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Letter to the Editor

Direct effect of the Directive Euratom 2013/59 on European hospitals hosting radionuclide therapies

Introduction

Radiotherapy involves irradiating tissue, often cancer cells, by irradiating this target with particles such as x rays, gamma rays, electrons, protons or ions. These particles interact with the tissue and produce by ionization free electrons and toxic free radicals proportionally to the energy imparted per unit of mass (named absorbed dose or shortly dose). Along their path, these particles produce by ionization toxic free radicals proportionally to the energy delivery per unit of mass (named dose). Irradiations are mainly performed in two ways. In external beam radiotherapy (EBRT), a medical device set outside the patient produces a particle beam that is focussed to the target. In brachytherapy sealed radiation sources are placed inside or close to the target, while in radionuclide therapy a vector labelled with a radionuclide is injected to the patient, the vector being designed to be preferably taken up by the target.

In both modalities, patient organs are also irradiated. In EBRT the particle beam has to cross the patient to reach the target. In radionuclide therapy, all currently developed vectors are always taken up by some organs. For 3 decades, highly sophisticated methods have been developed in EBRT to individually plan and verify the dose delivered to the target and to the organs. In contrary, most of radionuclide therapies, in EU and elsewhere, are performed on a fixed radioactivity scheme, i.e., by injecting a common radionuclide activity to all patients overlooking treatment planning and verifications. This practice is clearly illustrated by the recent approval of the Lutathera therapy by the European medicines agency (EMA) [1].

However, the optimisation article 56 of the Euratom Directive 2013/59 (further referred as "the Directive") is unconditional, clear and states [2]: "*For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.*".

Article 56 is in line with the abundant scientific evidence showing the benefit for the patient outcome to individually plan the radionuclide therapies [3–5]. The importance of this approach was also underlined by some national nuclear medicine societies [6,7].

In the article 58, the Directive states that, in nuclear medicine, for non-standardized radiotherapies a "*medical physics expert (MPE) shall be closely involved*", while for standardized ones a "*MPE shall be involved*": a rather marginal difference without any impact on the article 56. However, under the pressure of several lobbies, the article 56 provision was weakened in several national implementations, by stating that standardized radiotherapies in nuclear medicine do not require any individual planning. This posture was further supported by a position paper of the European association of nuclear medicine (EANM) [8]. This position paper also provided its own classification of standardized and non-standardized radiotherapies. Consequently, nuclear medicine departments widely believe to be solely bound by their national law.

Directives can be understood as binding EU legislative acts which set minimal objectives to be achieved, but leave national authorities to choose its form and methods of implementation.

Early in 1979, the European Court of Justice (ECJ) affirmed that the EU directives are capable of having direct effect, meaning that individuals can directly invoke their provisions in a national court. However, the ECJ has established certain conditions for this direct effect. The provision has to be clear, precise and unconditional, and the implementation period of a directive must have passed (Ratti Case C-148/78 [9]).

Direct effect means that any individual or body can invoke the provision of a directive in front of a national court, and that this court has to apply the directive setting aside the conflicting national law. This jurisprudence was extended in 2002 to cases with incorrect implementation of a directive (Marks & Spencer Case C-62/00 [10]).

Importantly, it implies that an MPE or a physician cannot be held liable for having followed the Euratom Directive rather than a conflicting national law.

In principle, EU directives are capable of having only vertical direct effect, meaning they can be only invoked against a state. So, individuals cannot invoke the provisions of a directive horizontally, i.e., against other private individuals. However, as will be illustrated, the ECJ has provided a wide definition of the concept of a "State" which allows to invoke the provisions of the directive against a large range of bodies.

In 1990, the ECJ stated that a private body has to compensate the damages linked to a violation of a directive provision, when this private body can be considered as an "emanation of the state" (Foster Case C-188/89 [11]). In this case, the ECJ gave three criteria needed to consider a private body as an "emanation of the state":.

1. It is governed by public law and is part of the State.
2. It is subject to the authority or control of a public body.
3. It performs a task in the public interest and for that purpose has been given special powers.

The legal form of an emanation of the state is irrelevant as long as it satisfies the specified conditions [12]. In 2006, a hospital was already held liable for not having followed a directive (Marrosu & Sardino Case C-53/04 [13]). In the course of the time, the ECJ has even further eased the conditions for determining if a body is considered as an "emanation of the state".

In 2017, the ECJ decided that meeting only one of the three Foster

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case criteria was sufficient to consider the private body as an "emanation of the state" (Farrell Case C-413/15 [14]). Note that most hospitals in Europe have their expenses controlled, and often limited, by their national health security system (criterion 2); all perform tasks in the public interest and some obtained special powers for that purpose, e.g., public funds to buy equipment, authorisation to run a PET system, … (criterion 3).

Any national court should thus likely arbitrate that these hospitals are considered as emanations of the state and article 56 of the Directive can be invoked against them. For the sake of preventing legal threat on hospitals, and for patient safety and outcome, the authors hope that knowledge of such potential rulings will motivate hospitals to follow the article 56.

Radiotherapeutic posologies using fixed radioactivity scheme approved and promulgated by EMA are in conflict with the Euratom Directive 2013/59 article 56 as already noticed by MPEs [15]. Such posologies also directly violate the point 18 of the preamble of pharmaceutical Directive 2001/83/EC [16] stating that any rules governing radiopharmaceuticals must take into account the provisions of Council Directive 84/466/Euratom [17]. This directive has been replaced by the directive 97/43/Euratom already including the optimization principle (see Art. 1 (b) of [18]).

The EMA is a European agency having the mission to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the EU [19]. The delegation of powers for adoption of rules which supplement or amend certain legislative non-essential act element is allowed by the article 290 of the treaty on the functioning of the EU (TFEU).

However, in 2013 the opinion of the Advocate General at the ECJ was that agencies necessarily have to be precluded from the article 290 delegation (case C-270/12 point 85. [20]). One of the invoked reasons, is that the principle of democracy, enshrined in Articles 2 and 10 of the treaty of EU (TEU), necessarily dictates that any power to adopt an EU measure that can alter an EU legislative act must be exercised by an EU institution that is democratically accountable, in other words by the Commission, which is ultimately accountable to the European Parliament.

In more recent cases, the ECJ tolerated some power acts from EU agencies as long as there was a democratic oversight. In response to a request from the European parliament, the commission already implemented such democratic oversight to the European environment agency in order to prevent decisions which may not comply with the mandate of the agency, may violate EU law or be in manifest contradiction with EU policy objectives [21]. Such democratic oversight of the EMA still appears missing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf (accessed 2022 Feb 24).
[2] https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2014:013:0001:0073:EN:PDF (accessed 2022 Feb 24).
[3] Strigari L, Konijnenberg M, Chiesa C, Bardies M, Du Y, Gleisner KS, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imag 2014;41:1976–88.
[4] Cremonesi M, Ferrari ME, Bodei L, Chiesa C, Sarnelli A, Garibaldi C, et al. Correlation of dose with toxicity and tumour response to 90Y- and 177Lu-PRRT provides the basis for optimization through individualized treatment planning. Eur J Nucl Med Mol Imag 2018;45:2426–41.
[5] Walrand S, Jamar F. Renal and red marrow dosimetry in peptide receptor radionuclide therapy: 20 years of history and ahead. Int J Mol Sci 2021. https://doi.org/10.3390/ijms22158326.
[6] Chiesa C, Strigari L, Pacilio M, Richetta E, Cannatà V, Stasi M et al. Dosimetric optimization of nuclear medicine therapy based on the Council Directive 2013/59/EURATOM and the Italian law N. 101/2020. Position paper and recommendations by the Italian National Associations of Medical Physics (AIFM) and Nuclear Medicine (AIMN). *Physica Medica*. 2021;89:317-26.
[7] Flux G, Buscombe J. BNMS position statement on molecular radiotherapy. Nucl Med Com 2021;42:1061.
[8] Konijnenberg M, Herrmann K, Kobe C, Verburg F, Hindorf C, Hustinx R, et al. EANM position paper on article 56 of the Council Directive 2013/59/Euratom (basic safety standards) for nuclear medicine therapy. Eur J Nucl Med Mol Imag 2021;48:67–72. https://doi.org/10.1007/s00259-020-05038-9.
[9] https://curia.europa.eu/juris/liste.jsf?language=en&T,F&num=148/78, para 22 (accessed 2022 Feb 24).
[10] https://curia.europa.eu/juris/liste.jsf?language=en&num=C-62/00 (judgement para. 2) (accessed 2022 Feb 24).
[11] https://curia.europa.eu/juris/liste.jsf?num=C-188/89 (opinion 21, accessed 2022 Feb 24).
[12] Bakhtina KR. Farrell II and the concept of an 'Emanation of the State'. Ind Intl Comp L Rev 2018;18:241–8. https://doi.org/10.2478/iclr-2018-0035.
[13] https://curia.europa.eu/juris/liste.jsf?language=en&num=C-53/04 para 29. (accessed 2022 Feb 24).
[14] https://curia.europa.eu/juris/liste.jsf?language=en&num=C-413/15 para 35 (accessed 2022 Feb 24).
[15] Chiesa C, Sjogreen Gleisner K, Flux G, Gear J, Walrand S, Bacher K, et al. The conflict between treatment optimization and registration of radiopharmaceuticals with fixed activity posology in oncological nuclear medicine therapy. Eur J Nucl Med Mol Imaging 2017;44:1783–6.
[16] https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32001L0083 (accessed 2022 Feb 24).
[17] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A31984L0466 (accessed 2022 Feb 24).
[18] https://eur-lex.europa.eu/eli/dir/1997/43/oj (accessed 2022 Feb 24).
[19] https://www.ema.europa.eu/en (accessed 2022 Feb 24).
[20] https://curia.europa.eu/juris/document/document.jsf?docid=140965&doclang=EN (accessed 2022 Feb 24).
[21] https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52013SC0349 (point 363. art. 59, accessed 2022 Feb 24).

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