



Original article

Ethical reflections on proton radiotherapy

Reflejos éticos en la radioterapia con protones

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Introduction

Radiation oncology is a medical discipline mainly involved in the treatment of cancer with ionizing radiation. It is based on full knowledge of individual patient cancer disease, delineation of the target volume including tumor that has to receive therapeutic radiation dose, delineation of normal tissues to be spared, treatment planning with dedicated calculation algorithms, radiation delivery to patient with radiation emitting machines as a linear accelerator, patient follow up for tumor response and toxicity evaluation (Clifford Chao, Mohan, Marinetti, & Dong, 2013; Purdy, 2013).

These procedures must be preliminarily discussed with the patient, in particular as regards benefit and possible damage as a consequence of treatment. Then, fully informed consent must be obtained from the patient before starting irradiation.

Radiation oncology is subject to the same ethical principles as other disciplines of medicine and surgery but at the same time must satisfy requirements that are more

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specific, especially as far as patient clinical radio protection and full availability of resources are involved.

The recent development and wider applications of proton therapy with its inherent possibility of optimal dose distribution inside patient tumor and normal tissues in comparison to other irradiation modalities highlights the need to better focus attention to more complex ethical issues in this field ([Shultz-Ertner & Tsuijii, 2007](#)).

In fact, currently more than 150,000 patients have been treated with proton therapy in more than 70 centers in the world. Almost 50 new centers are under construction to be followed by other 20 in project.

General ethical principles

It is certainly not necessary to mention here the fundamental principles of medical ethics that we shall briefly recall only for the sake of explicitness ([AMA, 2011](#)).

The principles of compassion, respect and safeguard of patient welfare, dignity, rights and confidence are mentioned in the Code of Ethics of the American Society of Radiation Oncology as the first step in assuring ethical behavior ([Donaldson, 2017](#)). Then, a common point of understanding with the patient concerning treatment objectives, risks, alternatives shall be reached. This holds true particularly in the case of patient entering a clinical trial ([Hellman & Hellman, 1991](#)).

Eventually, any potential conflict of interest, real or perceived, should be avoided to ensure independent medical judgment in pursuing the genuine patient interest. The duty of the physician to treat and manage disease in the best interest of the patient sometimes can, at least partially, conflict with the principle that it is necessary to maximize the health of the entire community rather than that of the individual ([Tepper, 2017](#)). This holds true for example when resources are limited.

General ethical principles applicable also in medicine can be related to the moral obligation as delineated by Immanuel Kant, while in clinical medicine an example of framework to analyze ethical issues has been developed by Tom Beauchamp and James Childress ([Beauchamp & Childress, 2012](#); [Stanford, 2016](#)), who proposed the following four principles:

Respect for autonomy (particularly stressed in Kantian ethics) entails that the patient has the right to accept or refuse the proposed treatment, and has the right to decide if it is or not his best interest to adhere to the proposal.

Beneficence. The physician must believe that the disease management envisaged by him is the best for his patient.

Non maleficence. First do not harm. In radiation oncology this, in most cases, consists in a compromise between benefit and harm.

Justice. Concerns the distribution of scarce resources and the related patient selection for treatment.

Proton therapy

Proton Beam Therapy is a technology for delivering conformal beam radiation with positively charged atomic particles to a well-defined treatment volume ([Price Mendenhall & Li, 2013](#)).

In particular, in radiation oncology especially when dealing with Proton Therapy it is necessary to take into account several other issues. Complexity is one of the main characteristics of Proton Therapy and among several issues involving ethics there is evidence that the following ones have to be particularly highlighted.

Informed consent. By definition, the consent must be informed.

This means that the radiation oncologist has to explain to the patient in an understandable way why, when, how that particular treatment is indicated and has to be performed; this explanation must be satisfactory whatever is the current ability of the patient to fully understand what is told him, and independently from his level of education and communication ability through a sort of customization of the informed consent.

It is therefore in charge of the radiation oncologist to ensure that the single patient understand what is implied in the proposed therapy and to respect his/her right to ask further explanation until deemed satisfactory or refuse the treatment.

Difficulties in describing and comparing special techniques and proton therapy with conventional radiation therapy can be easily imaged and a good balance between diffidence and enthusiastic adherence to this advanced cancer treatment modality must be pursued to ensure both patient autonomy and the choice of the best treatment for the individual patient interest.

Clinical research is an even worse problem, if possible.

In fact in this case the informed consent is made more complicated by the fact that in clinical research not only the individual patient interest is to be considered in choosing to enter a study involving the possibility to undergo an experimental treatment that is associated with risk to receive partially unknown or even totally unknown harms. In fact there is also the aim to improve, through the clinical research, the health of the entire community, and this must be explained by presenting the pros and cons of a new treatment even if it entails a certain risk for the individual patient.

Equipoise is the other ‘face of the Moon’ of ethics in clinical research applied to proton therapy and it is particularly important in this field.

In fact many oncologists believe that proton therapy could be applied only after that the advantages of this therapy are fully demonstrated according to evidence based medicine criteria, following randomized clinical trial in comparison to more conventional radiation therapy modalities including X-rays special techniques.

The concept of equipoise, however, states that physicians must decide through randomized clinical trial which of two treatments is better, when there is a genuine uncertainty, because they actually do not know which one is better.

This is often not the case when proton therapy is compared with X-rays radiation therapy.

In fact, it is always possible to preliminarily evaluate in a treatment planning inter comparison whether a dose distribution with proton beams is better than one with X-ray beams or not. It is better if there is evidence of a higher dose to the tumor or less dose to normal tissues or both of them (Claxton, Sculpher, & Drummond, 2002; Eckermann & Willan, 2007; Goozner, 2010).

This fact is associated, according to radiobiology in most cases to better probabilistic tumor control and/or less normal tissue toxicity.

Therefore, in this case, the principle of equipoise cannot be applied because there is not a genuine uncertainty about whether one treatment is better and hence there is no rationale for a randomized clinical trial.

This is the same reason why in the Seventies and Eighties cobalt therapy machines have been superseded by linear accelerators in radiation therapy without the need of randomized clinical trials and the same happened more recently in the shift from 3 dimensional conformal therapy (3D-CRT) to widespread use of Intensity Modulated Radiation Therapy (IMRT) techniques with linear accelerators. If paradoxically a patient were treated with cobalt therapy in the Western World today instead of a linear accelerator, this behavior could be easily sued for malpractice in case of toxicity because of the much better dose distribution obtained with linear accelerator in largely most cases.

This is why in Holland four proton therapy centers have been established to satisfy the need of particle therapy of cancer patient population, and the patients are selected with a procedure where proton and X-rays plans are compared and differences in dose distribution to tumor and healthy tissues are transformed in probability percentage of tumor control (TCP) and/or normal tissue complication probability (NTCP) ([Langendijk et al., 2013](#)).

According to what is defined a ‘model-based’ approach, if these percentages regarding different tumor and healthy tissue types are within a clinically significant benefit range in terms of improved tumor control or decrease of normal tissue damage probability, proton therapy is then deemed necessary for the patient as alternative to X-rays radiation therapy.

In particular both in USA and Europe cancer patients to whom proton therapy can be recommended have been divided into two groups.

The first one includes patients affected by tumors that can be treated effectively only with protons instead of X-rays and they sum up to 5% of cancer patients where radiation therapy is recommended. In this case a model based approach is not applied because the advantages of proton therapy are so evident that it would be almost unethical to treat the patients with other modalities than protons.

The second one includes those patients with tumors that can be better treated with protons for their inherent advantages. These advantages can be aptly evidenced with the model based approach. They sum potentially up to 30% of the cancer patients

where radiation therapy is recommended. This percentage is also heavily influenced by the availability of proton therapy centers. Therefore, the model based approach is an ethical method to select patient for a scarcely available treatment modality by adjusting the threshold level of clinical significance attributed by radiation oncologists to the probability of increased TCP and decrease of NCTP due to protons consequent to inter comparison of proton treatment plans with X-rays plans.

Pediatric cancer patients are a special group of patients because, almost independently from tumor type and site, they take advantage from proton therapy because the optimal sparing from useless radiation to still growing and most radiation sensitive normal tissues reduces the risk of secondary radiation induced tumors.

It is clear that something expensive and complex as proton therapy cannot be implemented on large scale without control, safety and quality assurance, evaluation of the performance, results, adverse events.

Randomized trials cannot be considered mandatory to start a widespread clinical application of proton therapy and they can paradoxically delay full development of proton therapy because their results are too long to obtain in comparison to faster and safer technological improvement of proton therapy procedures. For example, closing today a randomized trial conducted with proton passive scatter system could bring results already obsolete while nowadays proton beam scanning is rapidly wide spreading with inherent decrease of neutron activation, so decreasing normal tissue useless radiation. These advantages could have been today unavailable if it had been necessary to wait for their development the conclusion of previous trials.

Therefore, like in other situations where technological advancement of the same technological modality (in this case protons vs. X-rays in ionizing radiation therapy) is at stake, methods of evaluation and acceptance different from randomize trial must be devised and applied.

The Adopt and Trial approach derived from the economical domain can satisfy ethical requirements because it combines the possibility to apply a new technique as soon as it is available while starting at the same time a very strict prospective and continuous control on the procedure by gathering and storing as much as possible detailed information on the patient disease, on the treatment and on follow up.

This method can be very powerful if applied in a network of centers practicing proton therapy.

It can also satisfy the need of safety in treating cancer patients with protons while at the same time minimizing the risk of delaying implementation of useful innovation provided by technological advancement.

There are possibly other three options available: adopt without trial, like it happened in the last two decades with the shift from most 3D conformal radiation therapy (3DCRT) to intensity modulated radiation therapy (IMRT); delay adoption and undertake a trial, when the trial results are essential for decision; delay without trial is only a theoretical hypothesis because there is no need to delay a potentially advantageous procedure if there is no intention to verify its performance.

The choice of the ‘adopt and trial’ approach instead of the ‘delay and trial’ one depends on the calculated net gain of both approaches; if both are below zero or if adopt and trial has a net gain greater than the other it means that benefit of trials are less than its cost and the adopt and trial approach should be chosen (Grutters et al., 2011).

Further advancement of the rationale and practical application of up to date method to select patient for proton therapy without waiting for preliminary randomized studies is the introduction of knowledge-based planning solution with the use of information gathered from several previously stored examples of different treatment solutions. These solutions provide a prediction of X-rays and proton plan dosimetry in single patient without necessitating actual plan creation (Delaney et al., 2017). This is a process that is in part related to the natural mechanism to make rapid decision based on learning from experience.

Similar prediction can be made even for estimated improvement in quality-adjusted life years to support individual patient selection (Quik, Feenstra, Postmus, & Slotman, 2016).

The *Conflict of Interest (COI)*, last but not least, from a general ethical point of view, it is to be considered in financial relationship with industry in proton therapy.

Collaboration with biomedical industries is essential for the advancement of cancer care and therapy, but financial relationship between physicians and device and machine production company can bring to COI.

This can be defined as ‘a set of circumstances’ that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest (Lo & Field, 2009).

Physician decision making and its impact on patient care are at risk to be influenced by external factors and the highly specialized and technologically focused physicians, as the radiation oncologists are, involved in high spending settings, are sensitive target for selected industry marketing.

Even if (according to COI analysis by American Society of Clinical Oncology) medical oncologists, involved mainly with drug therapy, are more at risk by the large number of general industry payments in comparison to other physicians and in particular to radiation oncologists, this does not exclude the COI risk in the proton therapy field that is among the most technical and device oriented cancer therapeutic options.

The problem is that generally physicians themselves often do not recognize their own vulnerabilities to financial and non financial inducements (Marshall, Moy, Jackson, & Hattangadi-Gluth, 2014).

This scenario is further complicated by the fact that in radiation oncology and in proton therapy in particular other professions are involved and have great influence and are at risk for COI.

This holds true for medical physicists who can have great influence over device purchase and so indirectly on patient care but their financial interactions with industry in general are less evaluated than those of physicians.

Conclusion

Proton therapy is not a quite new therapeutic modality to treat cancer, but it is currently favored in its diffusion by the shift from very large and expensive facilities to more compact, less expensive and so more affordable systems.

Cancer can be treated with higher efficacy with protons, due to better dose deposition in the tumor, and less toxicity, due to unsurpassed sparing of normal tissues, in comparison to other methods of delivering ionizing radiation to tumor.

The wide spread diffusion of this technology that allows the optimized use of ionizing radiation, (an already very well known method on millions of people for cancer treatment) has evolved and improved for decades, every time an inherent advantage of dose delivery and distribution to human tumor tissues was implemented. This trend, however, could be dramatically slowed by the possible envisioned request that every new clinical application of proton therapy be accepted by the medical community only after formal randomized clinical trial are performed among different methods to deliver ionizing radiation.

With protons, however, we are dealing with a modification of delivery and distribution, in terms of optimization, of the same therapeutic mean (ionizing radiation) already well known and not with the comparison of different drugs and different mechanisms of action as in most of pharmacological inter comparison.

This request of preliminary randomized trials ignores that there is a clear cut evidence that proton therapy can very often create a better dose distribution in cancer patient tissue that is absolutely necessary or at least very useful in 5% and from 20 to 30% respectively of patient population with recommended patient population.

Moreover, there are useful and very rationale methods alternative to randomized trial to validate proton therapy choice even in every single patient as the adopt and trial approach.

These alternatives are satisfactory from the ethics point of view including safety of patient and economic issues and can avoid delaying wide spread adoption of proton therapy and make it fully available to the entire patient population which needs it.

Conflicts of interest

The authors have no conflicts of interest to declare.

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