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PRODUCTION OF RADIOISOTOPES FOR CANCER IMAGING AND TREATMENT WITH COMPACT LINEAR ACCELERATORS*

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Abstract

Accelerator-produced radioisotopes are widely used in modern medicine, for imaging, for cancer therapy, and for combinations of therapy and diagnostics (theragnostics). Clinical trials are well advanced for several radioisotope-based treatments that might open the way to a strong request of specific accelerator systems dedicated to radioisotope production.

While cyclotrons are the standard tool in this domain, we explore here alternative options using linear accelerators. Compared to cyclotrons, linacs have the advantage of modularity, compactness, and reduced beam loss with lower shielding requirements. Although in general more expensive than cyclotrons, linacs are competitive in cost for production of low-energy proton beams, or of intense beams of heavier particles.

After a review of radioisotopes of potential interest, in particular produced with low-energy protons or helium, this paper presents two linac-based isotope production systems. The first is a compact RFQ-based system for PET (Positron Emission Tomography) isotopes, and the second is an alpha-particle linac for production of alpha-emitters. The accelerator systems are described, together with calculations of production yields for different targets.

INTRODUCTION

In the last decades, the use of radioisotopes for applications in medicine that include both diagnostics and therapy has shown a significant increase, generating a clear demand for novel solutions to produce standard and new radioisotopes with low-cost, easy-to-use, accelerators possibly located close to the hospitals where they are used.

At present, several hospitals are equipped with small proton cyclotrons at energy between 10 and 25 MeV, supplying radioisotopes which, via chemical purification and biological manipulations, are then transformed into radiopharmaceuticals and quickly provided to local patients.

Although cyclotrons are fairly small, the required massive shielding around accelerator and target imposes serious limitations to their installation in hospitals. Moreover, the costs related to the frequent and expensive maintenance required by commercial cyclotrons can be prohibitive for small hospitals. In this respect, linear accelerators (linacs) might provide a viable alternative to cyclotrons, because thanks to their well-defined beam optics up to the production target they are not affected by the large beam loss, particularly at extraction, leading to the sensitive activation levels of cyclotrons. In a linac, nearly all particles produced by the ion source impinge on the target, which is the only element that requires substantial radiation shielding: a linac can be hence operated in a simple radiation-controlled area with only the target placed inside a shielding casing. Linacs are lighter in weight than cyclotrons (they do not need large magnets), which makes them easier to handle and install and are very reliable, with few moving or high voltage components.

The first part of this paper reports calculations of the doses that can be produced at saturation with currents and energies achievable with a compact linac. In the second part, two linac configurations are presented, the first for production of Positron Emission Tomography (PET) imaging radiotracers ^{18}F or ^{11}C via low energy protons, and the second for production of ^{211}At for Targeted Alpha Therapy (TAT) via alpha particles.

PRODUCTION YIELDS

A numerical calculation method to estimate the production yields of two PET (^{18}F, ^{11}C) and one TAT (^{211}At) radioisotopes was developed [1], and after benchmarked to existing data [2-4], was applied for dose calculation at different conditions (energy, current), where no data were available. ^{18}F is produced via the nuclear reaction ^{18}O(p,n)^{18}F, ^{11}C via ^{14}N(p,α)^{11}C and ^{211}At via ^{209}Bi(α,2n)^{211}At. Yields were calculated for protons in the energy range 3÷15 MeV and for alphas in the energy range 21÷30 MeV.

Production Yields for ^{18}F and ^{11}C

The ^{18}F saturation yields, calculated via the numerical calculation method, are reported in Fig. 1. The corresponding PET doses are also shown, knowing that an average dose of ^{18}F-FDG is ~400 MBq for a patient of 80 kg, based on literature data and routine experience of a hospital [1, 5, 6].

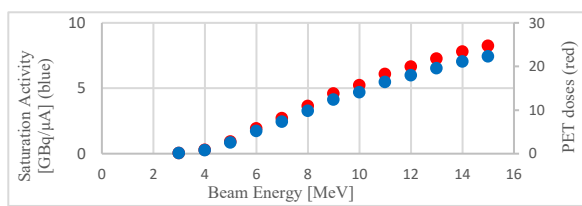

Figure 1: Saturation yield of ^{18}F (blue) and PET doses (red) as a function of E_b (saturation time of 3.5 $T_{1/2}$= 6.4 h).

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For a 7 MeV final proton energy, the saturation yield is 2.71 GBq/μA, resulting, for 30 μA beam current, in ~80 GBq, which is equivalent to ~200 doses at saturation.

For ^{11}C production, a ^{14}N gas was taken as target material, which makes the extraction of ^{11}C from the produced carbon dioxide ($^{11}CO_2$) easy. Special care has to be taken on the selection of the appropriate conditions of temperature and pressure, as the gas chamber length should exceed the stopping range of the proton beam. The saturation yield (in GBq/μA) of the ^{11}C nuclear reaction was calculated for a proton energy up to 10 MeV onto a target at 20ºC and 1 atm. The range of the 10 MeV proton beam turns out to be ~120 cm, calculated via the SRIM code [7]. The obtained ^{11}C production yield, after a saturation time of $3.5T_{1/2} \cong 1.2$ hours, is 2.63 GBq/μA. ^{11}C saturation yields and PET doses vs E_b are reported in Fig. 2. In this case, an average dose of ^{11}C (to then compose ^{11}C(CH) – choline as the related radio molecule) is ~370÷740 MBq [8, 9]. With a 7 MeV, 20 μA beam current, the saturation yield is ~24 GBq, providing, at 350÷750 MBq average dose per patient, 32÷70 doses.

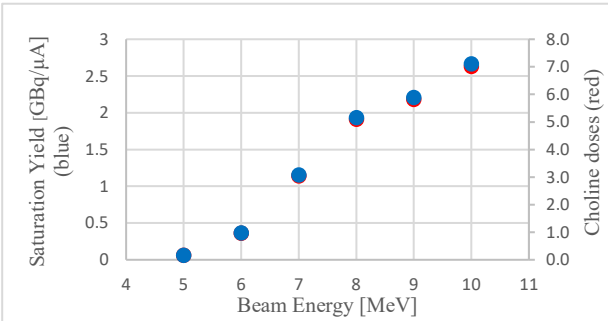

Figure 2: Saturation yield of ^{11}C (in GBq/μA) and Choline doses at saturation time of 3.5 $T_{1/2=}$ 1.2 h, versus E_b. The two series of points almost overlap in the graph.

Production Yields for TAT Radioisotope ^{211}At

^{211}At is at an advanced stage of testing and expected to become the main component of new TAT radiopharmaceuticals. To calculate the most appropriate specifications for the TAT linac, we consider the reaction ^{209}Bi(α,2n)^{211}At, with the alpha beam impinging onto a solid ^{209}Bi target. The energy is limited in this case at 28 MeV (i.e. 7.5 MeV/u), set by the production of the undesirable ^{210}At (onset at ~28.5 MeV). Figure 3 shows the saturation yield (in GBq/μA) vs. E_b, between 20.7 MeV (lower threshold for the considered reaction) and 28 MeV.

The ^{211}At yields, with 28 MeV and 20 μA, an activity of 5.2 GBq after a saturation time of 3.5 $T_{1/2} \cong 24$ hours.

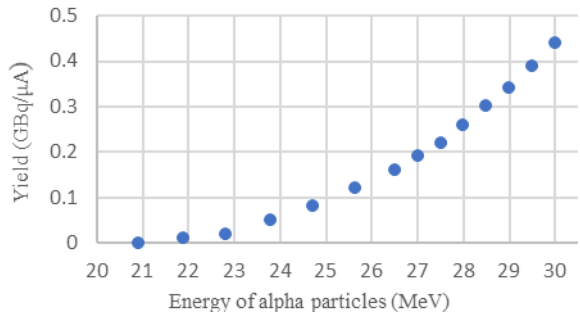

Figure 3: Saturation yield in GBq/μA of ^{211}At, at saturation time of 3.5 $T_{1/2} \cong 24$ h, as a function of $E_{b,alpha}$.

Data available in the literature [10] allow calculating the equivalent doses required for treatment: 52÷260 doses for post-surgery treatment of ovarian cancer (dose/patient: 20÷100 MBq), and 15÷74 doses for post-surgery brain tumour therapy (dose/patient: 70÷350 MBq).

COMPACT LINAC DESIGNS

A Compact Linac for PET Radioisotopes

Calculations in the previous section have shown that a useful number of doses per day of ^{18}F and ^{11}C can be generated by proton beams at relatively low energies.

The basic layout of the PET-isotopes production system is shown in Fig. 4, and its key parameters are presented in Table 1. Following a general scheme already developed by the AccSys company in the 90's [11], this scheme differs in the use of an innovative compact RFQ design at 750 MHz recently developed at CERN [12] and in that it exploits the potential of modern solid-state RF technology. With respect to previous versions [13], this configuration is based on a simpler RFQ at lower energy (7 MeV) operating with higher average current.

The beam from the proton source is sent into a 2.5 m long 750 MHz RFQ made of a sequence of 0.5 m mechanical modules, which is the only accelerating structure of the linac. The RFQ RF amplifiers, feeding the 5 modules, consist of 100 kW solid-state elements.

The target system can house two interchangeable targets, to produce both ^{18}F and ^{11}C. A preliminary and conservative calculation of target shielding was made for E_b= 10 MeV assuming 2 μSv/h as maximum dose on the outside of the enclosure corresponding, in most legislations, to a simple radiation-controlled area accessible to personnel wearing a radiation dosimeter. Different configurations based on successive layers of iron, polyethylene and borated (5%) polyethylene were compared and progressively optimised for minimum overall thickness using genetic algorithms. The calculation indicates that a shielding with a total radius of 1 m can reduce the dose at contact during operation down to the required value [14].

The accelerator modules are water-cooled with the cooling circuit being connected to an external heat exchanger. The RFQ operates at 10% duty cycle, with a peak proton current of 300 μA generating a 210 W average beam power on target. The system weighs less than 5 tons for a floor space of less than 10 m^2, most of the weight being related

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to the local shielding of the target. The power from the mains is about 35 kVA.

It has been estimated that the 7 MeV isotope production system can be produced and commercialised at a 20% lower cost than equivalent cyclotron-based systems [15]. Additional savings would come from lower maintenance costs with respect to cyclotrons.

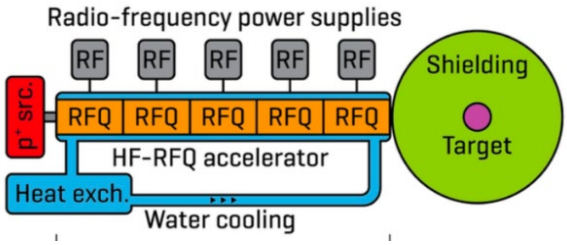

Figure 4: Scheme of the 7 MeV RFQ-based PET isotope production system.

Table 1: Parameters of the PET 7 MeV RFQ System

Input / Output Energy	20 keV / 7 MeV
Accelerator length	2.5 m
Operating Frequency	750 MHz
Output peak current	300 μA
Duty cycle	10 %
Beam pulse repetition frequency	200 Hz
Beam pulse length	500 us
Output average current	30 μA
RF Power, peak	400 kW
RF Power, average	<30 kW
Surface (accelerator, source, target)	10 m^2
Surface (RF and equipment room)	10 m^2
Total weight of accelerator	350 kg
Total system weight	<5 tons
Mains power	35 kVA

A Dedicated Linac for ^{211}At Production

The relatively low production energy and short half-life of ^{211}At make it an ideal therapeutic isotope to be produced by a compact linear accelerator close to a hospital. Cyclotrons for production of intense alpha beams would present unacceptable beam loss levels at extraction, giving a clear advantage to linacs for this specific application.

To achieve the required 28 MeV energy, a simple and cost-effective design consists in a newly designed 750 MHz RFQ for A/q=2 up to 5 MeV/u, followed by an A/q=2 750 MHz Quasi-Alvarez DTL (QA-DTL) up to 7 MeV/u. The latter is a DTL where only one drift tube out of three contains a quadrupole [16] . The 15.5 cm diameter of the main drift tubes is sufficient to house a permanent quadrupole and the cooling channels required for 10% duty cycle.

The basic layout is shown in Fig. 5 and the accelerator parameters are presented in Table 2. A commercial ECR source for alpha-particles produces a 0.5 mA current that is accelerated by the 750 MHz RFQ to 5 MeV/u. The latter is optimised for minimum length and RF power with a resulting beam transmission of 50%, following a design recently developed for carbon-ion therapy. The RFQ is followed by a QA-DTL with 27 cells and operating at an average accelerating field of 4 MV/m, bringing the energy to 7 MeV/u (28 MeV total). The accelerator operates at 10% duty cycle, producing an average current of 20 μA. Its total length, considering the ion source and the locally shielded production target, does not exceed 10 m. The overall RF power is < 800 kW, to be provided by 8 SSPA at 100 kW each. Assuming a 50% amplifier efficiency, the total mains power is about 160 kVA.

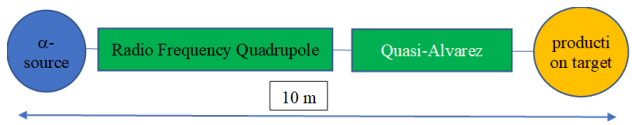

Figure 5: Scheme of the ^{211}At production system.

Table 2: Alpha Accelerator Parameters

	RFQ	QA-DTL
f (MHz)	750	750
Input Energy (MeV/u)	0.015	5.06
Output Energy (MeV/u)	5.06	7
Length (m)	4.8	1.6
Peak current (μA)	200	200
Average current (μA)	20	20
Duty cycle (%)	10	10
Peak RF Power (kW)	600	171

CONCLUSION

A compact linear accelerator is a very attractive option for producing an interesting selection of medical radioisotopes in a hospital site. With proton beams of 7 MeV and 30 μA protons, or alpha beams of 7 MeV/u and 20 μA, the production of radiopharmaceuticals containing respectively ^{18}F, ^{11}C and ^{211}At (the first two for PET imaging, the latter for therapy) is sufficient to cover the daily needs of a small-medium size hospital. Doses made available at the beginning of a therapy day by the two linac-based systems are shown in Table 3. With respect to proton PET-cyclotrons of comparable beam specifications, compact proton linacs have smaller shielding and radiation concerns, lower cost, easier maintenance, lower weight. An α-linac to produce ^{211}At, necessarily limited to 7 MeV/u energy to avoid co-generation of ^{210}At, would be suited for targeted-alpha-therapy and might produce PET-imaging isotopes too, produced by an additional proton source.

Table 3: Accelerator-produced doses for patient treatment ($Doses_{treat}$), considering the preparation time (t_{prep}) after the End Of Bombardment (EOB).

Element	Half-life [min]	t_{PREP} [min]	$Doses_{EOB}$	$Doses_{TREAT}$
^{18}F	109,7	30	200	181
^{11}C	20,4	40	32÷70	8÷17
^{211}At - ovarian cancer	432	420	52÷260	27÷132
^{211}At - brain cancer	432	420	15÷74	8÷38

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REFERENCES

[1] A. Mamaras, "Production of Radionuclides in Cyclotrons and Linear Accelerators for Medical Applications", BSc thesis, Phys. Dept., Aristotle University, Thessaloniki, Greece, 2020

[2] E.Hess *et al.,* "Excitation function of the 18O(p,n)18F nuclear reaction from threshold up to 30 MeV", *Radiochimica Acta* vol. 89, no. 6, p.357-362, June 2001. doi:10.1524/ract.2001.89.6.357

[3] NDS-IAEA, https://www.nds.iaea.org/medical/n4p11c6.html

[4] A Alfarano *et al.,* "Thick target yield measurement of 211At through the nuclear reaction 209Bi(α,2n)", *J. Phys.: Conf. Ser.* Vol. 41 no. 115 September 2005. doi:10.1088/1742-6596/41/1/009

[5] N. Jain *et al.,* "Determining optimal F18-FDG dose in clinical whole body PET acquisitions using Acquisition-Specific NEC", *J. Nucl. Med.* vol. 58, no. supplement 1, p.780, May 2017.

[6] B.Quinn *et al*, "Radiation dosimetry of 18F-FDG PET/CT: incorporating exam-specific parameters in dose estimates" *BMC Med. Imaging*, vol. 16, no.41, June 2016.

[7] SRIM, http://www.srim.org/.

[8] Drugs, https://www.drugs.com/pro/choline-c-11.html

[9] M. A. Seltzer *et al,* "Radiation Dose Estimates in Humans for (11)C-acetate Whole-Body PET", *J. Nucl. Med.* vol. 45, no. 7, p.1233-6, July 2004.

[10] F. Guerard *et al*, "Production of [211At]-Astatinated Radiopharmaceuticals and Applications in Targeted a-Particle Therapy", *Cancer Biother. Radiopharm*., vol. 28, no. 1, January 2013. doi:10.1089/cbr.2012.1292

[11] R.W. Hamm *et al*, "A compact proton linac for positron tomography", in *Proc. 1986 Lin. Acc. Conf.,* SLAC-Report-303, p. 141, June 1986. doi:10.1109/PAC.1989.73323

[12] M. Vretenar *et al.,* "A Compact High-Frequency RFQ for Medical Applications", in *Proc. LINAC'14,* Geneva, Switzerland, Aug.-Sep. 2014, paper THPP040, pp. 935-938. doi:10.13140/2.1.1217.4084

[13] M. Vretenar *et al.,* "High-Frequency Compact RFQs for Medical and Industrial Applications", in *Proc. LINAC'16,* East Lansing, MI, USA, Sep. 2016, pp. 704-709. doi:10.18429/JACoW-LINAC2016-TH1A06

[14] V. Vlachoudis *et al*, "A versatile multi-objective FLUKA optimization using Genetic Algorithms", in *Proc. ICRS13-RPSD2016*, October 2016. doi:10.1051/epjconf/201715306004

[15] P. Krawczyk, "Modular Energies – Business Plan", 2019.

[16] D.J. Warner, "Heavy-Ion Acceleration Using Drift-Tube Structures with Optimised Focusing", Proc. Of 1988 Linear Accelerator Conference, CEBAF-Report-89-001, p.109, Nov. 1988.