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Istituto Nazionale di Fisica Nucleare
Sezione di Pavia

ADMIRAL
ISOLPHARM
SPES exotic beams for medicine

In vitro experiments on cells and computational studies on ^{111}Ag

From the cells (UMR-106 and LNCaP) to the patient.

S. Bortolussi on behalf of the Pavia radiobiology group

June 18th, 2025

Special thanks to Laura Cansolino and Francesca Rana

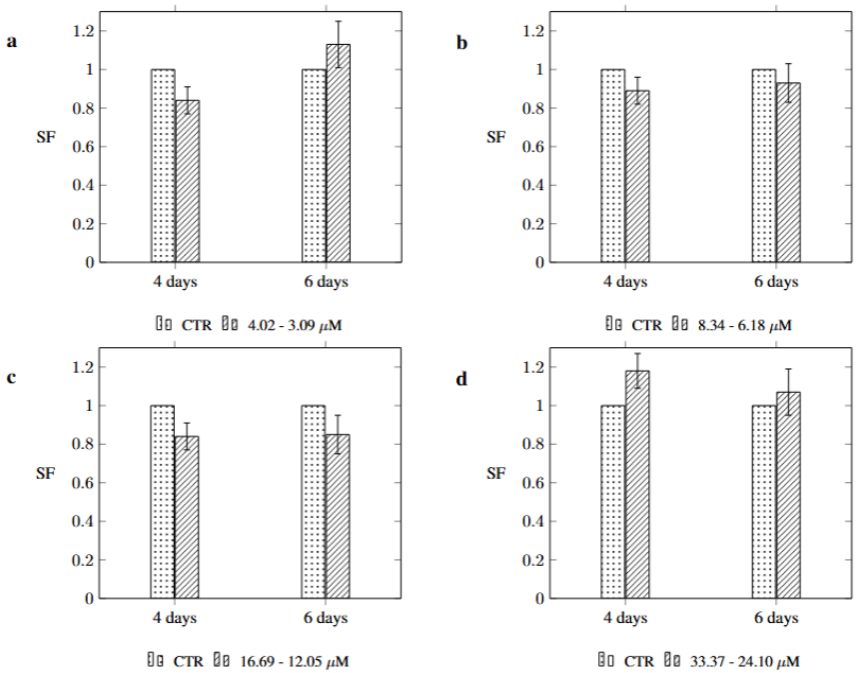
Outline

I. Cytotoxicity study of cold Ag, Pd and Ag+Pd on UMR-106 cells
II. Clonogenic assay for ^{111}Ag on UMR-106 cells
III. Computation of the cellular S-values for ^{111}Ag on LNCaP cells
IV. Clonogenic assay for ^{111}Ag on LNCaP cells
V. Nuclear foci assay for ^{111}Ag on UMR-106 cells
VI. Radiation dosimetry of ^{111}Ag in a clinical case study
VII. Next experiment

Cytotoxicity study of Ag, Pd and Ag+Pd on UMR-106 cells

Ag effects

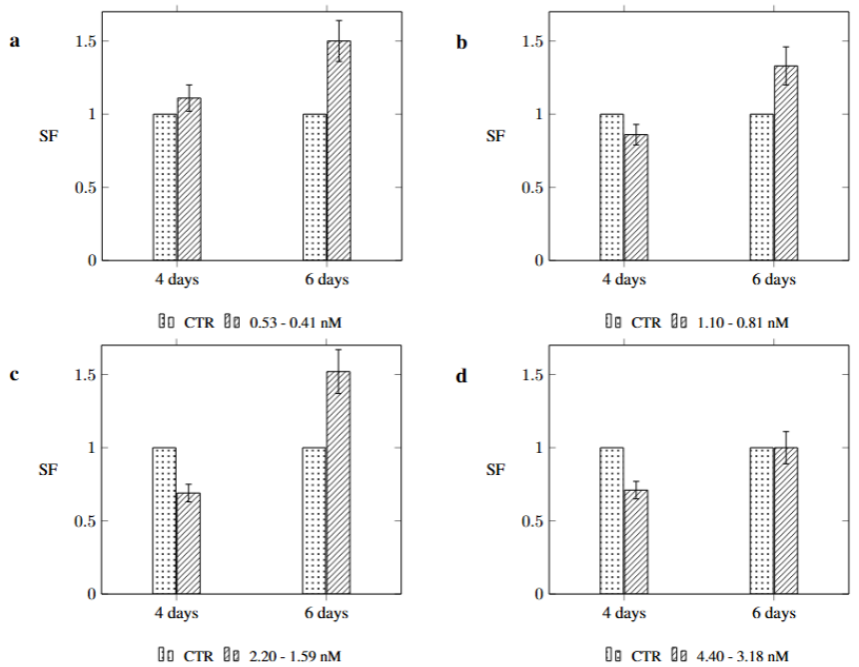
Time point	C_{Ag} [μM]	SF
4 days	4.02	0.84 ± 0.07
	8.34	0.89 ± 0.07
	16.69	0.84 ± 0.07
	33.37	1.18 ± 0.09
6 days	3.09	1.13 ± 0.12
	6.18	0.93 ± 0.10
	12.05	0.85 ± 0.10
	24.10	1.07 ± 0.12



Cytotoxicity study of Ag, Pd and Ag+Pd on UMR-106 cells

Pd effects

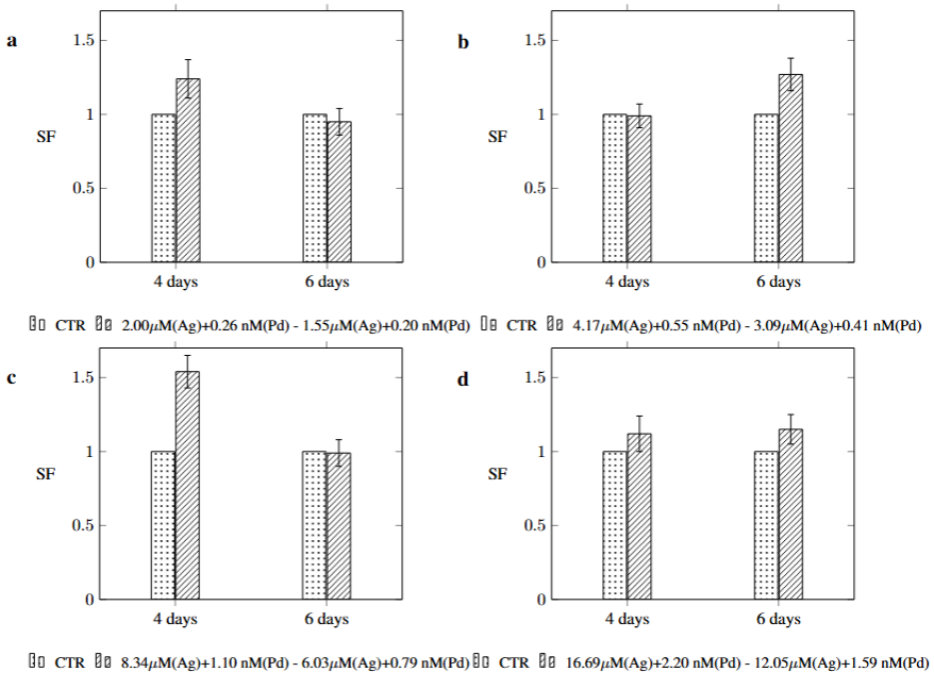
Time point	C_{Pd} [nM]	SF
4 days	0.53	1.11 ± 0.09
	1.10	0.86 ± 0.07
	2.20	0.69 ± 0.06
	4.40	0.71 ± 0.06
6 days	0.41	1.50 ± 0.14
	0.81	1.33 ± 0.13
	1.59	1.52 ± 0.15
	3.18	1.00 ± 0.11



Cytotoxicity study of Ag, Pd and Ag+Pd on UMR-106 cells

Ag+Pd effects

Time point	C_{Ag} [μM]	C_{Pd} [nM]	SF
4 days	2.00	0.26	1.24 ± 0.13
	4.17	0.55	0.99 ± 0.08
	8.34	1.10	1.54 ± 0.11
	16.69	2.20	1.12 ± 0.12
6 days	1.55	0.20	0.95 ± 0.09
	3.09	0.41	1.27 ± 0.11
	6.03	0.79	0.99 ± 0.09
	12.05	1.59	1.15 ± 0.10



Cytotoxicity study of Ag, Pd and Ag+Pd on UMR-106 cells

Discussion

- No evidence of *in vitro* cytotoxicity for cold Ag, Pd and Ag+Pd compounds at the concentrations administered.

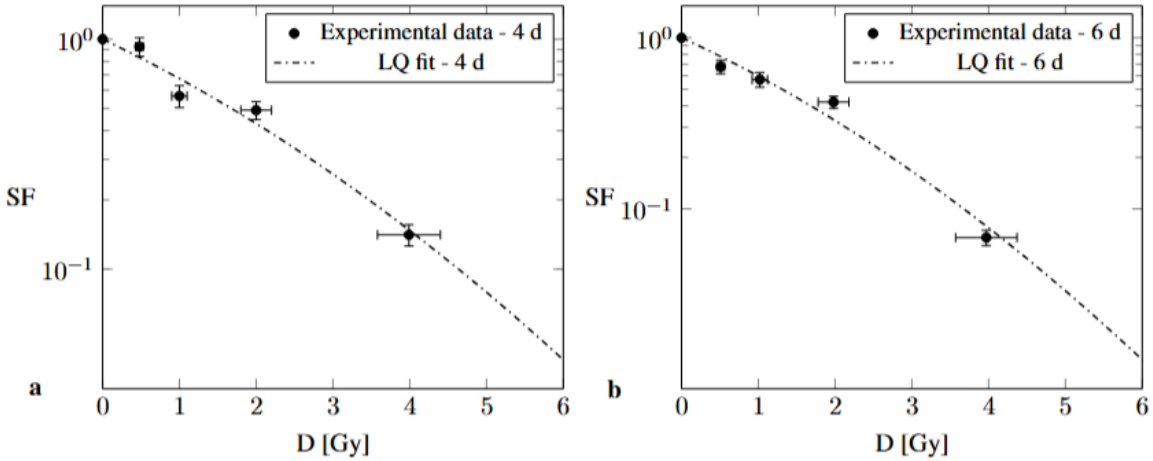
- Why did rats die?
  Possible arising of physiological effects that cannot be translated *in vitro*.

- So what?
  The sole responsible for the clonogenic death of UMR-106 cells irradiated by ^{111}Ag is the radiation.

Experimental data on the survival fraction can be fitted with radiobiological models.

Clonogenic assay for ^{111}Ag on UMR-106 cells

Data analysis and modelling - LQ

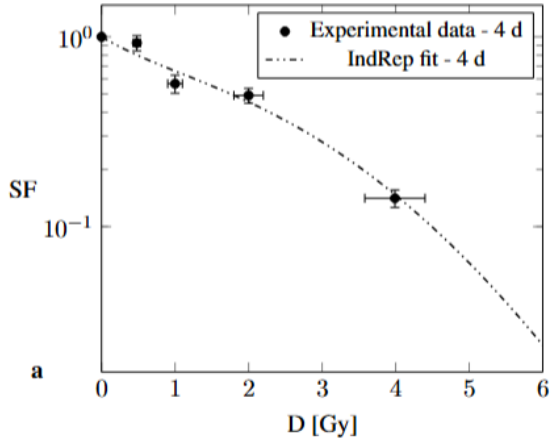


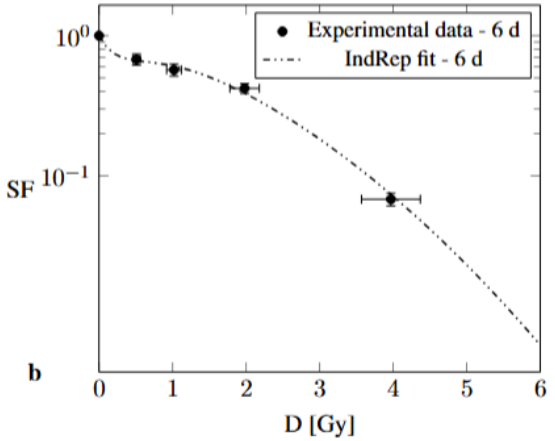
α [Gy^{-1}]	β [Gy^{-2}]
0.37 ± 0.12	0.03 ± 0.04

α [Gy^{-1}]	β [Gy^{-2}]
0.48 ± 0.13	0.04 ± 0.05

Clonogenic assay for ^{111}Ag on UMR-106 cells

Data analysis and modelling - IndRep





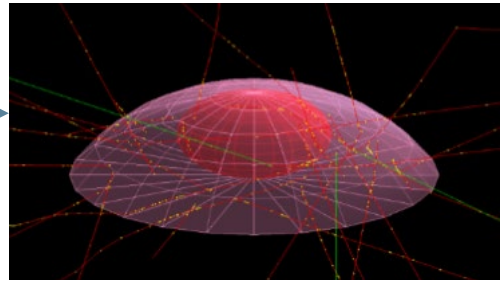
α_s [Gy^{-1}]	α_r [Gy^{-1}]	β [Gy^{-2}]
0.53 ± 0.48	0.12 ± 0.70	0.08 ± 0.17

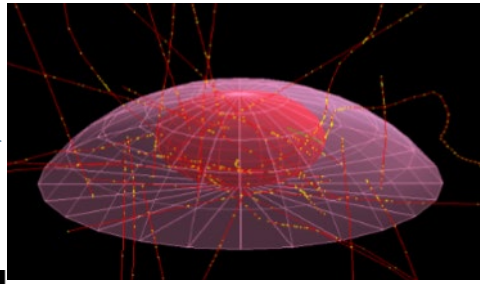
α_s [Gy^{-1}]	α_r [Gy^{-1}]	β [Gy^{-2}]
2.32 ± 0.58	0.29 ± 0.09	0.09 ± 0.03

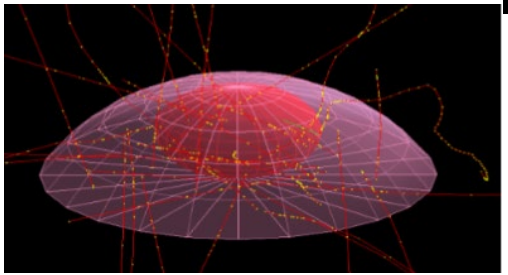
Computation of the cellular S-values for LNCaP cells

Self-absorbed dose

^{111}Ag decay site	Target region	S_{self} [μGy/(Bq·s)]
Membrane	Cytoplasm	163.0
	Nucleus	113.3
Cytoplasm	Cytoplasm	163.5
	Nucleus	159.0
Nucleus	Cytoplasm	107.0
	Nucleus	654.1



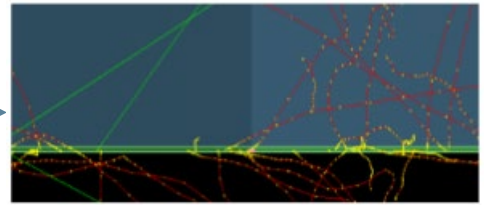


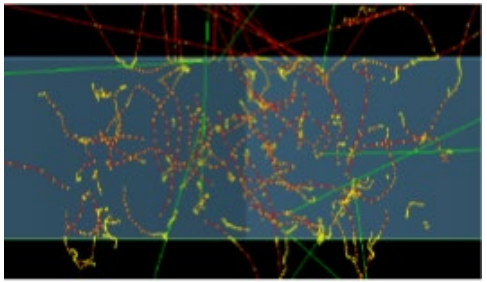


Computation of the cellular S-values for LNCaP cells

Cross-fire dose

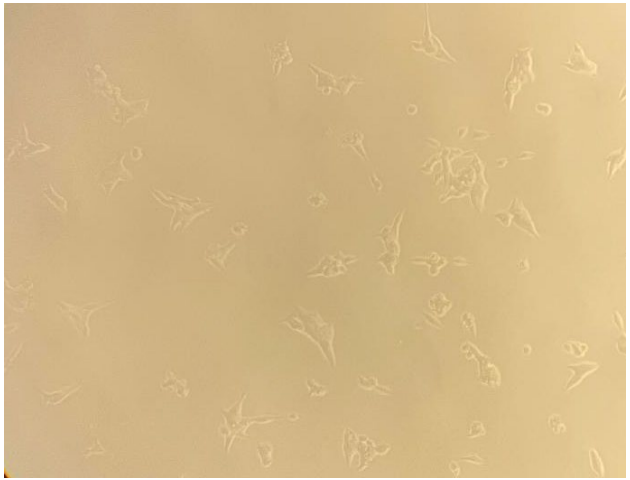
^{111}Ag decay site	Radioactive volume [ml]	Target region	S_{env} [Gy·ml/(Bq·s)]
Bottom culture medium	2.827×10^{-4}	Cytoplasm	1.09×10^{-12}
		Nucleus	1.18×10^{-12}
Top culture medium	4.9395×10^{-2}	Cytoplasm	1.98×10^{-11}
		Nucleus	2.26×10^{-11}





Clonogenic assay for ^{111}Ag on LNCaP cells

A new cell line for our laboratory



LNCaP cells observed at the microscope

Administration of ^{111}Ag in the Petri dishes

Clonogenic assay for ^{111}Ag on LNCaP cells

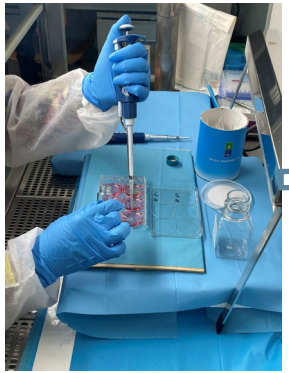
Results

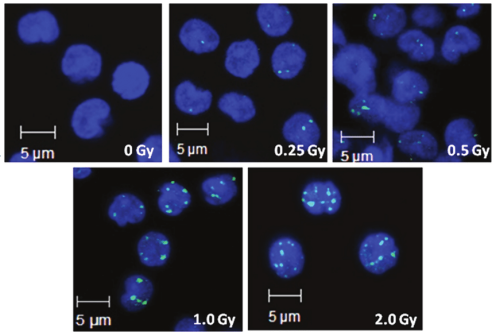
CONDITION	INITIAL CELL SEEDING
CTR	100, 250, 500
13 -10 µl	100, 250, 500
27 - 20 µl	100, 250, 500
54 - 39 µl	250, 500, 1000
108 - 78 µl	250, 500, 1000, 5000

Time point	D [Gy]	SF
4 days	0.37 ± 0.04	0.64 ± 0.06
	0.78 ± 0.09	0.30 ± 0.04
	1.56 ± 0.18	0.08 ± 0.01
	3.11 ± 0.37	0.05 ± 0.01
6 days	0.40 ± 0.05	0.72 ± 0.08
	0.79 ± 0.09	0.45 ± 0.06
	1.55 ± 0.18	0.34 ± 0.04
	3.10 ± 0.37	0.19 ± 0.02

Nuclear foci assay for ^{111}Ag on UMR-106 cells

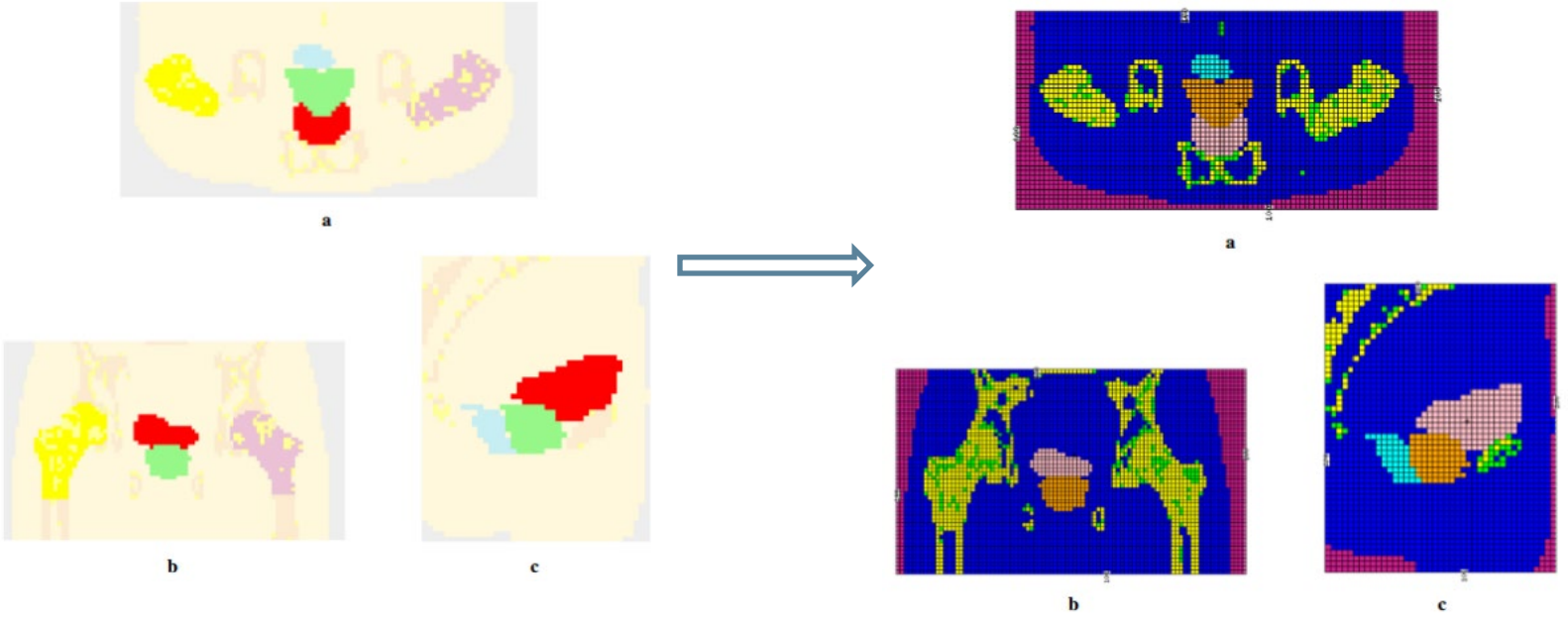
UMR-106 cells treated with ^{111}Ag on February 2025 will be soon analyzed using the fluorescence microscopy technique to count the *nuclear foci* induced by the ionizing radiations. The dedicated microscope has been recently installed at the authorized hot laboratory in Pavia.





Radiation dosimetry of ^{111}Ag in a clinical case study

MNCP simulation on a human prostate CT voxelized model



Radiation dosimetry of ^{111}Ag in a clinical case study

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Radiopharmaceutical in the whole prostate – Energy deposition meshes

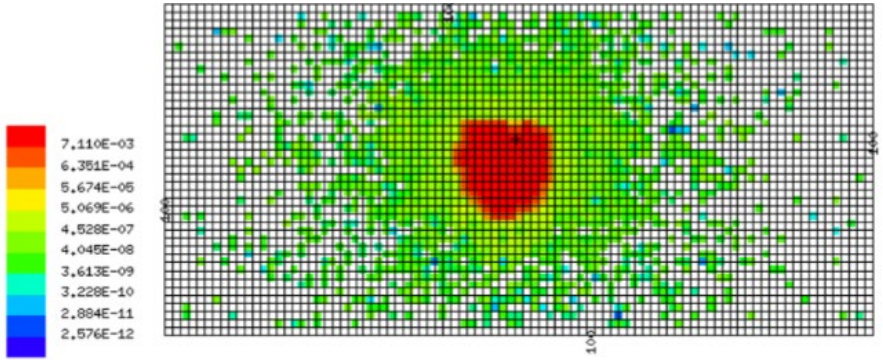

Figure 6.8: *MCNP* plotter rendering the TMESH Type 3 data following the 350 keV β^- emission from the whole prostate, with the legend showing the energy deposition ranges (in MeV/cm^3) for each voxel within the mesh.

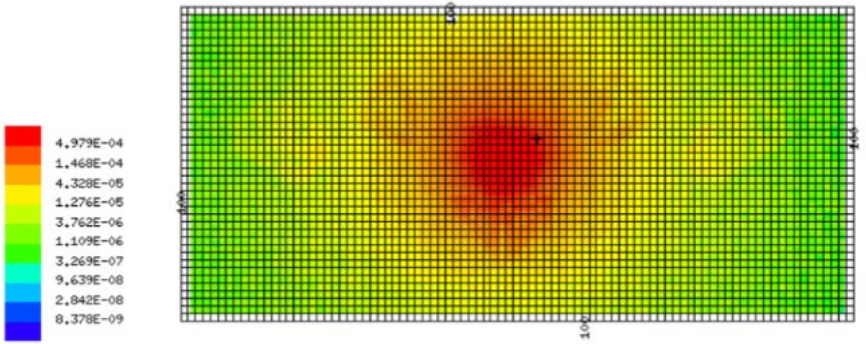

Figure 6.9: *MCNP* plotter rendering the TMESH Type 3 data following the 342 keV photon emission from the whole prostate.

Radiation dosimetry of ^{111}Ag in a clinical case study

Radiopharmaceutical in the whole prostate - Mean dose to the prostate per decay

Radiation	Tally	Score
Electron (E = 350 keV)	+F6	$6.045 \cdot 10^{-3}$ [MeV/g]
	*F8	$4.032 \cdot 10^{-4}$ [MeV]
Photon (E = 342 keV)	+F6	$2.092 \cdot 10^{-4}$ [MeV/g]
	*F8	$1.395 \cdot 10^{-5}$ [MeV]

$$D = 9.71 \cdot 10^{-13} \text{ Gy/decay}$$

Radiation dosimetry of ^{111}Ag in a clinical case study

Radiopharmaceutical in a 0.5 cm^3 nodule – Energy deposition meshes

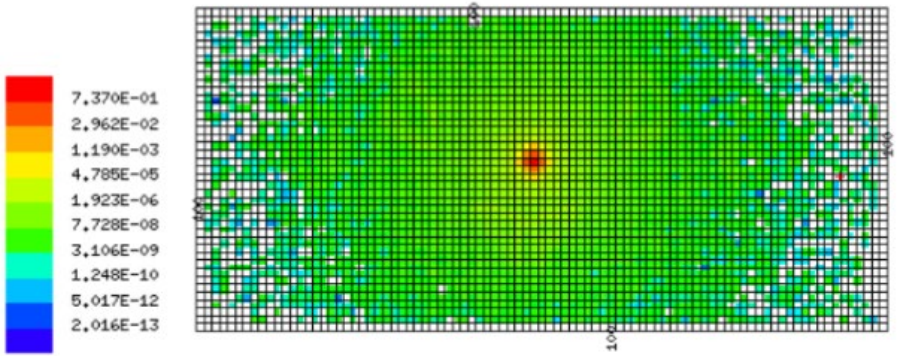

Figure 6.12: *MCNP* plotter rendering the TMESH Type 3 data following the 350 keV electron emission from the nodule.

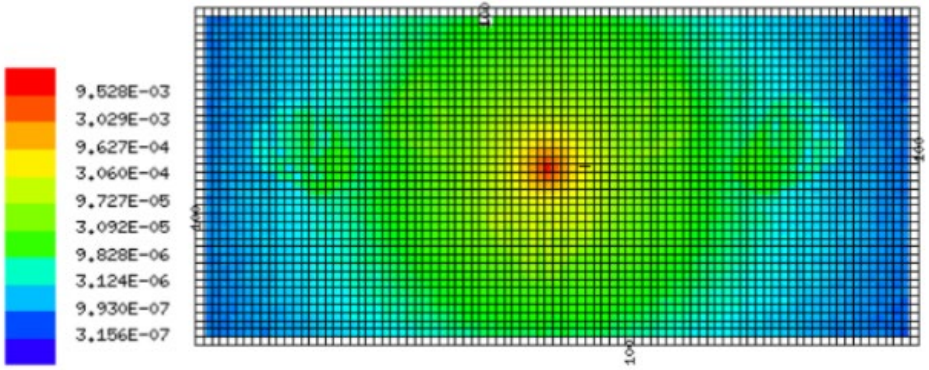

Figure 6.13: *MCNP* plotter rendering the TMESH Type 3 data following the 342 keV photon emission from the nodule.

Radiation dosimetry of ^{111}Ag in a clinical case study

Radiopharmaceutical in a 0.5 cm^3 nodule - Mean dose to healthy and cancer tissue/ decay

Radiation	Tally	Score
Electron (E = 350 keV)	+F16	$6.356 \cdot 10^{-1}$ MeV/g
	*F18	$4.239 \cdot 10^{-2}$ MeV
Photon (E = 342 keV)	+F16	$6.881 \cdot 10^{-3}$ MeV/g
	*F18	$4.590 \cdot 10^{-4}$ MeV

$$D_{\text{nodule}} = 1.02 \cdot 10^{-10} \text{ Gy/decay}$$

Radiation	Tally	Score
Electron (E = 350 keV)	+F6	$3.388 \cdot 10^{-7}$ MeV/g
	*F8	$2.260 \cdot 10^{-8}$ MeV
Photon (E = 342 keV)	+F6	$1.115 \cdot 10^{-4}$ MeV/g
	*F8	$7.438 \cdot 10^{-6}$ MeV

$$D_{\text{healthy tissue}} = 1.25 \cdot 10^{-15} \text{ Gy/decay}$$

Next experiment

- The nuclear foci assay will be repeated on the LNCaP cell line.
- Apart from the CTR conditions, the Petri dishes will be put in contact with $^{111}\mathrm{Ag}$ on 3 July 2025: half of them will be kept in contact for 4 d, half for 6 d, as done in the previous assays.
- The protocol for the nuclear foci assay will be applied.

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Thank you!