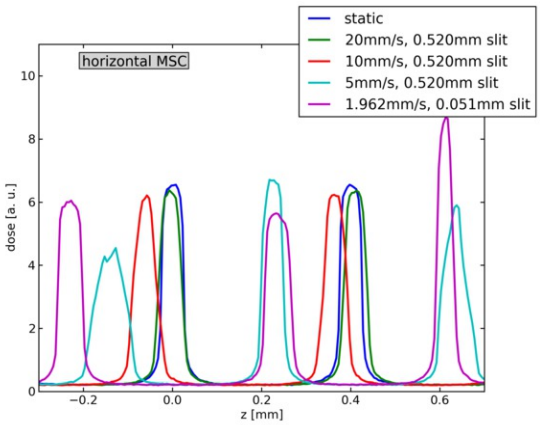

Keywords: Microbeam Radiation Therapy, brain motion, Monte Carlo

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Radiotherapy and the immunocytokine L19-IL2: a perfect match for an abscopal effect with long-lasting memory

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Although radiotherapy (RT) is one of the major cancer treatment modalities to kill malignant cells, advanced-stage disease is often hard to control. Radiation-induced tumor cell death provides a plethora of pro-immunogenic effectors associated with inflammation. Although the potential for RT to generate anti-tumor immunity is apparent, the evidence that it does so in the clinical situation is limited. Stimulation of the immune system to assist in eliminating cancer cells within, and outside, the radiation field could be beneficial in advanced-stage or metastasized disease. Recently, it has been demonstrated that cancer patients have increased levels of cytotoxic T-cells after radiotherapy, making them eligible for immunotherapy. Interleukin-2 (IL2) is one of the essential cytokines for driving proliferation and differentiation of T-cells and NK-cells resulting in increased cytotoxic activity, eventually leading to tumor regression. Several studies have shown synergistic anti-tumor effects when combining RT with systemic IL2 administration, although this strategy was accompanied with severe adverse effects.
Monoclonal antibodies, such as the human recombinant scFv fragment L19, have been designed as "targeting vehicle" for the selective delivery of immune-stimulatory cytokines to the tumor microenvironment while sparing normal tissue. The L19 antibody selectively localizes at the tumor neovascular fibronectin extra-domain B (EDB) positive sites following systemic administration and can serve as delivery vehicle for IL2. Our lab has combined single high-dose RT with systemic L19-IL2 administration in a number of murine xenograft models and found outstanding, long-lasting complete response rates mediated by cytotoxic CD8+ T-cell (1,2) or NK-cell (3) activity depending on the tumor model. L19-IL2 is thus an immunocytokine with strong immune response enhancing properties in EDB-positive tumors.
The combination therapy resulted also in anti-tumor immune effects outside the radiation field, an effect associated with CD4+ T-cell response. Growth of secondary un-irradiated tumors was significantly delayed with even 20% cure. Similar results were found when irradiation was delivered in a fractionated manner, although without resulting in cures. An increased PD-1 expression on T-cells infiltrating these tumors suggests a more regulatory immunological phenotype after fractionated radiotherapy compared with a single high RT dose. Re-challenging cured animals with tumor cells did not result in tumor formation, associated with high CD127 expression. Our recent data show that radiotherapy combined with the immunocytokine L19-IL2 results in long-lasting complete response rates, also outside the radiation field (abscopal effect) and this effect is associated with a memory potential.

Keywords: Radiotherapy, immunocytokine, abscopal effect, memory effect

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How to produce the highest tin-117m specific activity?

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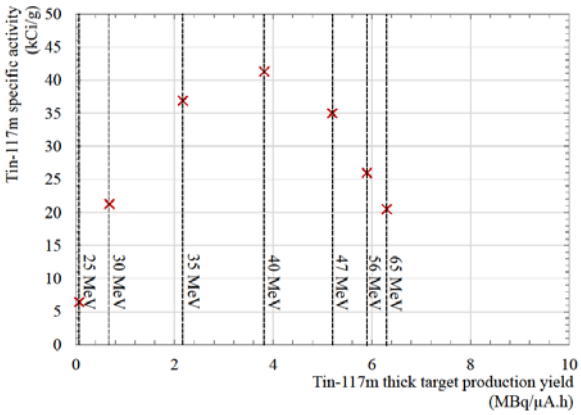
Purpose: Tin-117m is a radionuclide of interest for cancer and cardiovascular disease therapies. It has a half-life of 13.6 days and emits conversion and Auger electrons. It is actually used in clinical trials, where the radiopharmaceutical is developed by Clear Vascular Inc., to treat vulnerable plaque [1]. For this application, tin-117m is produced by the irradiation of Cd-116 enriched target with alpha particles. The goal of this study is to determine the irradiation conditions to get the highest specific activity of the final product, based on this reaction.
Materials/methods: Tin-117m production study has been investigated at the ARRONAX [2] cyclotron (France) that is able to deliver alpha particles at 67.4 MeV. Production cross section measurements of tin-117m as well as radioactive contaminants have been made using the stacked-foils technique. It consists in the irradiation of a group of thin foils: target, monitor and degrader. The stacks were made of thin natural cadmium as targets and aluminum foils as degraders. Monitor foils acted also as catcher and were made of different material depending on the energy. After irradiation, the activity of each radionuclides produced in the foils has been determined by γ spectrometry [3]. Production of stable and long live isotopes has been estimated with the TALYS code [4]. From the cross section data, thick target production yields (TTY) have been calculated as well as tin-117m specific activity (SA).
Results: The production cross section values obtained for the Cd-116(α,x) reaction up to 65 MeV have been compared with the literature. From these data, Sn-117m TTY has been calculated considering a 100% Cd-116 enriched target. A TTY of 6.3 MBq/(μA.h) is obtained for 65 MeV alpha particles on a thick target. Our results are compared with the value reported by Clear Vascular Inc. at 47 MeV. A difference of only 6.3 % has been found. In order to determine the SA, the mass of stable and long live tin isotopes produced during the irradiation have been determined using the TALYS code. The figure 1 shows the tin-117m SA in kCi/g from 25 to 65 MeV. The maximum tin-117m SA is reached around 40 MeV with 41 kCi/g and corresponds to a TTY of around 4 MBq/(μA.h). Clear Vascular Inc. reported a value of 25 kCi/g at 47 MeV. This value is 28 % lower than what is expected from our calculation.



Conclusions: New experimental data have been obtained at the ARRONAX cyclotron that permits to expand the knowledge of the tin-117m TTY up to 65 MeV. The results of the TALYS 1.6 code, which reproduce correctly the tin-117m production cross section, have been used to determine the tin-117m SA taking into account the stables and long live tin isotopes produced during the irradiation. The highest tin-117m SA could be obtained using 40 MeV alpha beams which gives a TTY of 3.9 MBq/(µA.h). It is possible to get higher production yields but with a lower SA of the final product.

Keywords: tin-117m, ARRONAX cyclotron, specific activity

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Tb-155 production with gadolinium target: proton, deuteron or alpha beam?

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Purpose: Terbium is an element of growing interest for medical applications, considered as the "Swiss-knife of nuclear medicine" [1]. Indeed, four terbium radioisotopes can be used in nuclear medicine. Tb-149 is considered for alpha targeted therapy, Tb-161 for beta- targeted therapy, Tb-152 for Positron Emission Tomography (PET) and Tb-155 for Single Photon Emission Computed Tomography (SPECT). However, terbium-155 can also be used as a radionuclide that emits Auger electrons for therapy. The interest on this radioisotope is increased by the conversion electrons emitted and the possibility to follow the treatment by SPECT imaging in a theranostic approach. The Tb-155 production has been investigated using the deuteron beam delivered by the ARRONAX cyclotron [2] and natural gadolinium target, motivated by the lack of data for this reaction at the beginning of our experiments.
Materials/methods: Tb-155 production study has been considered at the ARRONAX cyclotron (France) taking advantage of the deuteron beam ranging from 15 to 35 MeV. Production cross section measurements of Tb-155 as well as radioactive contaminants have been made using the stacked-foils technique. The stacks were made of thin natural gadolinium as targets, aluminum foils as degraders and thin natural titanium as monitor foils. After irradiation, the activity of each radionuclides produced in the foils has been determined by γ spectrometry [3]. From the cross section values obtained during these experiments, the Tb-155 Thick Target production Yield (TTY) has been calculated and compared with the other Tb-155 production routes using data available in the literature. When no experimental data were available, the TALYS code [4] version 1.6 helped to estimate the TTY.
Results: In 2014, cross section values have been published for the Gd-nat(d,x)Tb-155 reaction [5]. Our set of data is in good agreement therewith. Tb-155 production cross section values for the Gd-nat(p,x) and Gd-nat(α,x) are also available in the literature. The Tb-155 TTY have been compared for each routes. Close values are obtained for the proton and the deuteron route. The Gd-nat(α,x) reaction gives the lowest TTY, whatever the incident beam energy. However, the use of a natural gadolinium target leads to the production of several contaminants and especially of Tb-156g which has the same half-life as Tb-155. Results based on calculations for two reactions using Gd-154 and Gd-155 enriched targets with, respectively, deuterons and protons as projectiles, are also discussed [3,6]. The Tb-159(p,5n)Dy-155(ε)Tb-155 reaction, with results published in 2014 [7], is also discussed as a promising production route using high energy protons.
Conclusions: New experimental data have been obtained at the ARRONAX cyclotron for the Gd-nat(d,x) reaction with a special emphasis on the Tb-155 production. The results have been compared with different production routes, using natural and enriched gadolinium target. Based on the calculations published in 2012 [6], the Gd-155(p,n) reaction seems to be the most promising for the production of Tb-155 with gadolinium as target element. However, the Tb-159(p,5n)Dy155(ε)Tb155 seems an interesting alternative.

Keywords: terbium-155, production routes, Thick Target production Yield

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RapidArc commissioning and dosimetric verification using EPID portal dosimetry system

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Purpose: In this study, we report the rapid arc commissioning and dosimetric verification measurements performed with the electronic portal imaging device (EPID) having portal dosimetry software.
Material and Methods: The dosimetric tests were performed on RapidArc capable Varian Unique linac, which is equipped with millennium 120 Dynamic Multi Leaf Collimators (DMLCs) and having 6 MV X-ray beam. The Varian RapidArc QA files, Eclipse treatment planning system (TPS) and EPID portal dosimetry system were used in this study. The RapidArc QA files incorporate following tests. 1) DMLC dosimetry. 2) Picket Fence (PF) test vs. gantry angle. 3) PF test during