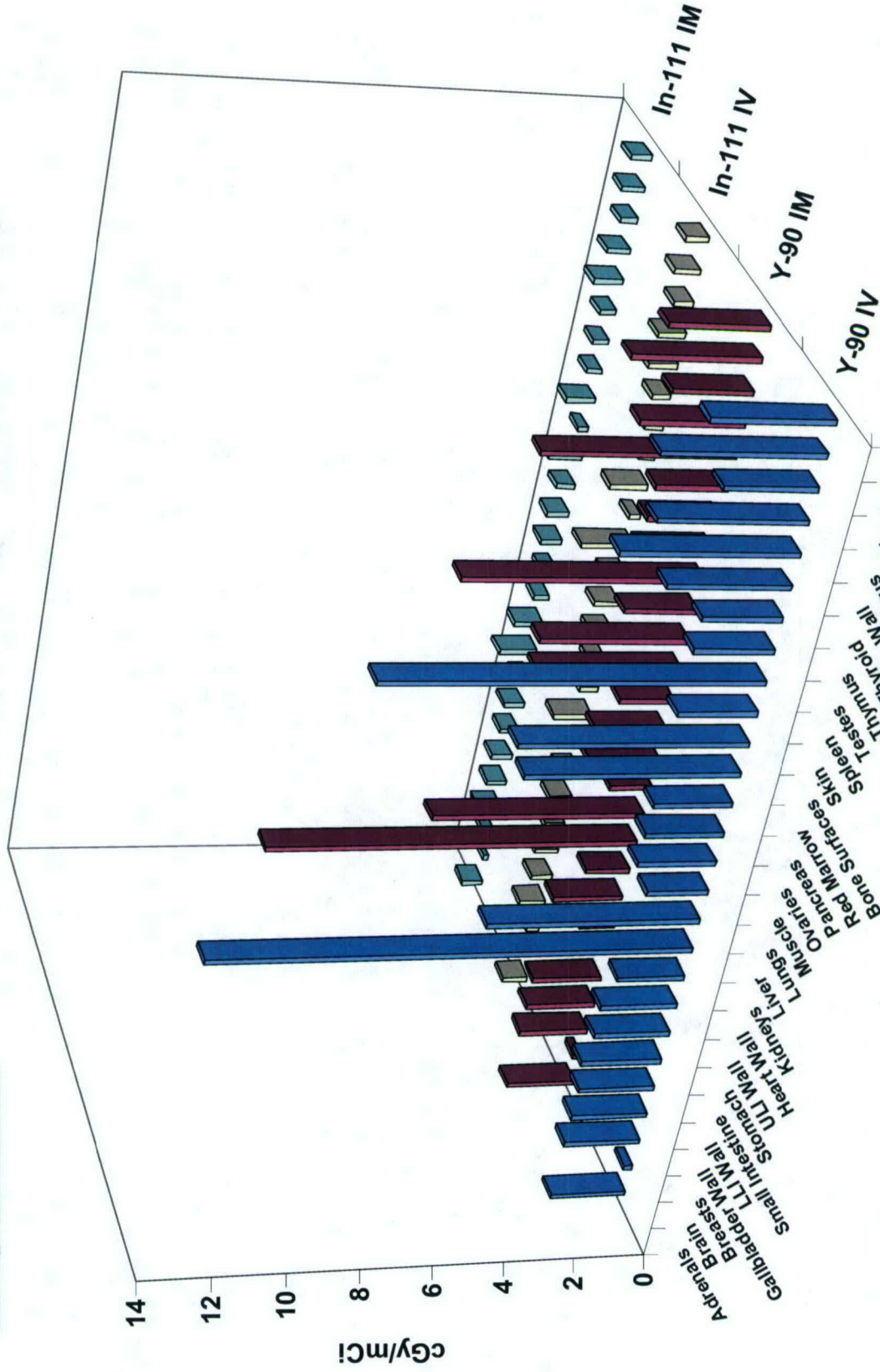
Abstract #5

Wong, F. et al, JNM 45 (5 Supp):435P, 2004



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Figure 3. Human Radiation Dosimetry Estimates



Abstract #5

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 Supp):435F, 2004
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Table 1. Summary of Radiation Absorbed Dose Estimates of Y-90 Cl or In-111 Cl, by IV or IM

c Gy/mCl	Y-90 IV	Y-90 IM	In-111 IV	In-111 IM	IM to IV Y-90	IM to IV In-111	Y to In IM	Y to In IV
Adrenals	2.1400	2.0000	0.7280	0.6470	0.93	0.89	3.09	2.94
Brain	0.2470	0.2270	0.2010	0.1680	0.92	0.84	1.35	1.23
Breasts	2.1400	2.0000	0.3630	0.3460	0.93	0.95	5.78	5.90
Calbladder Wall	2.1400	2.0000	0.7900	0.7000	0.93	0.89	2.86	2.71
LLI Wall	2.1400	2.0000	0.6230	0.6010	0.93	0.96	3.33	3.43
Small Intestine	2.2825	1.3159	0.7067	0.6321	0.58	0.89	2.08	3.23
Stomach	2.1185	1.0400	0.6069	0.5407	0.49	0.89	1.92	3.49
ULI Wall	2.1400	2.0000	0.6550	0.6090	0.93	0.93	3.28	3.27
Heart Wall	1.8600	1.2400	0.5570	0.4860	0.67	0.87	2.55	3.34
Kidneys	13.1000	10.4000	1.4700	1.1300	0.79	0.77	9.20	8.91
Liver	5.8400	5.9800	1.1100	0.8590	1.02	0.77	6.96	5.26
Lungs	1.6800	1.1600	0.5370	0.4560	0.69	0.85	2.54	3.13
Muscle	2.1400	2.0000	0.4870	0.4600	0.93	0.94	4.35	4.39
Ovaries	2.1400	2.0000	0.6570	0.6290	0.93	0.96	3.18	3.26
Pancreas	2.1300	1.5000	0.7210	0.6270	0.70	0.87	2.39	2.95
Red Marrow	5.7700	4.0100	0.6470	0.5470	0.69	0.85	7.33	8.92
Bone Surfaces	6.1300	4.1200	1.4900	0.9780	0.67	0.66	4.21	4.11
Skin	2.1400	2.0000	0.3270	0.3120	0.93	0.95	6.41	6.54
Spleen	10.1000	6.6200	1.0700	0.8520	0.66	0.80	7.77	9.44
Testes	2.1400	2.0000	0.4580	0.4520	0.93	0.99	4.42	4.67
Thymus	2.1400	2.0000	0.5060	0.4850	0.93	0.96	4.12	4.23
Thyroid	3.2700	1.9800	0.5180	0.4760	0.61	0.92	4.16	6.31
Urin Bladder Wall	4.6900	5.2400	0.8230	0.8560	1.12	1.04	6.12	5.70
Uterus	3.9600	2.8300	0.7640	0.6710	0.71	0.88	4.22	5.18
Total Body	2.4800	2.1800	0.5350	0.4880	0.88	0.91	4.47	4.64
EFF DOSE EQUV	4.2900	3.4700	0.7370	0.6370	0.81	0.86	5.45	5.82
Abstract #5	3.2400	2.7000	0.6260	0.5920	0.83	0.92	4.55	5.02

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0.6260, 0.5920
Suppl. 435P, 2004