

**RADIOIMMUNOTHERAPY OF
NON-HODGKIN LYMPHOMA
WITH ^{131}I -RITUXIMAB**

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**WARMTH INTERNATIONAL WORKSHOP ON RADIONUCLIDE
THERAPY KUWAIT and ANNUAL CONFERENCE OF
KUWAIT SOCIETY OF NUCLEAR MEDICINE**

28 – 30TH March 2011

NON HODGKIN LYMPHOMA (NHL)

FIFTH COMMONEST MALIGNANCY

INDOLENT INCURABLE

B-CELL LYMPHOCYTE CLONE CD-20 Ag

PREDOMINANTLY BONE MARROW

BIOPSY ASSESSMENT MAY BE UNRELIABLE

DIAGNOSIS: FLOW CYTOMETRY

¹⁸F-FDG PET

TREATMENT: R-CHOP x 6 CYCLES x 21 D

FOLLICULAR NHL : PFS 3 – 4 YEARS

OVERALL SURVIVAL: OS 50% @ 9 YEARS

ANTI-CD 20 Mabs

- MURINE:** B₁ TOSITUMOMAB (¹³¹I) BEXXAR
IBRITUMOMAB TIUXETAN (⁹⁰Y) ZEVALIN
- CHIMERIC:** RITUXIMAB (¹³¹I) RITUXIMAB
- HUMAN:** OFATUMUMAB
- HUMANIZED:** VELTUZUMAB
GA 101
- SMIP:** SMALL MOLECULAR IMMUNO-
PHARMACEUTICAL (FRAGMENTS)

RITUXIMAB THERAPY NHL (TYPE I)

ADCC ANTIBODY- DEPENDENT
CYTOTOXICITY

MACROPHAGE PHAGOCYTOSIS

CDC COMPLEMENT- DEPENDENT
CYTOTOXICITY

PCD DIRECT INDUCTION OF CELL DEATH

TOSITUMOMAB (TYPE II) PCD>CDC

STANDARD THERAPY NHL

RITUXIMAB-CHOP 6 CYCLES (21 DAYS)

MAINTENANCE RITUXIMAB 3 MONTHLY

2 YEARS

80% SURVIVAL @ 5 YEARS

R-CHOP > CHOP OS x 20% PER ANNUM

RITUXIMAB INDUCTION ALONE INEFFECTIVE

¹³¹I-RITUXIMAB

**80% OF B CELLS IN NHL EXPRESS
CD-20 SURFACE ANTIGEN**

ACCESSIBLE

NOT INTERNALIZED

NOT SHED

NOT MODULATED

PROLONGED EFFECTIVE IRRADIATION

^{131}I -ANTI CD-20 Mab RATIONALE

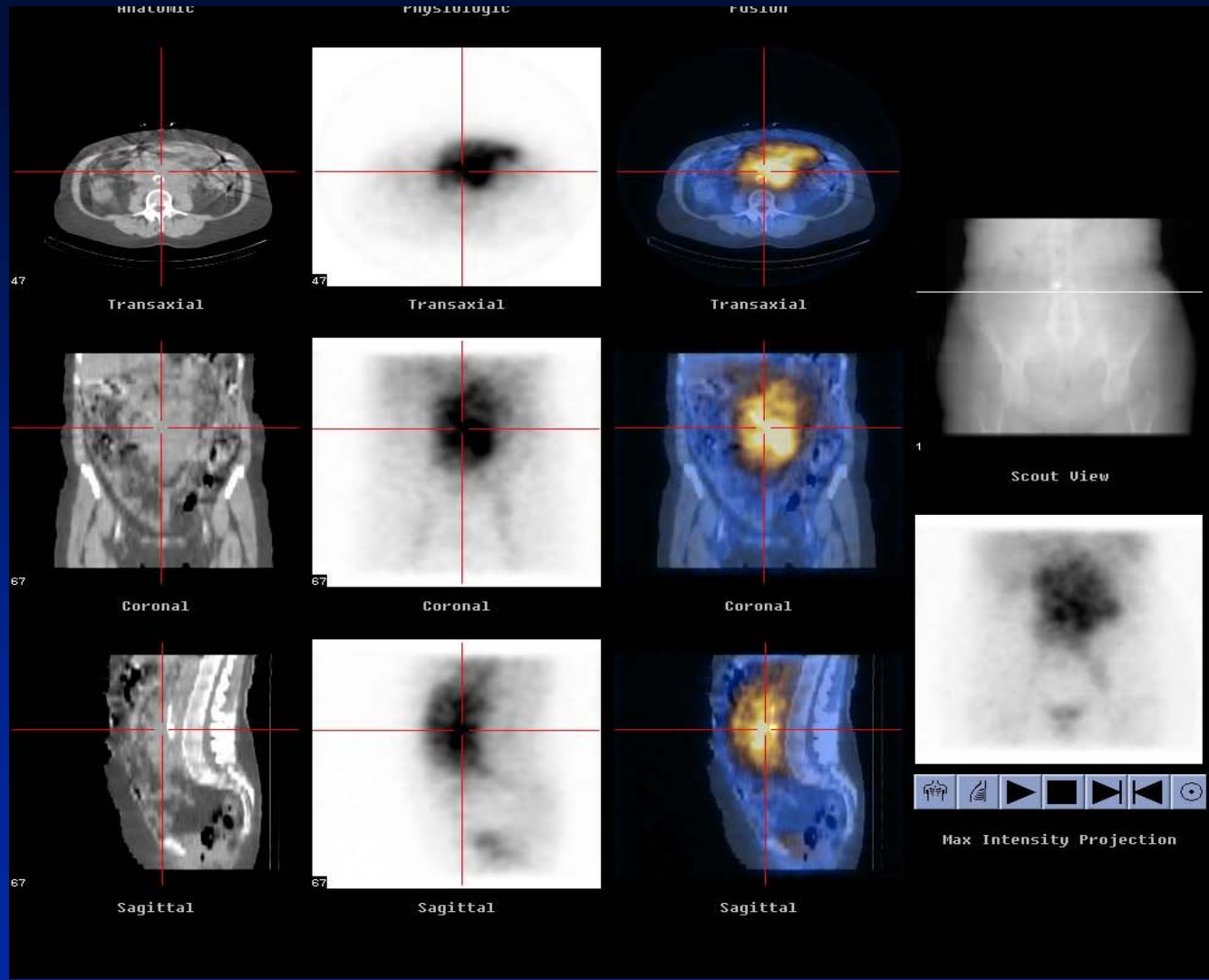
INHERENT RADIOSENSITIVITY

CROSS-FIRE EFFECT

BY-STANDER EFFECT

RITUXIMAB RADIOSENSITIZATION

I-131 RITUXIMAB THERAPY NHL



**RITUXIMAB IMMUNOTHERAPY
¹³¹I-RITUXIMAB RADIOIMMUNOTHERAPY
RELAPSED/REFRACTORY INDOLENT NHL**

	ORR	CR	TTP
RITUXIMAB	50%	5%	9 M
¹³¹I-RITUXIMAB	75%	54%	22 M

**Leahy M, Seymour JF, Hicks RJ, Turner JH.
J Clin Oncol 2006 24:4418-4424**

RIT RELAPSED INDOLENT NHL

¹³¹I-TOSITUMOMAB &

⁹⁰Y-IBRITUMOMAB TIUXETAN

CLINICAL TRIAL v CLINICAL PRACTICE

ORR 50 - 80% v 47%

CR 15 - 50% v 13%

TOXICITY GRADE III / IV : BEXXAR[®]-ZEVALIN[®]

PLATELETS 3 - 5% v 56 - 57%

NEUTROPHILS 16 - 32% v 50 - 57%

Wahl R et al. J Nucl Med 2007 48:1767-1776

RIT RELAPSED INDOLENT NHL

¹³¹I-RITUXIMAB

CLINICAL TRIAL v CLINICAL PRACTICE

ORR	76%	v	67%
CR	53%	v	50%

TOXICITY	GRADE III / IV		¹³¹I-RITUXIMAB
PLATELETS	4%	v	6%
NEUTROPHILS	16%	v	10%

Leahy MF et al. J Clin Oncol 2006 24:27, 4418-4424

Leahy MF & Turner JH. Blood 2011 117:1, 45-52

Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with ¹³¹I-rituximab in routine clinical practice: 10 year single institution experience of 142 consecutive patients

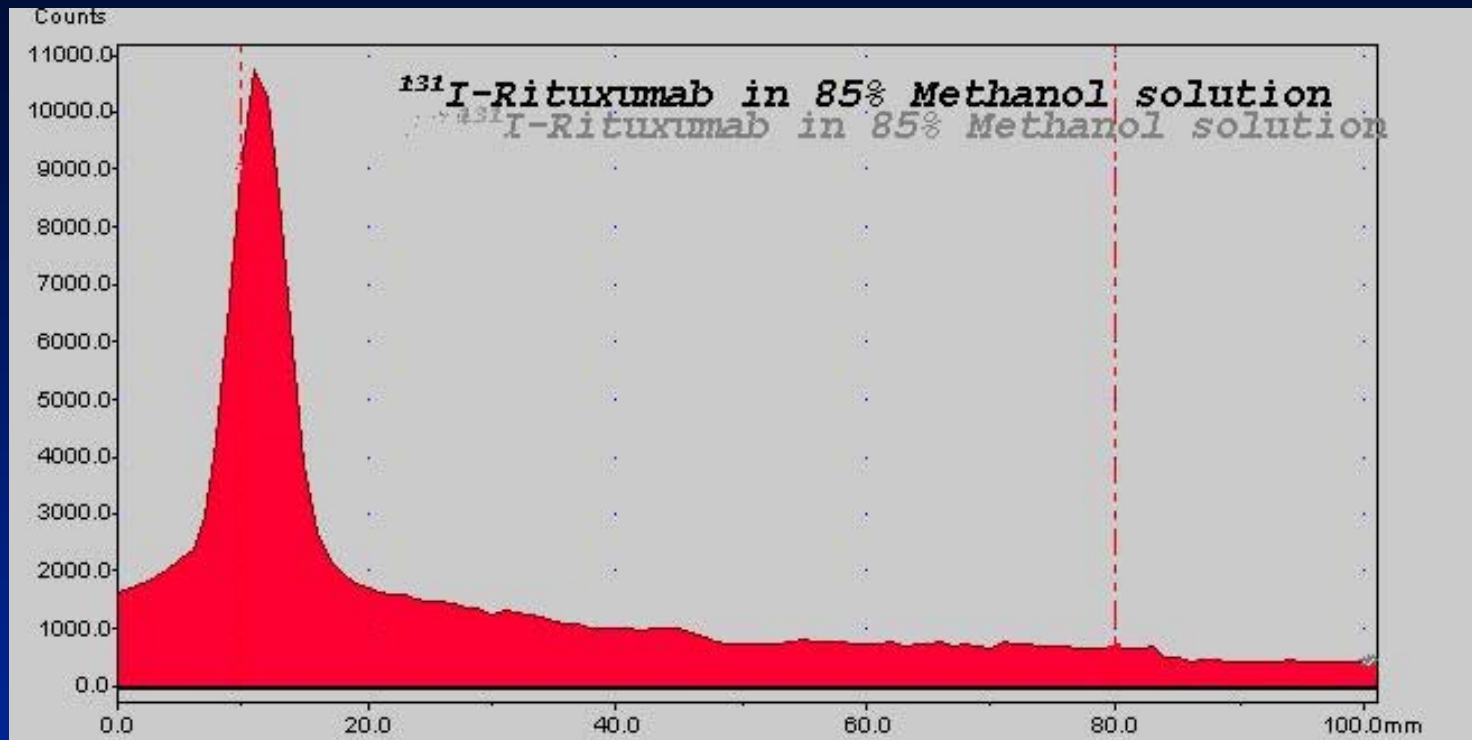
Michael F. Leahy and J. Harvey Turner, The University of Western Australia

Radioimmunotherapy of indolent non-Hodgkin lymphoma (NHL) has achieved objective response rates (ORR) in clinical trials comparable with standard R-CHOP chemotherapy, but is relatively underutilized in routine practice. We report our clinical experience in 142 consecutive patients who received Iodine-131 rituximab radioimmunotherapy for low grade, predominantly follicular, relapsed NHL. ORR of 67% with complete remission (CR) in 50% and median overall survival (OS) 32 months, matched the response rates in Phase II clinical trial of 131I-rituximab radioimmunotherapy and compares favourably with those reported for 131I-tositumomab or 90Y-ibritumomab tiuxetan. Progression-free survival (PFS) was 18 months overall and 32 months in complete response (CR, CRu) patients. Our patients comprised 107 (75%) follicular lymphoma, 21 (15%) small lymphocytic lymphoma, 6 (4%) mucosa associated lymphoid tissue/marginal zone lymphoma and 8 (6%) mantle cell lymphoma, median follow-up 32 months and 8 year OS 48%. Toxicity was limited to hematological grade 4 neutropenia occurring in 10% and thrombocytopenia in 6%. There were no episodes of bleeding or infection requiring hospital admission. Radioimmunotherapy with 131I-rituximab in routine clinical outpatient practice provides cost-effective, safe treatment of relapsed/refractory indolent NHL, with over half the patients achieving durable complete remission with potential for repeat radioimmunotherapy on relapse.

The logo for the journal 'blood' is displayed in a stylized, lowercase, serif font. The letters are a dark red color and are set against a white rectangular background.

BLOOD, 6 January 2011 Volume 117, Number 1

^{131}I -RITUXIMAB PREPARATION



**IN-HOUSE 30 MIN CHLORAMINE-T STERILE AUTO/
SEMI-AUTOMATED 7GBq Na ^{131}I 15 mg RITUXIMAB**

Turner JH et al. Cancer Biotherapy Radiopharm 2003 18:4, 513-524

De Decker M. Internat Symp Radiopharm Sci 2011 Amsterdam

¹³¹I - RITUXIMAB RIT NHL DOSIMETRY

**PROSPECTIVE INDIVIDUAL CALCULATION
PRESCRIBED RADIATION ABSORBED DOSE**

0.75 Gy TO WHOLE BODY

1.9 Gy TO RED MARROW

Turner JH et al

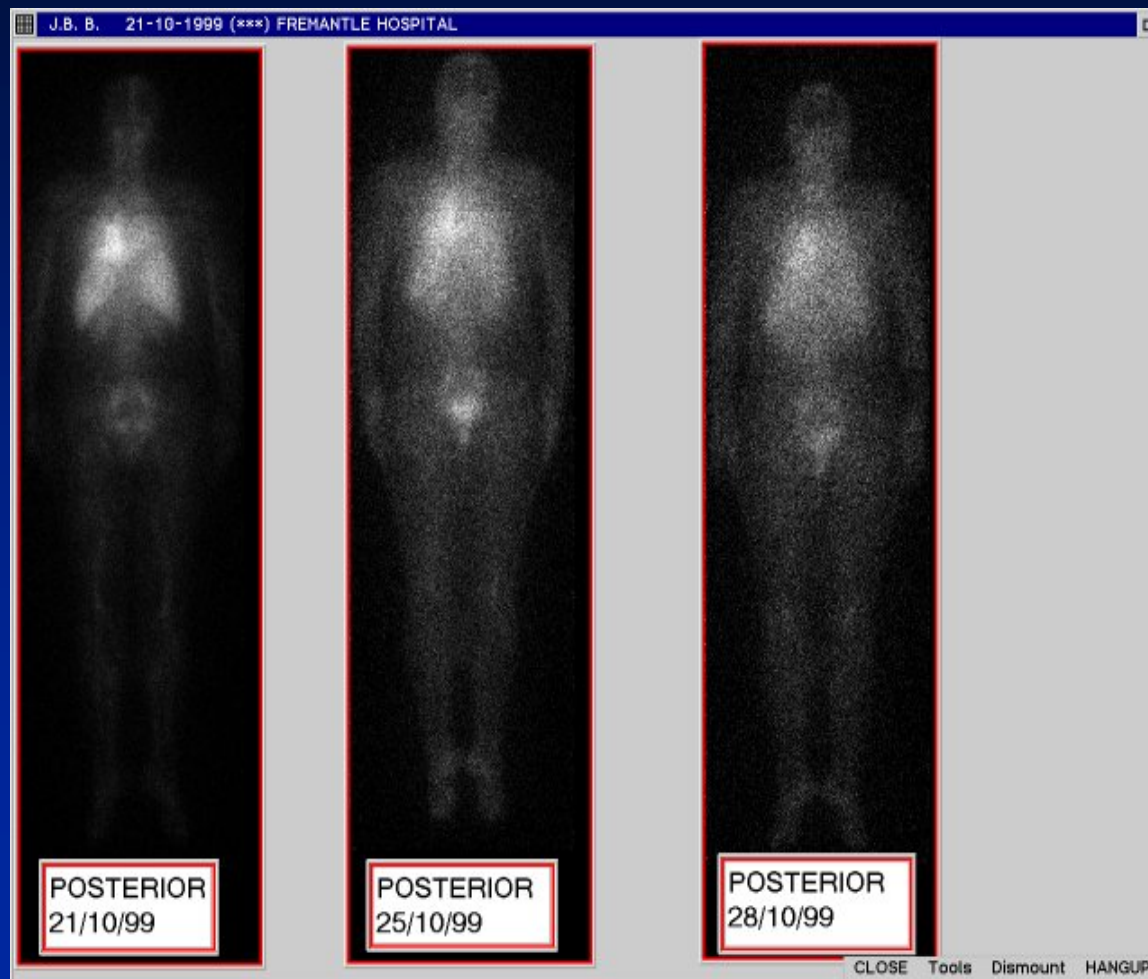
Cancer Biotherapy & Radiopharm (2003) 18:4, 513-524

Boucek JA & Turner JH

Eur J Nucl Med & Molec Imaging (2005) 32:4, 458-469

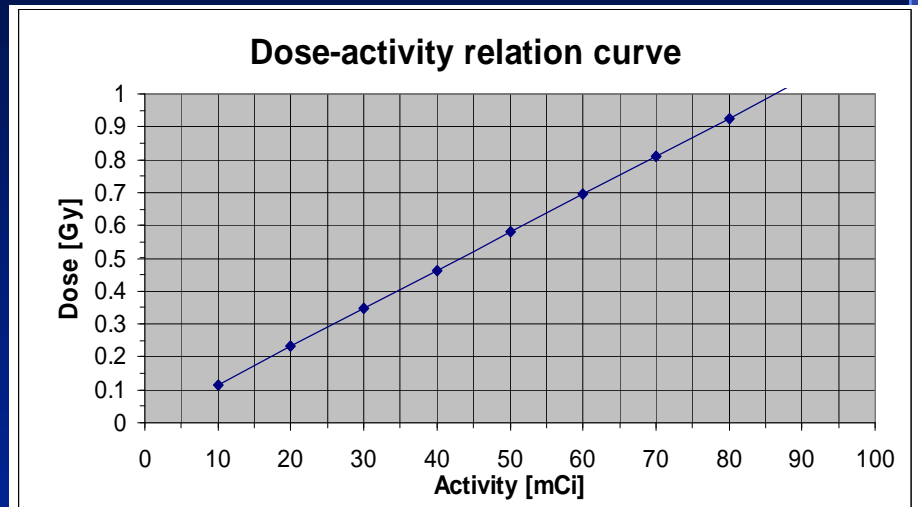
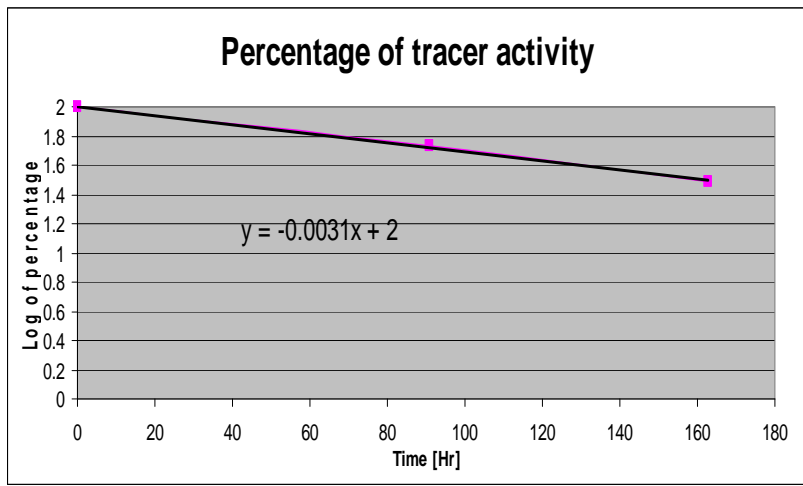
I-131 RITUXIMAB DOSIMETRY

WHOLE BODY IMAGES 1 HOUR, 4 DAYS, 7 DAYS

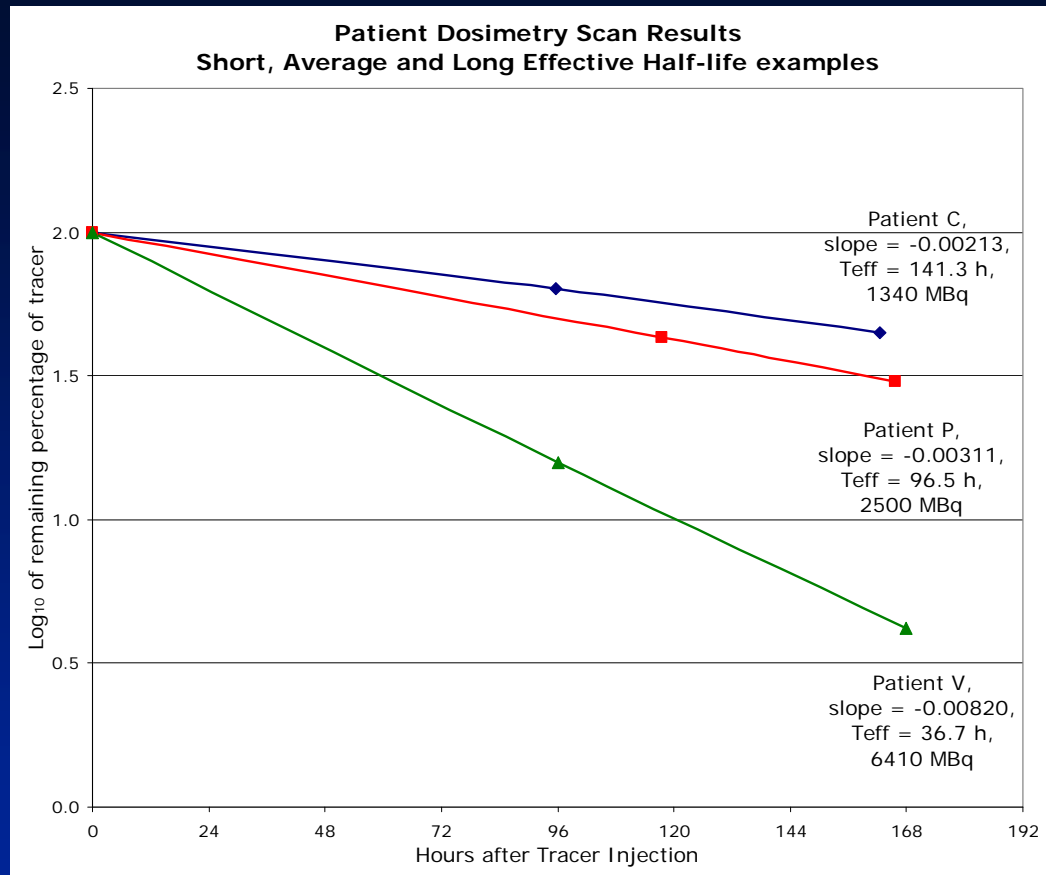


I-131 RITUXIMAB DOSIMETRY RETENTION CURVE CALCULATION OF ADMINISTERED ACTIVITY FOR MPD NHL RADIOIMMUNOTHERAPY WHOLE BODY DOSE 0.75 Gy

Patient details		Results	
Patient name	B.,J.	Desired total body dose [Gy]	0.75
Sex (MF)	F	Therapeutic dose [MBq]	2396.080879
Height [cm]	172	Therapeutic dose [mCi]	64.75894268
Weight [kg]	84	Slope of the curve	-0.0031
Max. effective mass [kg]	87.3416	Residence time [h]	139.2897664
Activity hours [mCi hr]	9020.258	Effective T1/2 [h]	97.10645021



Dose administered [Gy]	Activity [mCi]	Activity [MBq]	Dose administered [Gy]	Activity [mCi]	Activity [MBq]
0.115814121	10	370	1.273955327	110	4070
0.231628241	20	740	1.389769448	120	4440
0.347442362	30	1110	1.505583568	130	4810
0.463256483	40	1480	1.621397689	140	5180
0.579070603	50	1850	1.73721181	150	5550
0.694884724	60	2220	1.85302593	160	5920
0.810698844	70	2590	1.968840051	170	6290
0.926512965	80	2960	2.084654172	180	6660
1.042327086	90	3330	2.200468292	190	7030
1.158141206	100	3700	2.316282413	200	7400



Prescribed whole body radiation dose 0.75 Gy
Administered activity 1- 4.5 GBq ¹³¹I-Rituximab

**¹³¹I-RITUXIMAB THERAPY NHL
TOXICITY n = 350**

**MYELOSUPPRESSION
MILD & TRANSIENT**

NO BLEEDING

NO INFECTION

NO SAE HOSPITAL ADMISSION

¹³¹I-RITUXIMAB RIT NHL INDICATIONS

FIRST-LINE (FOLLICULAR NHL)

RELAPSED / REFRACTORY (INDOLENT)

RELAPSE AFTER RIT RESPONSE: (**REPEAT**)

CONSOLIDATION OF R-CHOP (PR → CR)

CONDITIONING BEAM CHEMOTHERAPY

BONE MARROW TRANSPLANT

(**TRANSFORMED / AGGRESSIVE NHL**)

LYMPHOMA RADIOIMMUNOTHERAPY FOLLICULAR NHL FIRST-LINE RIT

n = 76 ¹³¹I-TOSITUMOMAB BEXXAR®

ORR 95%

CR 75%

MOLECULAR

CR 80% (of CR)

PFS 59% @

5 YEARS

MEDIAN PFS

6.1 YEARS

NO TRANSFUSION OR GROWTH FACTORS
NO MYELOYDYSPLASTIC SYNDROME OR AL
HAMA 63%

Kaminski MS et al N Engl J Med 2005 352:441-9

¹³¹I-RITUXIMAB INITIAL STUDY

FIRST-LINE RIT FOLLICULAR NHL n = 50

PRESCRIBED WHOLE BODY DOSE 0.75 Gy

¹⁸F- FDG PET FOLLOW-UP AT 3 MONTHS

OBJECTIVE RESPONSE RATE (ORR) 98%

COMPLETE REMISSION (CR) 78%

PARTIAL RESPONSE (PR) 20%

MEDIAN PFS NOT REACHED @ MEDIAN F/U 2Y

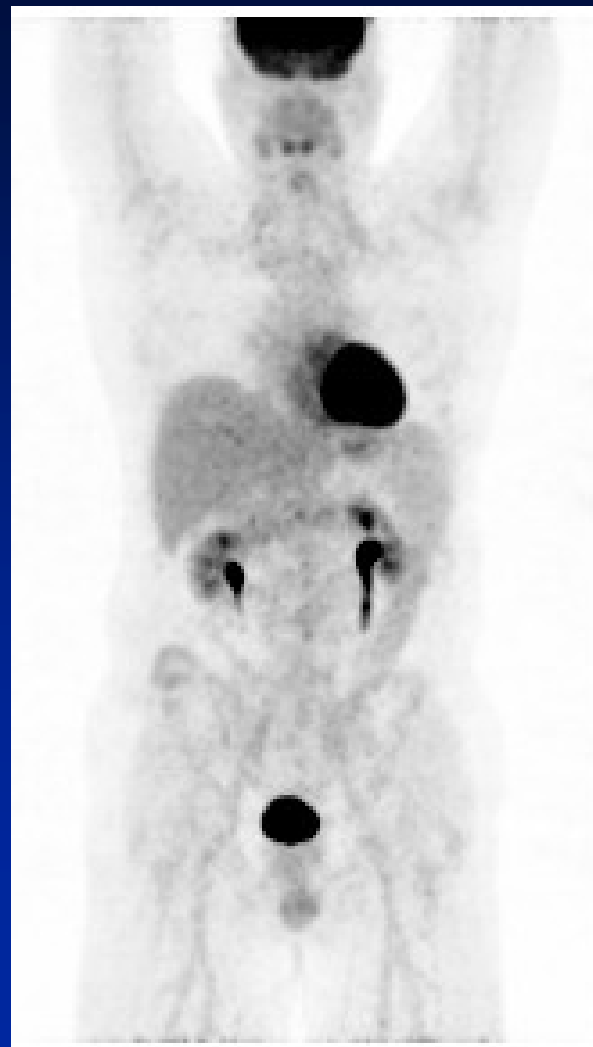
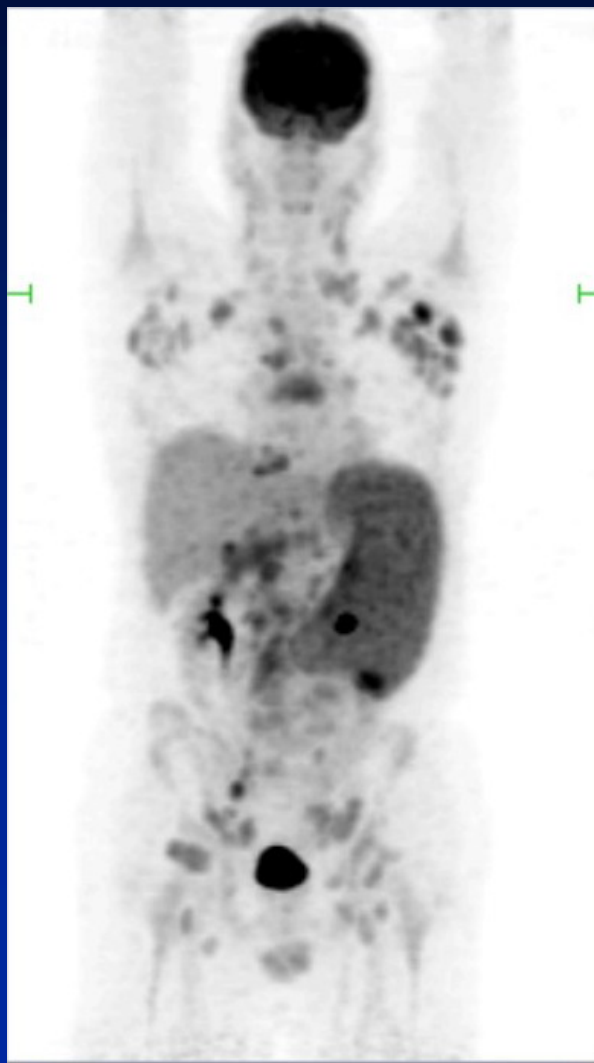
TOXICITY GRADE IV NEUTROPENIA 10%

THROMBOCYTOPENIA 10%

NO EPISODE OF BLEEDING OR INFECTION

McQuillan AD, Macdonald WBG, Turner JH UWA 2011

^{131}I -RITUXIMAB INITIAL Study 3m F/U



REPEAT TREATMENTS

¹³¹I – RITUXIMAB RIT NHL

n = 16 FOLLICULAR 15 MANTLE 1

MEDIAN RE-TREATMENT INTERVAL 19 M

ORR 88% CR 56%

INITIAL TTP 14 M REPEAT TTP 11 M

GRADE III / IV TOXICITY: REPEAT (INITIAL)

THROMBOCYTOPENIA 27% (25%)

NEUTROPENIA 9% (25%)

Bishton M, Leahy MF, Hicks RJ, Turner JH et al.

Ann Oncol 2008 19: 1629-1633

**¹³¹I-RITUXIMAB RIT NHL
TRANSFORMED / AGGRESSIVE
MYELOABLATION RIT BEAM CHEMOTHERAPY
AUTOLOGOUS STEM CELL TRANSPLANT**

0.75Gy WHOLE BODY ¹³¹I-RITUXIMAB D – 19

STANDARD DOSE BEAM CHEMOTHERAPY D – 12

2.65x 10⁶/kg STEM CELLS D 0

n = 8 MANTLE 3, MALT 1, DLBCL 4

CR 7 OS 88% @ MEDIAN F/U 24M (2-70)

PFS MEDIAN 14 M (2-70)

NEUTROPHIL ENGRAFTMENT MEDIAN 12D (9-25)

PLATELET ENGRAFTMENT MEDIAN 20D (11-61)

Gangatharan S, Leahy MF, Turner JH et al. UWA 2010

¹³¹I-RITUXIMAB RIT NHL

**CONSOLIDATION RADIO-IMMUNOTHERAPY
AND INDUCTION CHEMOTHERAPY
APPROACH IN LYMPHOMA (CRITICAL)**

R-CHOP x 3 CYCLES + ¹³¹I-RITUXIMAB

v

R-CHOP x 6 CYCLES

Work in progress UWA 2011

¹³¹I-RITUXIMAB PREPARATION SAFETY

**RECEIPT, LABELING, DISPENSING
MANUAL LABELING v SYNTHERA® AUTO**

7 GBq ¹³¹I-IODIDE → RITUXIMAB

RADIOPHARMACIST RADIATION EXPOSURE:

WHOLE BODY 55 v 11 micro-Sv

20 milli-Sv pa allowable

HANDS

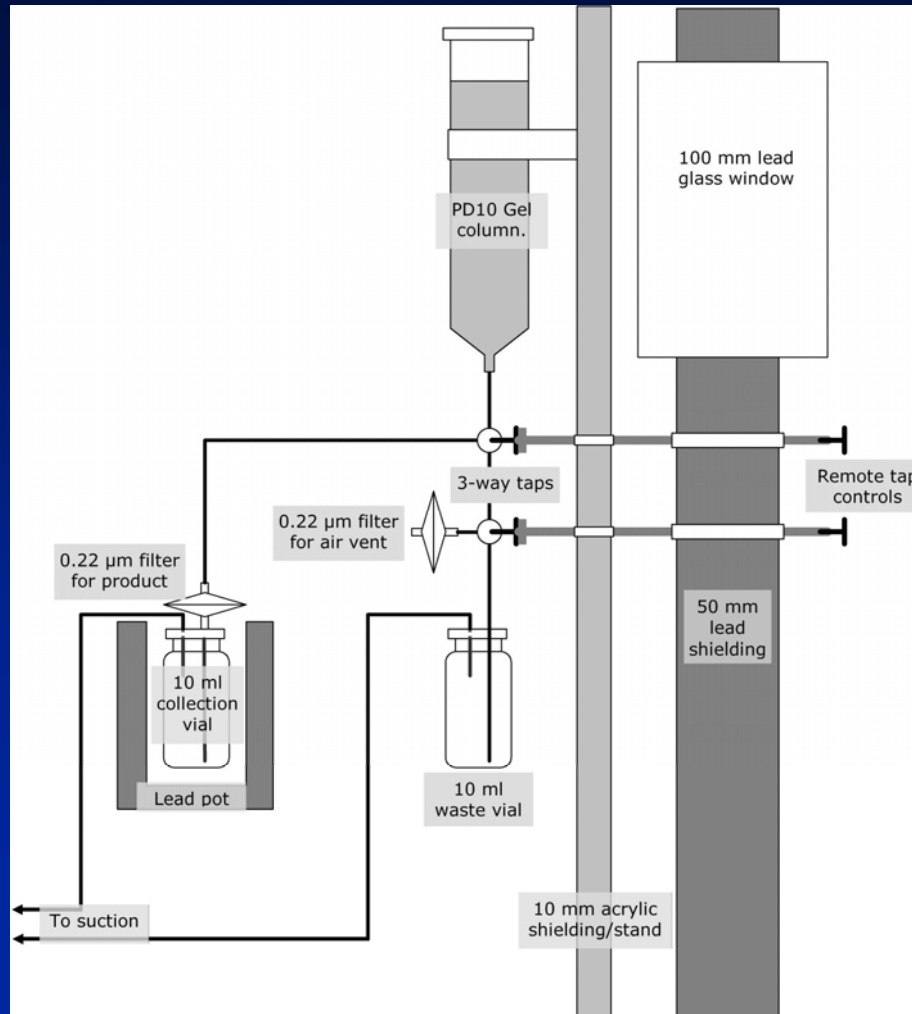
335 v 84 micro-Sv

500 milli-Sv pa allowable

ARPANSA guidelines

Radiological Council WA regulations

^{131}I -RITUXIMAB MANUAL LABELING



^{131}I -RITUXIMAB SYNTHERA[®] LABELING

Synthera v1.0

File View Tools Options Help

^{131}I -Rituximab

● Kit
● Ext
● Snd
● Grn Btn

GBq
 Ext
 I 131
 Recovery
 He
 Vac
 Output (to Waste)
 PD-10 Column
 Waste
 Final prod.
 GBq
 °C
 kPa
 set point
 °C
 kPa
 Htr

Start 10/21/06 07:00:32
Pause
 Script Elapsed
 Cmd Elapsed
BOX 1 Cmd Left 0
 Script Left 24:12

Type	Name	Value	High	Description
1	? ID KitIn	1	I131_F	primary RBO script
2	? SA Prs	300	_	reset
3	? SD V15	0	_	reset

w999

^{131}I -RITUXIMAB : OUTPATIENT n=200

ADMINISTERED ACTIVITY 1 - 4.5 GBq ^{131}I

WHOLE BODY RADIATION DOSE 0.75 Gy

CARER EXPOSURE < 2 mSv (5 mSv)

FAMILY / VISITOR / PUBLIC < 0.5 mSv (1 mSv)

EXPOSURE RATE @ 1 WEEK < 25 $\mu\text{Sv/h}$ @1m

Calais PJ, Turner JH, UWA 2011

RADIOIMMUNOTHERAPY OF NHL
ZEVALIN[®] BEXXAR[®] SHORTCOMINGS
MURINE Mab IMMUNOGENICITY → HAMA

HIGH COST: US\$25,000 PER PATIENT DOSE

HAEMATOLOG / ONCOLOGIST RESISTANCE
MARKET FORCES THREATEN AVAILABILITY

TOXICITY SIGNIFICANT CONSEQUENT UPON
INABILITY TO PERFORM ⁹⁰Y DOSIMETRY

Illidge TM. J Clin Oncol 2010;28(18):2944-2946

¹³¹I-RITUXIMAB THERAPY NHL

SAFE

EFFECTIVE

OUTPATIENT TREATMENT

AVAILABLE WORLD-WIDE

PRACTICAL

AFFORDABLE

PRESERVES QUALITY OF LIFE

ACCEPTABLE TO PATIENTS,

HAEMATOLOGISTS & ONCOLOGISTS