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EMPLOYING Bi-BASED NANOPARTICLES TO SENSITIZE TUMOR CELLS TO X-RAY

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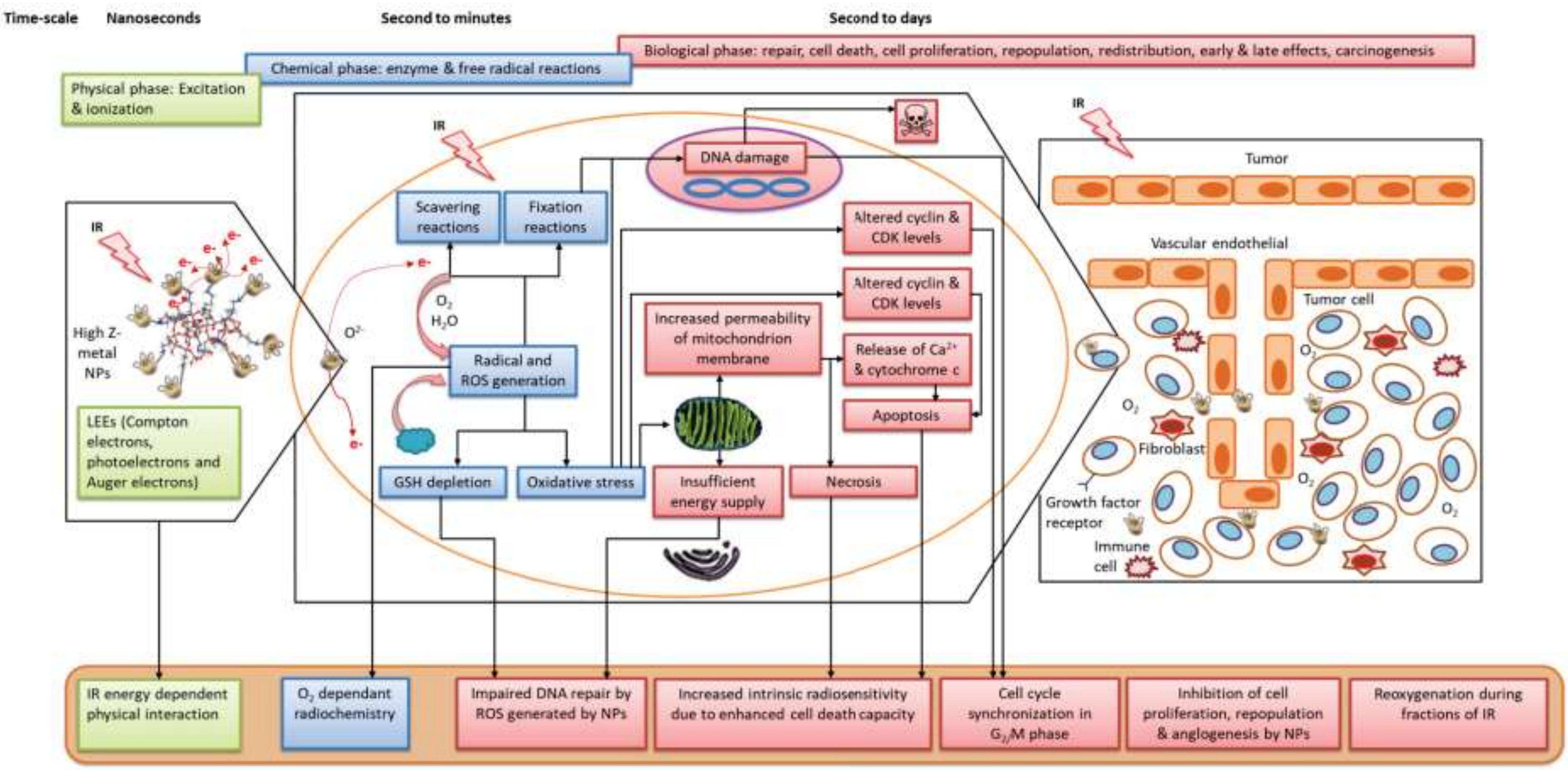
Motivation

We investigated in our work the interest in metallic bismuth nanoparticles as radiosensitizers. Bismuth has been described as a biocompatible element that encourages its use in medical applications [1-4].Bismuth (Z = 83) has a higher atomic number than gadolinium (Z=64) but above all, the density of atoms at high Z is much greater in a metallic bismuth nanoparticle compared to AGuIx ® [5]. These two characteristics could confer an advantage in terms of the radiosensitization efficiency of metallic bismuth nanoparticles. A few studies have described preclinical proofs of concept for the use of metallic bismuth nanoparticles to sensitize radiotherapy [2, 6-8] or for other theranostic applications [2, 3, 9, 10].

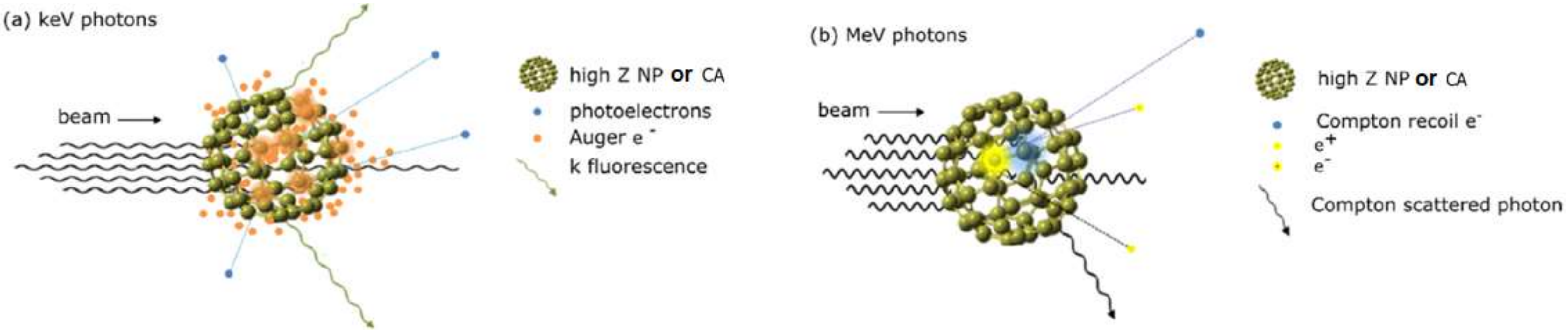
Limiting the dose of irradiation delivered to healthy tissues is a major concern in all radiotherapy procedures. The combined use of a radiosensitizing agent and X-rays destroys the same fraction of cells as during conventional radiotherapy (X-rays alone) with the difference that the irradiation doses are reduced. Therefore, if the same local control can be obtained for external irradiation doses of an order of magnitude lower, healthy tissue are less exposed to radiation.

Schematic presentation of the physical, chemical, and biological phases following the interactions of X-rays with heavy metal nanoparticles.



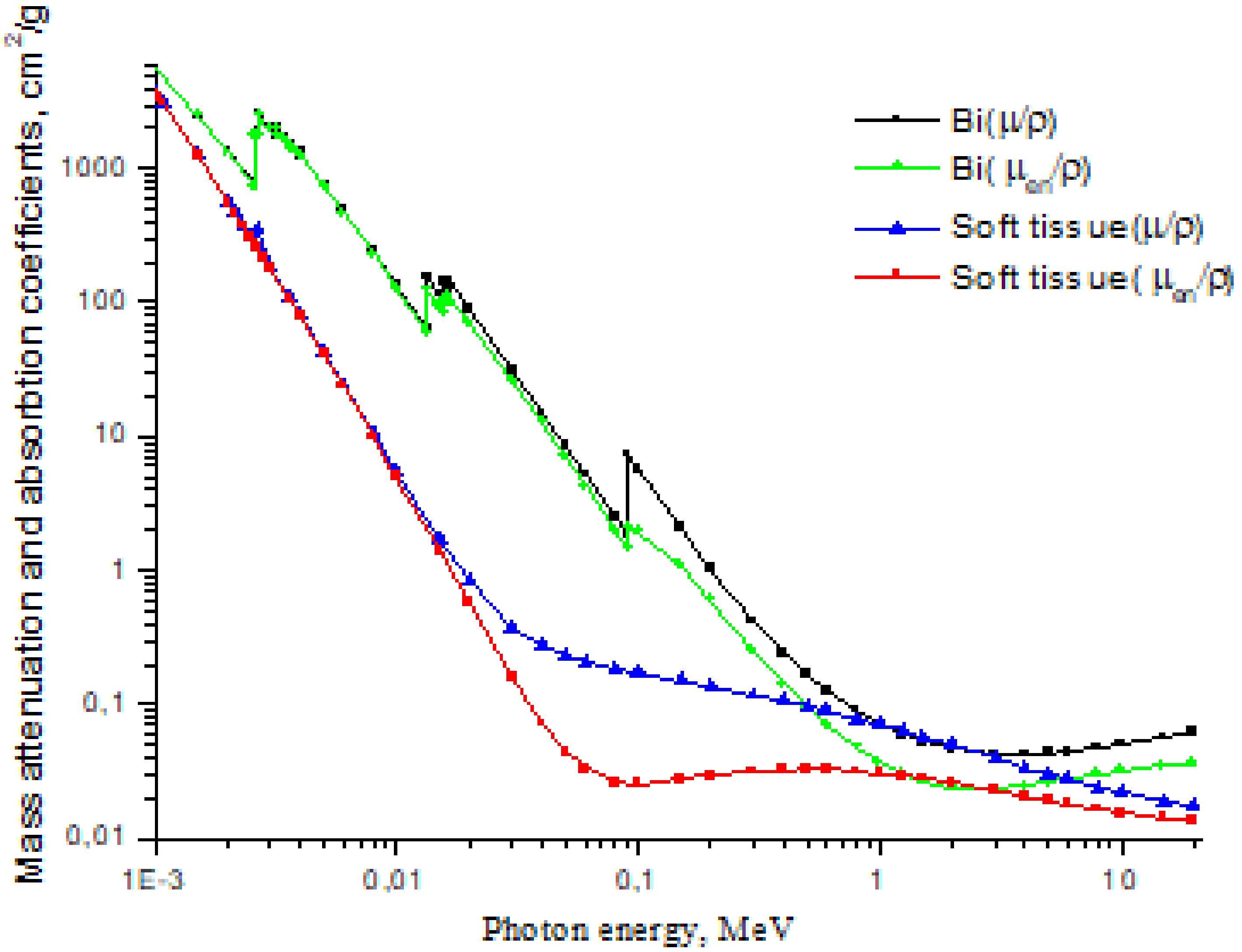
(from Cui et al., 2017; Joiner and van der Kogel, 2009)

Radiosensitization



The photoelectric effect, inducing an attenuation of the primary radiation, contributes to the movement of secondary electrons in the medium. The medium (biological tissue) absorbs the kinetic energy of the electrons, thanks to the ionization and excitations they cause the dose reflects this amount of energy absorbed. Between the absorbed dose and the mass coefficient of energy absorption exists the direct relationship. At equal energy fluencies, it seems logical to think that the absorbed dose in a material will be higher if it is composed of elements of high atomic numbers: the sharp increase in the coefficient of total attenuation of photon radiation must necessarily result in this increase. But what then becomes of the optimal irradiation energy? Is a photon energy is located just above the threshold K still interesting to deposit a maximum of energy despite a kinetic energy of the photoelectron K practically zero? What quantities of heavy elements are necessary in biological tissues to obtain a significant gain in absorbed dose?

In the first approximation consider the mass coefficient of energy absorption and discontinuities. It is appropriate to take as reference soft tissue and to study as a function of the irradiation energy the possible dose gain by adding elements of high atomic number to it. As an example the relative variations in the total mass attenuation - μ/ρ, and the mass energy-absorption - μ_{en}/ρ coefficients for pure bismuth and soft tissue are shown.



Total attenuation and energy-absorbtion mass coefficients of bismuth for photon energies located on either side of its thresholds K, L_1, L_2 and L_3.

Bi	K shell		L_1 shell		L_2 shell		L_3 shell	
cm^2/g	90.526 keV		16.388 keV		15.711 keV		13.419 keV	
	+	-	+	-	+	-	+	-
μ/ρ	7.38	1.856	147.8	128.2	141.6	106.9	156	64.91
μ_{en}/ρ	2.073	1.434	111.6	97.69	102.7	83.46	123.4	60.64

The photoabsorption in bismuth medium during the passage of the absorption threshold K consequently resulted in the formation of fluorescence photons or braking radiation. In comparison, these secondary photonic radiations have influence around the thresholds L. Total attenuation and energy-absorption mass coefficients of bismuth for photon energies located on either side of its thresholds K, L_I, L_{II}, and L_{III} according to [Hubbell J and_Seltzer S *Radiation Physics Division, PML, NIST Standard Reference Database*]

To perform a quantitative evaluation of the radiosensitization effect is determined a parameter called the **dose enhancement factor - DEF**. The DEF values were calculated based on the analysis of the mass absorption coefficients for bismuth and biological tissue. The computational expression for dose enrichment factor (DEF) takes on a different form depending on the incident X-ray nature, that is, the form of the expression is different for monoenergetic sources and spectral continuous beams [*Roeske J, Nuñez L, Hoggarth M, Labay E and Weichselbaum R 2007 Characterization of the Theorectical Radiation Dose Enhancement from Nanoparticles Technology in Cancer Research & Treatment* ***6****(5)*]. The DEF for monoenergetic source is given as follows:

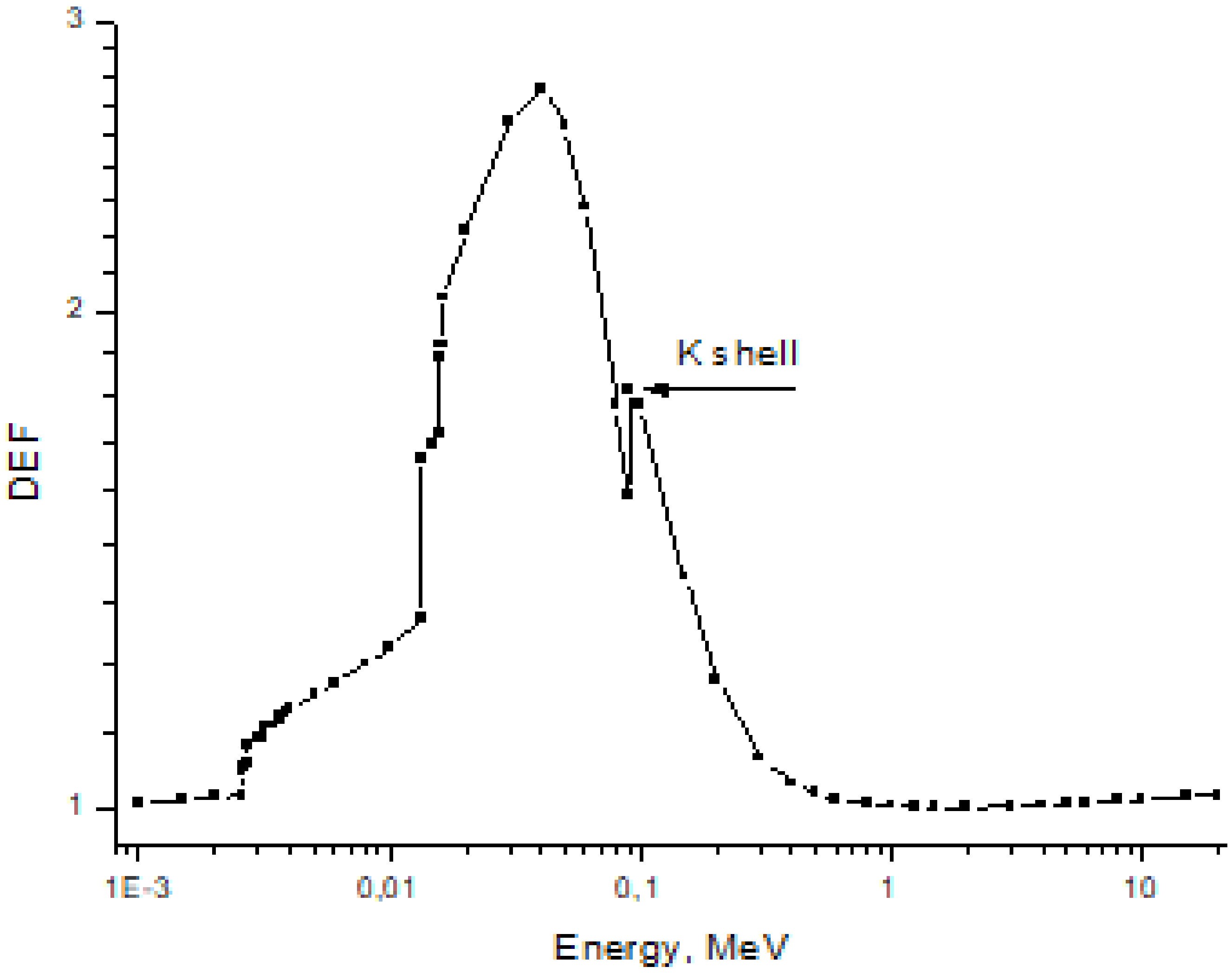
$$\mathrm{DEF} = \frac{k_{\mathrm{Bi}} \cdot \left(\frac{\mu_{en}}{\rho}\right)^{\mathrm{Bi}} + \left(1 - k_{\mathrm{Bi}}\right) \cdot \left(\frac{\mu_{en}}{\rho}\right)^{\mathrm{s.t}}}{\left(\frac{\mu_{en}}{\rho}\right)^{\mathrm{s.t}}}$$

$(\mu_{en}/\rho)^{\mathrm{Bi}}$ - mass absorption coefficient of photon radiation for Bi;

$(\mu_{en}/\rho)^{\mathrm{s.t.}}$ - mass absorption coefficient of photon radiation for soft tissue;

k_{Bi} - *Bi* content in soft tissue.

The factor of increased energy deposition due to the introduction of 10000 ppm Bi into soft tissue for photons of energy between 1 keV and 20000 keV



Photon radiation sources resulting in DEF.

Photon sources	Half-life	Energy, keV (Intensity, %)	Usage	DEF
^{67}Ga	3.27 d	91.263 (3.09) 93.307 (38.1)	Detector efficiency calibration, Medical applications.	1.78 1.81
^{131}I	8.02 d	80.150 (2.607)	Medical applications, Reactor neutron fluency.	1.75
^{147}Nd	10.987 d	91.105 (28.4)	Reactor neutron fluency, Burn up monitor.	1.80
^{153}Gd	240.4 d	69.67 (2.42) 97.43 (29.0)	Medical applications.	1.96 1.77
^{153}Sm	1.92 d	69.67 (4.69) 103.18 (29.19)	Medical applications.	2.00 1.73
^{170}Tm	127.8 d	84.25 (2.48)	Medical applications.	1.65
^{195}Au	184.7 d	98.82 (11.21)	Medical applications.	1.76
^{75}Se	119.78 d	66.058 (1.053) 96.734 (3.35)	Detector efficiency calibration.	2.08 1.78
^{99}Mo	2.748 d	40.58 (1.022) 140.511 (89.6)	^{99m}Tc generator, Fission yield determination.	2.71 1.42
^{108m}Ag	438 a	79.131 (6.9)	Fission product, Waste manager.	1.77
^{109}Cd	461.4 d	88.034 (3.628)	Detector efficiency calibration.	1.58
^{109}Pd	13.58 h	88.034 (3.66)	Fission product.	1.58
^{127}Sb	3.85 d	61.16 (1.140)	Fission yield determination, Fission product.	2.25
^{129}I	$1.6*10^{7}$ a	39.578 (7.42)	Fission product.	2.78
^{155}Eu	4.753 a	86.54 (30.7) 105.3 (21.1)	Fission product, Burn up monitor.	1.62 2.66
^{169}Yd	32.018 d	63.12 (44.05) 93.614 (2.571) 103.7 (17.36)	Detector efficiency calibration.	2.17 1.80 1.71
^{234}Th	24.1 d	63.3 (3.75) 92.3 (2.18) 92.8 (2.18)	Naturally occurring ^{238}U chain.	2.18 1.80 1.78

Various ionizing radiation sources can be considered for DEF investigation.

The DEF calculations are summarized in Table.

➢ Conclusion

- Since 2016, six publications have confirmed the potential of metallic bismuth nanoparticles as enhancers via preclinical studies [2, 3, 6-9]. The quantification of the radiosensitizing effect and optimal energy irradiation for these metallic bismuth nanoparticles is necessary.
- An increase in DEF is observed when the radiation energy is higher than the K-shell ionization energy of Bi atoms. For the presence of 10000 ppm Bi in soft tissue the dose enrichment factor is maximum DEF = 2.73 at photon irradiation energy 40 keV GdCA. An increase in DEF is observed when the radiation energy is lower than the K-shell ionization energy of Bi atoms.
- This calculation must be more detailed for doses of clinical injections . To further optimize the effect of this binary radiation therapy with X-ray it would be interesting to study in more depth the mechanisms of Bi element action at monochromatic irradiation with ideal energy, nanoparticles sices and time dependency of their presence in the tumor to obtain a maximum lethal effect on the cellular scale. To explain all events (Auger electrons, recombination of charges, re-absorption of fluorescence, photoelectrons) and to predict the consequences of this type of resonant irradiation on cell survival a physic al model should be put in place.
- As with any type of binary radiotherapy, requiring the presence of a compound in the tumor to produce the desired effect, the precise determination of the quantities of pharmacological agents present at the time of irradiation is the first data essential to the dosimetric planning of the treatment. Knowledge of the magnitude of the effect is the second. These two primary aspects are the necessities of radiosensibilization effect achievement.

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Thank you for attention!