The potential future of targeted radionuclide therapy: implications for occupational exposure?

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Introduction: Targeted Radionuclide Therapy (TRT)

Systemic treatment

Molecule labelled with a radionuclide delivers a toxic level of radiation to disease sites

Can eliminate both primary tumour sites and metastatic cells ⟷ **External beam radiation therapy with high-energy X-rays**

Ionising radiation can exert "bystander" effects ⟷ **Tumour-directed drugs and toxins**

Current radionuclide therapies

Use β^- emitting radionuclides (^{131}I, ^{153}Sm, ^{89}Sr, , ^{90}Y, ^{32}P, ^{177}Lu)

β^- particles (electrons) deliver energy to tumour cells

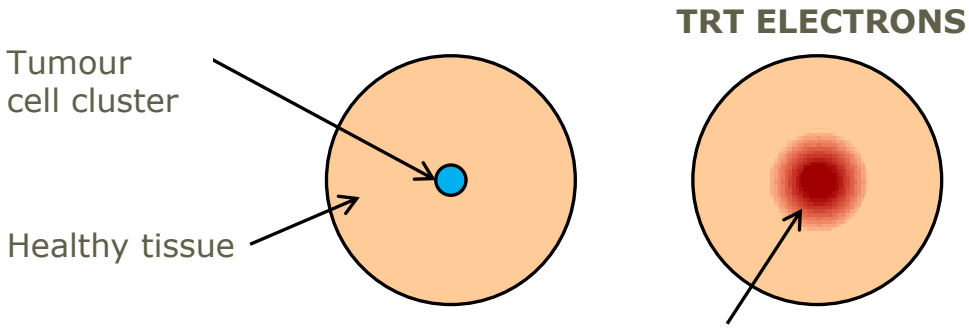
Some radionuclides have "theranostic" properties (^{131}I, ^{177}Lu)

(More) Targeted Radionuclide Therapy

β- (electrons) in radionuclide therapy

Emitted electrons do not deposit their main energy to the micro-metastatic tumour cells

Energy (and its effects) will be released along a several millimetre long electron track



TRT α, auger electrons

Energy deposition electrons from site of decay – track length (mm)	
^{177}Lu	2
^{131}I	4
^{90}Y	11

Energy deposition zone α, auger

More specificity?

Alpha particles (range 70-100 µm)

Auger electrons (range 0.2-10 µm)

Why α-particles? (1)

Typical α-particles emitted by radionuclides of interest

High Linear Energy Transfer (LET): 60-110 keV/µm

Short path length/range in tissue: 70-100 µm

High potency and specificity!

Radionuclide therapy with β-emitters

Long tissue range (…> 1 mm), difficult to sterilise individual tumour cells solely

Low LET: 0.1-1 keV/µm

Exception: Auger electrons!

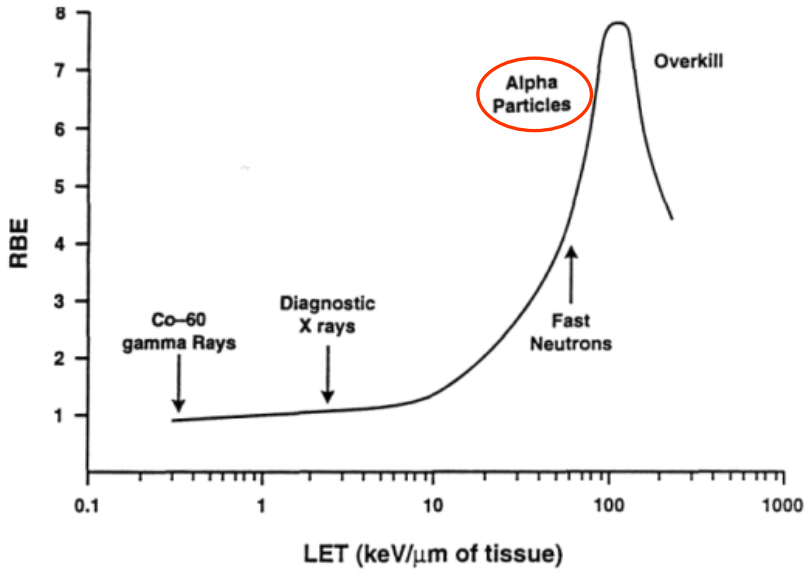
Why α-particles? (2)

High LET and RBE

Distance between ionisations ~ ∅ DNA

High possibility for DSB per unit of absorbed dose

High Relative Biological Effectiveness (RBE)!



$$RBE = \frac{Absorbed\_dose(Gy)\_reference-radiation}{Absorbed\_dose(Gy)\_test-radiation}$$

Particle type, LET

Total absorbed dose

Dose rate, fractionation

Biological system, biological endpoint

Why α-particles? (3)

RBE(α) for deterministic effects ≈ 5

Based on review of literature: 3 < RBE(α) < 5 for cell killing

Recommended for projecting the possible deterministic biological effects associated with α-particle absorbed dose!

$W_R(\alpha)$= 20 (radiation protection)

Relates to stochastic endpoints (e.g. cancer induction)

Important for occupational exposure

Why α-particles? (4)

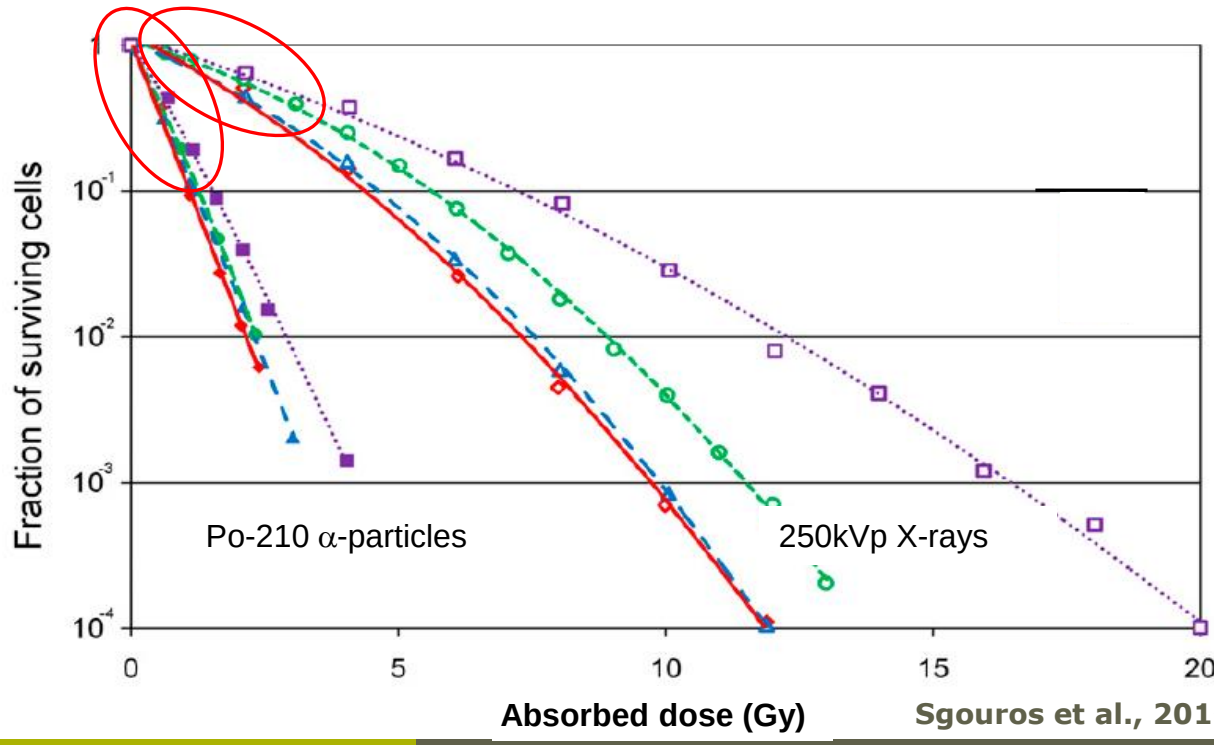
Log-linear cell survival curve

Low LET: initial shoulder on the cell survival curves reflects the repair (Linear-quadratic model), Quadratic: accumulation of damage

High LET: no initial shoulder (log-linear at both high and low doses)

Log-linear reflects a reduced repair capacity (not absence)

Log-linear reflects cell death from single event (without the need for accumulation)



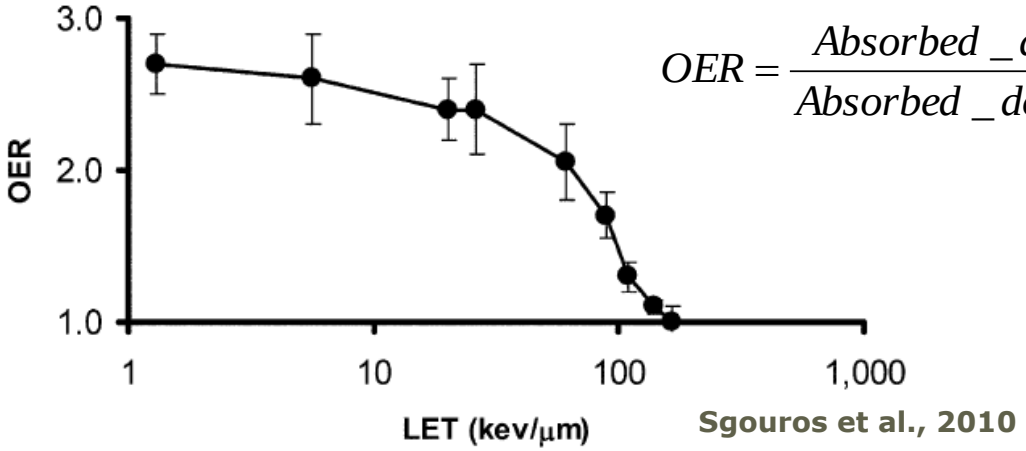
Sgouros et al., 2010

Why α-particles? (5)

Oygen enhancement ratio (OER)

Important factor in the response of cells to ionising radiation

Effect strongly influenced by the LET



Sgouros et al., 2010

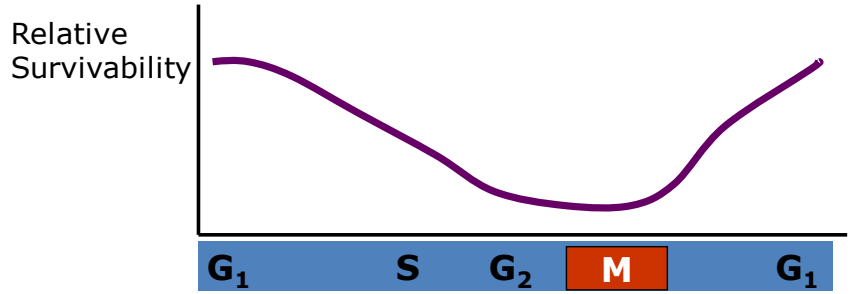
$$OER = \frac{Absorbed\_dose(Gy)\_with-presence-oxygen}{Absorbed\_dose(Gy)\_without-presence-oygen}$$

Ability of α-particles to overcome radioresistance due to hypoxia!

Why α-particles? (6)

Sensitivity of cells during cell cycle

Low LET: sensitivity varies during cell cycle



High LET: sensitivity is less cell cycle dependent

Delays at checkpoints are less pronounced and persistent in cells that are irradiated with high LET

Less dependent on active cell proliferation

Important in a clinical situation where both tumours and surrounding normal tissue irradiated with high LET

Radiobiological properties α-particles

Favourable with respect to β-particles

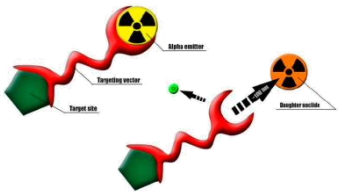
- **Specificity**
- **Potency**
- **Log-linear cell survival curve**
- **Less dependent on oxygenation**
- **Less dependent on active cell proliferation**

Standard in targeted radionuclide therapy?

The availability of suitable α-emitting radionuclides

α-emitting daughters: toxicity healthy tissues (recoil energy breaks chemical bound vector)

Many pre-clinical research and clinical trials going on, first targeted α-therapy entered clinical routine recently



α-emitting radionuclides in radiation protection?

α-emitting radionuclides are troublemakers!

Nuclear industry / NORM industry: long lived actinides, long-lived radium

Potential dispersion by noble gases (Rn)

High radiation weighing factor (W_R=20) for stochastic effects

Detection difficulties: specific α-detection systems not (yet) available in a clinical environment

High potential radiation dose to workers, general public?

How to tackle?

Be aware of the source characteristics and potential exposure pathways!

Dedicated risk analysis

α-emitter candidates for TAT

	Pre-clinical phase				Clinical routine
	^{225}Ac	^{213}Bi	^{211}At	^{212}Bi	^{223}Ra
$T_{1/2}$	10d	45.6m	7.2h	60m	11.4d
Equilibrium daughters	<1h	<1s	<1m	<1h	<1d
Imaging potential	x	x	x	x	x

Relatively short half-live

Daughter radionuclides in equilibrium

Presence of other emissions (β, γ, X)

α-emitter candidates for TAT

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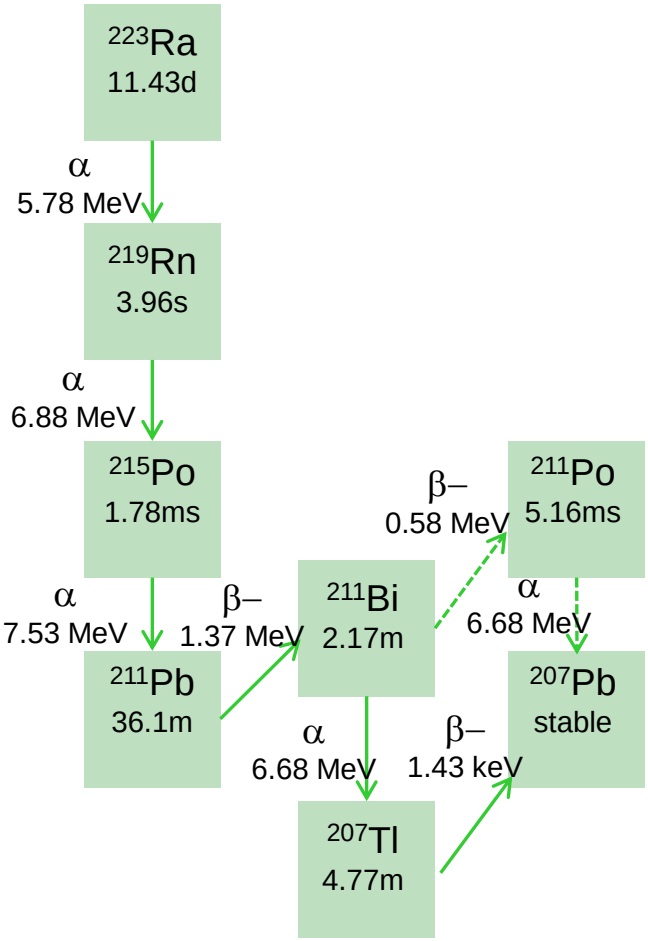
Daughters in equilibrium: ^{223}Ra



Daughter nuclides with very short half-lives are very fast in equilibrium (~ 5 h after production)

1 kBq ^{223}Ra after equilibrium:

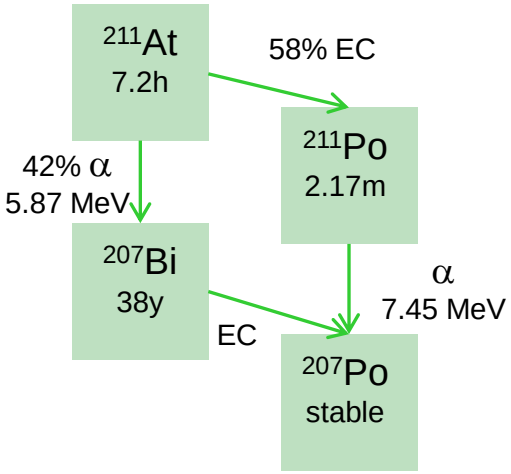
- **1 kBq ^{219}Ra**
- **1 kBq ^{215}Po**
- **1 kBq ^{211}Pb**
- **1 kBq ^{211}Bi**
- **~1 kBq ^{207}Tl**

4 α-emitters
2 β-emitters

Total: ~ 6 kBq

In practice all daughters have the same half-live of 11.43 days!!!

Daughters in equilibrium: ^{211}At



Branching decay of mother radionuclide

Daughter nuclide ^{211}Po with very short half-live is very fast in equilibrium (< 1 min after production)

1 kBq ^{211}At after equilibrium:

0.58 kBq ^{211}Po

<<<< activity ^{207}Bi (not in equilibrium)

Total: 1.58 kBq

In practice ^{211}Po has the same half-live of ^{211}At (7.2h)

Other emissions (β, γ, X)?

The decay of specific radionuclides denoted as certain particle emitter is rarely characterised to solely the emission of that certain particle!

Presence of other emissions (β,γ,X) during decay of mother radionuclide and/or daughters

Disadvantages

- **Medical absorbed dose to healthy tissues**
- **Potential for increased radiation exposure staff, public**

Advantages

- **Imaging capabilities → pharmacokinetics → patient dosimetry**
- **Calibration of therapeutic patient doses**
- **Detection capabilities in the framework of radiation protection (exposure staff and public, waste management,…)**

Patient references activities

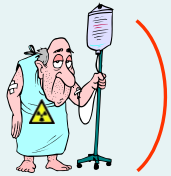
	Diagnoses	Ref. Activity
F-18	FDG PET-scan	250 MBq
Tc-99m	Bone scintigraphy	740 MBq
	Therapy	**Ref. Activity**
Sr-89	Palliation bone metastasis	150 MBq
I-131	Hyperthyroidism	370-1000 MBq
I-131	Thyroid cancer	3700-7400 MBq
Sm-153	Palliation bone metastasis	2600 MBq
Ra-223	Palliation bone metastasis	3.5 MBq
At-211	Clinical trial in treatment of recurrent brain tumor	70-100 MBq

Unusual low activities!

Danger of banalising α-therapy in the framework of radiation protection?

Evaluation of radiation protection data

External radiation to workers (no contribution of α-particles)

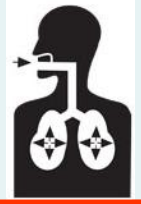
	^{223}Ra (3.5 MBq patient dose)	^{211}At (100 MBq patient dose)
 Dose rate patient 1 m	0.2 µSv/h **100% β/γ**	<0.1 µSv/h **100% X**
 Dose rate unshielded syringe in contact	90 mSv/h **>90% β**	~10mSv/h **100 % X**

Very low compared to typical bone scintigraphy procedure

Comparable to or lower than typical bone scintigraphy procedure

Evaluation of radiation protection data

Radiation to workers (very large contribution of α-particles)

	^{223}Ra (3.5 MBq patient dose)	^{211}At (100 MBq patient dose)	
 Dose rate droplet (20µl) in contact with the skin (1% injected act.)	120 mSv/h **>95% β**	5 mSv/h **100% X**	Comparable to typical bone scintigraphy procedure
 Effective dose after ingestion of activity in a 20 µl droplet (1% injected act.)	**6 mSv** **>95% α**	**11 mSv** **>99% α**	Very high compared to typical bone scintigraphy procedure
 Effective dose after inhalation of activity in a 20 µl droplet (1% injected act.)	**240 mSv!!!** **>95% α**	**110 mSv!!!** **>99% α**	Very high compared to typical bone scintigraphy procedure

Hygienic measures/contamination checks: cornerstone radiation protection procedures!

Hygienic measures in handling α-emitters

Important hygienic measures should be taken

- **Production**
- **Preparation**
- **Administration**
- **Patient care**

Focus Standard Operating Procedures

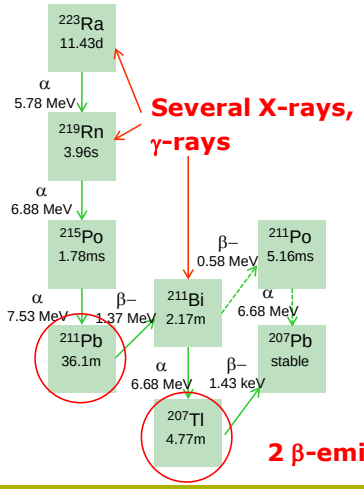
- **Prevention**
- **Contamination management**
- **Contamination survey**

Content of the SOP should be "especially α-emitter dedicated" (different from daily routine SOPs)

Contamination surveys of α-emitters

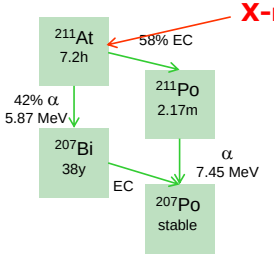
Run to the shop for α-counter?

Use other emissions in your advantage



Geiger-Müller counter

NaI-scintillation counter



X-rays

NaI-scintillation counter

Absolute efficiency for ^{223}Ra

NaI-scintillation counter

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Geiger-Müller counter

<

Alpha counter

Advantage only at short distance (< 1 cm)!

Advantage only if location contamination is known

Suitable for quantification but not for workplace survey

To conclude…

Based on the radiobiological properties of High LET radiation, TAT has a large potential

Several trials going on using typical radionuclides suitable for TAT

$^{223}RaCl_2$

Already entered in clinical routine

First routinely use of α-emitters in medicine

Despite the relatively low reference activities, dedicated radiation protection attention is needed

Thanks for the attention!