Nuclear Medicine decision makers in need of help: The remote places' cyclotron installation example

Although Nuclear Medicine (NM) has a history of three quarters of a century [1,2] and NM theragnostics are used by more than 1% of the European population per year [3, 4], NM is still of rather underestimated importance to the Health Care Decision Makers (HCDM). This is due to many factors, some of them being that:

- Although the average social status of doctors is very high [5], NM ones usually serve backdoors and are, thus, invisible to the public, while their average in-hospital numbers, compared to other specializations, is rather low for their voice to be heard ,
- Radiation has not cessed to cause fear [6], something not helpful when approaching HCDM (7) and
- Simple, straight-forward, yet complete cost-effectiveness analyses are rare, to say the best, for NM.

The last issue is largely aggravated when positron emission tomography (PET) is involved, not only due to its high initial acquisition and building costs, estimated at around 2.500.000€, but also due to problems created by its fluorine-18-fluorodeoxyglucose (^{18}F-FDG) production, since cyclotrons need to be close to PET devices [8]. Even worse, Europe has many remote locations, at least concerning the ease of access from radiopharmaceutical production sites, yet with population vastly justifying the existence of NM services, such as the big Mediterranean islands. Such remote places either have one cyclotron serving PET on the coastline, as is the case of Sardinia, or import all their needed radiopharmaceuticals, as is the case of Corsica, Crete, Cyprus, etc. This creates problems concerning dependency from the mainland, especially when the weather is bad, there is a strike or global pandemics break out, resulting in less or no flights at all. Of note that among these 4 islands PET only exist in Sardinia and Cyprus, while Crete will have its first in the next few months. The above simply mean that European islanders will surely face cancellations of their NM examination on few days per year, while others will have to travel to the mainland for their PET, resulting in extra social security costs, either immediate or in the long term via medical loss of chance and distress of patients. Yet another problem that importation of radiopharmaceuticals for even the simplest NM acts creates is that their final cost is bigger than the one close to their site of production, thus repelling public investments and private initiatives.

At the beginning of the last decade Schaffer et al. (2015) successfully tested if cyclotrons, used until then only for the production of PET radiopharmaceuticals, could be retrofitted and made suitable for the production of gamma-camera radiopharmaceuticals as well, via the use of different targets, at an affordable extra cost [9,10]. In this way the production of (almost) all radiopharmaceuticals for each diagnostic examination of NM could be achieved via a single machine, a Hybrid Cyclotron (HC), a method already described as feasible in 1971 [11] and making part of the International Atomic Energy Agency (IAEA) publications in 2017 [12].

Although in theory remote places would greatly benefit from such an installation, one need to also take into consideration the NM utilization rates (NMUR).These vary greatly among European countries and, as an example, in France there were 2 SPECT and 0,9 PET examinations per 100 people in 2018, while in Greece the respective numbers fell to 0,6 and 0,2 [3], thus a NMUR that seems to be independent from the number of gamma cameras and PET per population unit in these countries [4,13]. This means that for small NMUR a baby cyclotron, costing roughly one-third the price of a HC (2,5M€ versus 7,5M€ respectively), might prove more cost effective, at least in the short term, for ^{18}F-FDG production, while all other radiopharmaceuticals would be imported . However, not only cancer incidence in Europe is expected to be on the rise by about 1% per year [14], probably augmenting respectively NMUR as well, but baby cyclotrons produce only a handful of ^{18}F-FDG doses per production cycle. Thus , the more the demand is on the rise, the more production cycles will be needed and, thus, more highly skilled and well-paid personnel need to be employed, possibly exploding the initially low investment price.

On the other hand, HC production is also limited, yet much more important than the baby cyclotron one , and HC systems require more space and construction costs, besides their initially high price. Their advantage of offering local radiopharmaceutical production can be easily hindered by the potentially large time of travel within the remote place. HC work smoothly and effectively when they are within 2 hours from sites, more than 4 hours distance starts becoming very tricky and there is no reason of existence when distances exceed 6 hours. This means that a small cyclotron, either normal or hybrid, situated in the middle of a big Mediterranean island, might prove too far away from the seaside NM departments that it means to serve. Especially for limited NMUR, one baby cyclotron per site might prove more cost effective.

Since ^{99m}Tc is also produced, HC need to have a nominal energy of at least 12MeV, while cyclotrons of 20MeV and more are out of the scope of testing their cost-effectiveness in remote places. This still leaves a choice of at least 8 different companies that offer HC (we are aware of GE, Siemens, IBA, Positron, ACSI, Sumitomo Heavy Industries, BCSI and PMB Alcen, but there could be more) within this energy window with different acquisition prices, nominal energies, activities and production capabilities per cycle. As if this was not already complicated enough, Cyclomed99 team compared 30 cyclotrons used for medical purposes, with some of them being in the range of 12MeV-20MeV, thus being potentially capable to serve as HC efficiently [15].

In conclusion, there are still many places in Europe lacking local ^{18}F-FDG and/or ^{99m}Tc production, even if their population sizes could justify it, at least in theory, and HC, producing both, could be a suitable candidate for cost-effectiveness analyses. Full import versus normal cyclotron versus HC is not an easy decision for HCDM to make, since many different cyclotrons can be converted into hybrids and the expected growth in both NMUR and consequent raises in cyclotron employee costs cannot be neglected. It is thus of paramount importance that suitable economic models are invented for isolated places where the numbers of inhabitants justify the existence of NM services. With freedom come choices and this opens a new research path combining health economics and NM geodistribution.

Bibliography

1. Otte A. Medical history in the hellenic journal of nuclear medicine. *Hell J Nucl Med* 2017 ; 20(1): 2.
2. Grammaticos PC. Pioneers of nuclear medicine, Madame Curie. *Hell J Nucl Med* 2004; 7(1): 30-1.
3. The use of nuclear medicine diagnostics and Tc-99m varies significantly across countries. In: The Supply of Medical Isotopes. OECD; 2019. p. 42-7.
4. Healthcare resource statistics - technical resources and medical technology - Statistics Explained [Internet]. [cited 2021 Jun 1]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Healthcare_resource_statistics_-_technical_resources_and_medical_technology
5. Melidis C. Possible Impact of a European Agency for the Strategic Management Against Cancer (EASMAC) on Treatment, Diagnosis and EU Politics. *Clin Oncol* 2020; 3(2).
6. Giannouli V, Lytras N, Syrmos N. Is there a place for music in nuclear medicine? *Hell J Nucl Med* 2012;15(3):188-9.
7. Callen J, McKenna T. Saving Lives and Preventing Injuries From Unjustified Protective Actions - Method for Developing a Comprehensive Public Protective Action Strategy for a Severe NPP Emergency. *Health Phys* 2018; 114(5): 511-26.
8. PET Cyclotron and Radiopharmacy Facility. Available from: http://www.bccancer.bc.ca/our-services/services/pet-functional-imaging/pet-cyclotron-and-radiopharmacy-facility.
9. Hume M. In a breakthrough, Canadian researchers develop a new way to produce medical isotopes. Globe Mail 2012. Available from: http://www.theglobeandmail.com/news/national/british-columbia/in-a-breakthrough-canadian-researchers-develop-a-new-way-to-produce-medical-isotopes/article2343967
10. Schaffer P, Bénard F, Bernstein A et al. Direct Production of ^{99m}Tc via 100Mo(p,2n) on Small Medical Cyclotrons. *Phys Procedia* 2015; 66: 383-95.
11. Beaver JE, Hupf HB. Production of ^{99m}Tc on a medical cyclotron: a feasibility study. *J Nucl Med* 1971; 12(11): 739-41.
12. Cyclotron Based Production of Technetium-99m | IAEA. Available from: https://www.iaea.org/publications/10990/cyclotron-based-production-of-technetium-99m
13. Equipment | European Society of Radiology. 2017. Available from: https://www.myesr.org/eu-international-affairs/imaging-observatory/equipment
14. World Health Organisation (WHO). Cancer Tomorrow. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/bars?mode=population
15. Schmor PW. Review of cyclotrons used in the production of radioisotopes for biomedical applications. Cyclotrons 2010; 19th International Conference on Cyclotrons and Their Applications. 419-24.

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