E Poster Nr. EP-1239 (corrected)

A dosimetric study of bladder endocavitary therapy using astatine-211

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Aim

Non-muscle-invasive bladder cancer (NMIBC) accounts for ~75% of bladder cancer cases, with ~100,000 new cases annually in the United States and Europe. The standard treatment involves repeated intravesical instillations of Bacillus Calmette–Guérin (BCG). However, high-risk tumours frequently fail BCG therapy, often leading to radical cystectomy despite its significant morbidity.

Radioimmunotherapy targeting carbonic anhydrase IX (CA-IX) with [^{211}At]At-girentuximab (ATO-101™) is a promising alternative. While previous dosimetric studies have mainly focused on healthy tissues [1], this work investigates dose deposition in superficial bladder lesions following endocavitary administration.

Materials and Methods

The urinary bladder anatomy and physiology are described according to ICRP report 89 [2] and Anderson [3] in figure 1.

Among NMIBCs, 70% are classified as pTa, 20% as pT1, and the remaining 10% as carcinoma in situ lesions (CIS). The binding characteristics of the [211At]At-girentuximab for RT112 cells showed a high binding affinity of the [211At]At-girentuximab for CA-IX expressed by RT112 cells with K_D lower than 0.8 nM and a number of binding sites near 10,000 sites per cell [1].

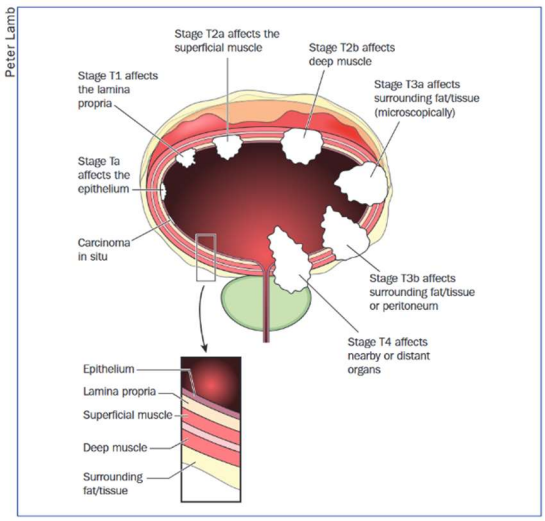


Figure 1: The layers of the bladder and stages of bladder cancer [3]. Only carcinoma in situ is of concern in this study.

The tumours are very superficial and concern the first layers of cells. The bladder is a deformable organ depending on the rate of filling. Figure 2 shows the relationship between pressure and volume in the adult bladder. For relative low volume the pressure is low and the bladder is considered relaxed.

Then the conformational of internal layers is considered to be as in the figure 3 (on the right). This configuration has been used for the Monte Carlo simulations.

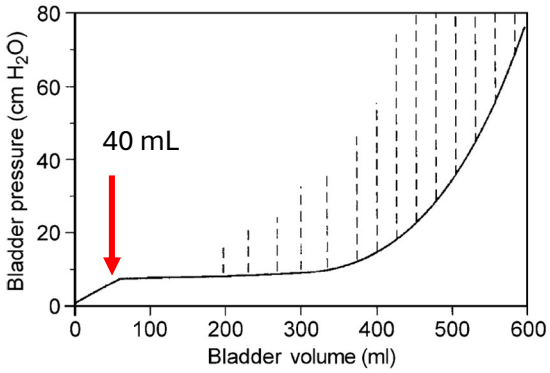


Figure 2: Relationship between pressure in the bladder and bladder volume in the adult. Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values – ICRP Publication 89 – 2002

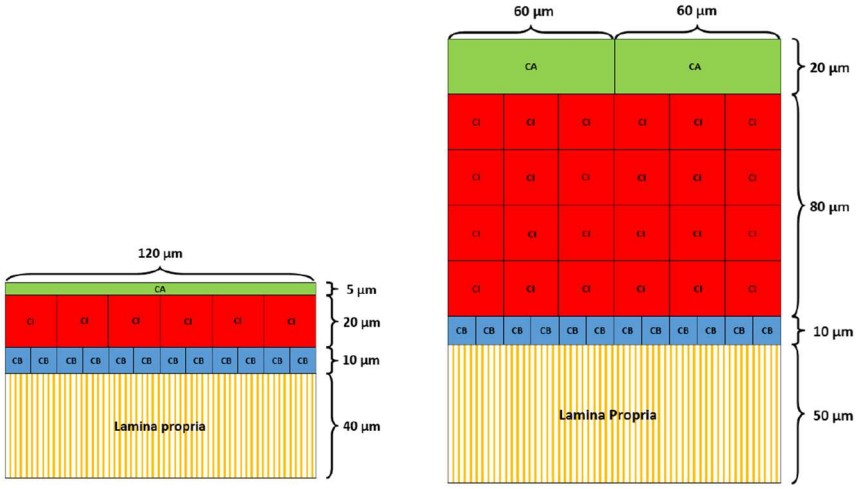


Figure 3: Bladder wall models: stretched bladder on the left and relaxed bladder on the right. CA: apical cells; CI: intermediate cells; CB: basal cells; Lamina Propria: connective tissue. Maïwenn Geffroy – Master degree report – 2022.

Absorbed dose to tumour cells was estimated using complementary approaches. OLINDA/EXM 1.0 and IDAC-Dose 2.1 were applied within the MIRD formalism, adapted to lesion-specific geometries [4,5]. Alpha particle ranges were evaluated using SRIM-2013 [6]. Figure 5 shows the decay scheme of astatine considered in this study.

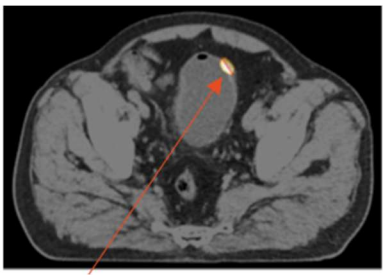


Figure 4. Focal [89Zr]Zr-girentuximab uptake in the bladder wall corresponding to tumour recurrence (arrow). Image from the PERTINENCE study (NCT04897763)

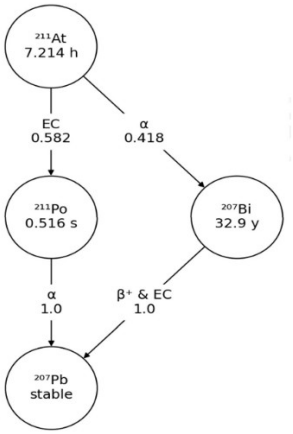


Figure 5: Decay scheme of astatine-211. Equivalent of one alpha particle is emitted within disintegration of astatine-211. Alpha particle emitted by astatine-211 in a 41.8% ratio with bismuth-207 has a kinetic energy of 5869.5 keV. Alpha particle emitted by polonium-211 in a 58.2% ratio with stable lead-207 has a kinetic energy of 7450.3 keV

A ballistic analytical model was used to estimate the number of alpha particle traversals per cell, assuming a correlation with cell lethality [7]. Monte Carlo simulations with Gate 9.1 [8] were performed to assess local dose deposition and particle hits in a multilayer bladder wall geometry derived from histological data, with tumour cells located near the apical layer.

To model the intended clinical application, we considered a total activity of 200 MBq in a 40 mL bladder volume corresponding to standard distension, for a 2-hour duration.

In addition, from a previous study [1], we defined different tumour cases in order to be closer to the clinical situation (table 1), as illustrated in figure 4.

Table 1: Imaging residual tumour cases based on images from the PERTINENCE study (NCT04897763).

Imaging residual tumour case	P1 tum1	P1 tum2	P1 tum3	P1 tum4	P2 tum1	P3 tum1
Feret diameter [mm]	13.18	18.84	12.87	11.25	23.71	20.03
Antibody density per cell – relaxed bladder	72431	66925	44830	11177	109086	31742
Cumulated activity [MBq.s]	2.11 E3	3.63 E3	1.04 E3	0.28 E3	8.85 E3	1.76 E3

Results

The maximum ranges of emitted alpha particles were 47.4 µm and 67.8 µm for energies of 5.87 MeV and 7.45 MeV, respectively (figure 6). In this configuration, highly radiosensitive basal cells (>70 µm depth) are not reached, while apical and intermediate layers are irradiated.

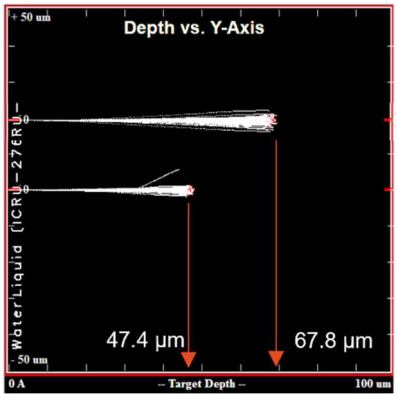


Figure 6: Maximum range in water of the two main alpha particles emitted during At-211 decay (5.87 and 7.45 MeV) - simulation with SRIM-2013

The mean energy deposited in the apical layer was 2129 keV per disintegration (table 2). GATE simulations showed good agreement with NIST and SRIM reference data (figure 7).

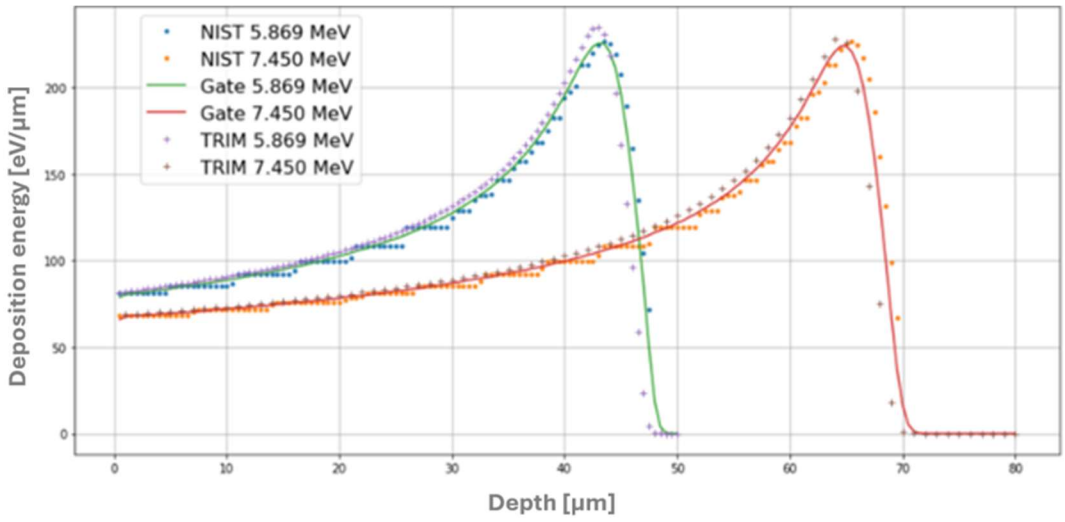


Figure 7: Comparison of energy deposited by alpha particles in water using Gate 9.1 with NIST and SRIM-2013 values. Simulation under monodirectional point source conditions.

Table 2: Deposited energy per disintegration in layers of vesical wall - relaxed bladder

layer	apical cells	intermediate cells 1	intermediate cells 2	intermediate cells 3	intermediate cells 4	basal cells	connective tissue
Energy deposition [keV]	2129.1	927.8	325.7	32.0	0.008	0.001	0.006
Ratio of deposited energies relative to the apical cell layer	100	43.6	15.3	1.5	0.0	0.0	0.0

The deposited energy occurs mainly in the first layer (apical cells assimilated to tumour cells) and becomes negligible (~ eV) starting from the fourth cell layer (table 2).

The mean absorbed dose in the apical layer (assimilated to tumour cells) was 200 Gy (figure 8), with an estimated ~6000 alpha particle hits per cell, relative to the different tumour cases (table 3).

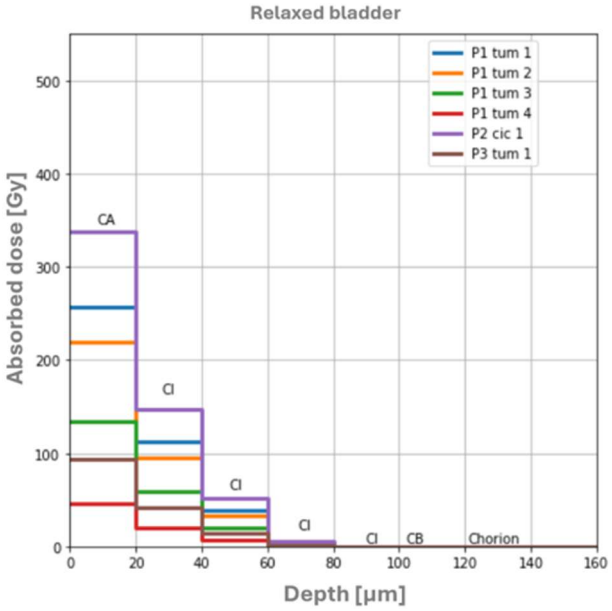


Figure 8: absorbed dose calculated for each layer and for different tumour cases – relaxed bladder

Table 3: Number of alpha-particles passing through each cell - relaxed bladder

Number of α particles passing through each cell – relaxed bladder	P1 tum 1	P1 tum 2	P1 tum 3	P1 tum 4	P2 tum 1	P3 tum 1
Apical cells	8847	7516	4600	1581	11602	3226
Intermediate cells 1	475	403	247	84	623	173
Intermediate cells 2	123	104	64	22	162	45

Conclusion

This study demonstrates that MC simulation enables separate estimation of energy deposition to both residual tumour cells and the cells in the bladder wall following intravesical administration. Monte Carlo Tools such as GATE is recommended for the study as models based on MIRD formalism do not take into account the local geometry energy deposition.

The results suggest a potential therapeutic effect of [^{211}At]At-girentuximab (ATO-101™), combining efficacy with a favorable safety profile for healthy tissues.

Disclosure statement

Jean-François Chatal is Founder and CMO of Atonco. Jacques Barbet is CSO of Atonco.

Yuni Dewaraja acknowledges institutional research funding from Atonco, GEHeathCare and Bristol Myers Squibb. Yuni Dewaraja is a consultant for GEHealthCare, Bristol Myers Squibb, AlphaSights, and Merit CRO.

[^{89}Zr]Zr-girentuximab PET images were obtained from the PERTINENCE study (NCT04897763); [^{89}Zr]Zr-girentuximab was supplied by Telix Pharmaceuticals.

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