Marco van Vulpen

Critical mass

Erasmus University Rotterdam

Universiteit Leiden
The Netherlands

TU Delft

HollandPTC
Proton Therapy Centre

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Lecture to be delivered by

Prof. Marco van Vulpen

upon the acceptance of the post of Professor in the field of radiotherapy,

in particular proton therapy, at the Erasmus University Rotterdam,

Leiden University and the Technical University Delft

on Friday 11 October 2019

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Lecture to be delivered by Professor M. van Vulpen on 11 October 2019, upon the acceptance of the post of Professor in the field of Radiotherapy, in particular proton therapy.

Rector Magnificus of Leiden University, Rector Magnificus of TU Delft and Rector Magnificus of Erasmus University Rotterdam, members of the Executive Board of Leiden University Medical Centre, members of the Executive Board of TU Delft, members of the Executive Board of the Erasmus Medical Centre, ladies and gentlemen in the audience, whose attendance here today is highly appreciated,

The purpose of my inaugural address here today is to officially accept my appointment as Professor at no fewer than three universities. And I do this with great pride and gratitude.

Introduction

The Holland Proton Therapy Centre, or HollandPTC, will ensure that proton therapy brings added value to people and to society. This is our mission. This is what we will be striving to achieve. And it is a very worthy goal, but achieving it will take a great deal of effort and commitment. In this lecture, I will be taking a critical look at the way in which we, as a society, currently view the concepts of value, market mechanisms, proton therapy, and reflecting on the way in which we organise healthcare. And I will also tell you more about my own personal mission. My ultimate goal is to transform our existing radiotherapy departments, with their at times somewhat narrow approach, and to make these into workplaces that are open and patient-centred. HollandPTC is the perfect model through which to achieve this. I very much hope that you will enjoy this journey, and the academic rigour and scrutiny that it will involve.

The End of Radiotherapy

My previous inaugural lecture at Utrecht University was entitled: ‘The End of Radiotherapy’.[1,2] This title caused something of a stir in June 2012 when I gave the lecture, and more than a little amusement. Announcing the end of your own specialism before you have even started work- it’s an unusual way to launch your career!

‘The End of Radiotherapy’ was chiefly about the way in which we organise healthcare and the consequences this has for patients. Our healthcare is divided into various disciplines which, in organisational terms, resemble a series of parallel vertical columns or silos. Within these columns, the primary focus is on one particular discipline, and interaction between these disciplines generally takes second place. Contact between the columns is packed into a weekly one-hour multidisciplinary meeting (or ‘MDG’), at which there are too many patients to discuss in too short a time. The same applies to other important areas, such as quality and safety, but also to funding. This traditional structure of a series of vertical silos also leads to competition between disciplines, even though cooperation between them would actually add an enormous amount of value. Under the existing organisational structure, it is very difficult to place the patient at the centre of what we do. And indeed, the fact that this does not happen can be seen in, for example, the number of complaints about inadequate patient transfers and poor communication between doctors from different disciplines in cases where treatment needs to be provided jointly. It would be better to change the organisational structure by lifting these columns and turning the whole structure through 90 degrees, so that we would have a structure in which all care providers would focus on the patient’s pathway through the healthcare system. To achieve this, we would need to replace competition with joint decision-making, and changes would also be needed to the way in which funding is provided and in other areas. Caregivers would once again play the lead role, and the patient could take the lead regarding his or her own care. Although some hospitals, such as cancer centres, are opting for this kind of new approach, there has been little response from medical specialists, health insurers or the government. In this lecture, I will be talking about HollandPTC in Delft as an example of precisely such a change.

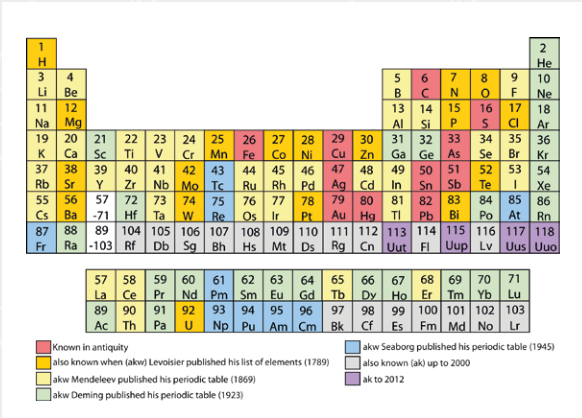
In my previous inaugural lecture, ‘The End of Radiotherapy’, I also touched on the large number of innovations that are now flooding the world of medicine, and the field of radiotherapy in particular. Every radiotherapy department seems to feel compelled to introduce innovations in order to compete with other radiotherapy departments and hospitals. Emotions play a role in this battle. The ‘p’ word- no, not ‘protons’ but ‘patients’- is often heard; promises are made, but without any evidence that patients will really benefit. Indeed, in my opinion, all too often patients become the victims. Technology and innovation are there to serve us and to help us treat patients more effectively. In my previous inaugural lecture, I described the idea of a shared language for evaluating innovations that could lead to more transparent decision-making and better acceptance of those decisions.

After ‘The End of Radiotherapy’, I did not expect to be making another inaugural lecture. So I was delighted to be given the opportunity for a sequel on Friday 11 October 2019, at 4 p.m. sharp, entitled ‘Critical Mass’.

Proton therapy in the Netherlands

In January 2009, the possible introduction of proton therapy in the Netherlands made the evening news. In November 2016, I had the great honour of starting work as a radiation oncologist and medical director at one of our three proton therapy centres, HollandPTC in Delft. This centre was established by TU Delft, Leiden University Medical Centre and Erasmus Medical Centre.

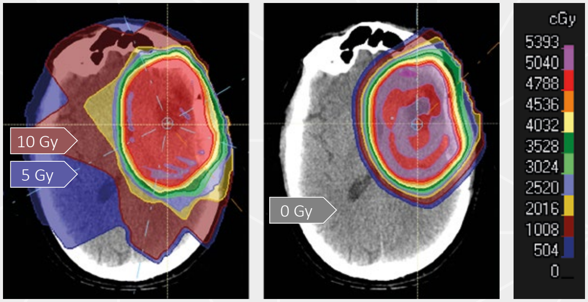
Standard radiation therapy for patients with a malignant cancer or tumour involves photon radiation. Photons are not matter and they therefore have no mass. They are packages of energy that are also emitted by the sun, for example, or by a light bulb. High-energy photons can be used to treat patients and destroy cancer cells. As everyone will know, if you hold up your fingers in front of a bright light, the light (low-energy photons) will shine right through. This is a good demonstration of how photons can simply travel right through things. This might sound negative, but radiation treatment using photons leads to good results. We are able to achieve a high degree of precision, with good outcomes for patients. But precisely because of these good results, we are also finding out more about the long-term damage that is caused by this type of treatment. This indicates that healthy organs need to be protected, and also the use of lower, more tolerable doses. There are several options for achieving this, such as better imaging, so that we can see where the tumour is better and target the radiation more precisely. Another option is to use a slightly different technique: radiation treatment using protons instead of photons.



Towards the end of the twentieth century, it became technically possible to administer radiation to patients using particles other than photons. This involves particles that have mass. In principle, you could use any type of atomic particle, such as carbon, fluorine or helium, but for technical reasons, the main focus has been on radiation therapy using hydrogen atoms. This is because the core of a hydrogen atom is made up of one single proton. These protons need to be accelerated to give them enough energy. This is done using a particle accelerator, such as the famous one located at CERN in Switzerland. Using an ingenious vacuum system and large magnets, the protons are accelerated to two-thirds of the speed of light and guided into the treatment room for use in radiation therapy. In a broadcast by Willem Wever from HollandPTC, the presenter showed us enthusiastically how this sophisticated piece of technology actually works.[3]

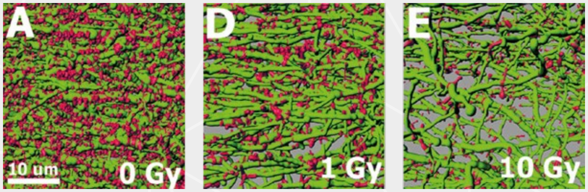
Unlike photons, protons are particles and have mass. When protons enter the body, they slow down. Almost all their energy is then released in one place. This is comparable to a depth charge which explodes at a pre-specified depth. So the mass that protons have is, in this sense, critical. After the dose deposition there is no further radiation. And that means no dose of radiation for the patient, and no damage to his or her healthy organs. The depth and position of the depth charge can be specified with a high degree of precision. Unlike photon therapy, proton therapy does not require you to irradiate from multiple angles in order to treat the target area properly and minimise the impact on the healthy surrounding tissues. For proton therapy, treatment from one angle works best.

In the following image, you can clearly see the differences between proton therapy and photon therapy. It shows two radiation therapy plans, which determine the dose and distribution of the therapy. In this example, the radiation plan is for a young patient with brain cancer and it shows both photon therapy and proton therapy. The dose of radiation is measured in Gray (Gy), or Joules per kilogramme. A total dose of 54 Gy is planned in order to complete the therapy. The photon therapy plan is shown on the left, and the proton therapy on the right. Under both plans, the tumour will receive the same target amount of 54 Gy. In the photon therapy plan, you can see that a significant portion of the healthy brain will also receive a dose of five Gy, ten Gy or even twenty Gy (the yellow area) while the tumour is being treated. In the proton therapy plan, the level of radiation in the healthy areas is zero Gy, so no dose of radiation at all. In radiotherapy, the goal of 'ALARA' (As Low As Reasonably Achievable) is always a priority. In other words, the ultimate goal is to give as little radiation as possible, preferably none, to regions other than the tumour itself. Clearly, there is no contest at all: the proton therapy plan is much better.



As we mentioned earlier, protons have a 'critical mass'. The location where the energy is released- that is, the depth of the charge- is easily affected by small movements such as breathing, passing air bubbles in the intestine or the shrinking of the tumour itself, and these factors are much more important than in photon therapy. With proton therapy, much of the work that needs to be done involves aiming the ‘depth charge’ as accurately as possible. Some ingenious methods of doing this have been developed, such as a robust method of planning the radiation therapy so that multiple uncertainties and changes can be taken into account simultaneously. In practice, these robust planning methods work very well.

But let’s get back to our patient! Because he or she already seems to have been forgotten a little. Is it really the case that when healthy organs are exposed to less radiation, better results are achieved? Well, yes it is. This figure shows brain cells in the hippocampus of a mouse.[4] The hippocampus plays a key role in our cognitive abilities, our sense of self, our IQ and our memory. The green stripes you can see here are dendrites, the brain cells. You can see that the number of these brain cells decreases considerably as the dose of radiation applied increases. And in the months following the radiation therapy, the number of brain cells actually continues falling. The evidence in these pictures corresponds with studies done in patients which show, among other things, that IQ decreases considerably in the aftermath of this kind of radiation therapy. For example, research has already been done into the damage done by photon therapy in patients with a relatively benign brain tumour. This type of brain tumour is more common in younger patients, between around thirty and forty years of age. They can still expect to have many years of life ahead of them and to participate fully in society. After more than ten years, the living situation of a total of twenty-seven



patients was described.[5] Some 59 percent of them were no longer able to work, and 19 percent could no longer live independently. The results were shocking. Of course, it is hard to pinpoint exactly what this dramatic deterioration is caused by: the surgery, the chemotherapy or the radiation therapy. But nevertheless, it is still worth finding out whether proton therapy might allow more people with this type of brain tumour to continue to participate in society and have a good quality of life.

Proton therapy in practice

In previous decades, there was a lot of experimentation with innovative therapies in the radiotherapy community. It was simple to bring promising new techniques into the clinic, without additional preconditions. This made the Netherlands into a global player in radiotherapy. Nowadays, this is less straightforward. Today, for every new development, a new question is rightly asked about the added value of a particular new technology: to what extent will this really benefit patients and do the costs of the new technology outweigh the expected benefits for patients? And as the cost of healthcare continues to escalate, that is a crucial question. But it is one that the radiotherapy community is understandably struggling with.

Partly on the basis of the Health Council of the Netherlands’ report entitled ‘Proton Therapy Review’ and three reports by the National Healthcare Institute, in 2012 the Ministry of Health, Welfare and Sport decided to grant licenses for four centres for proton therapy in the Netherlands, in Delft, Groningen, Maastricht and Amsterdam. The first two centres have been open since 2018, with Maastricht opening in early 2019. Amsterdam UMC and the National Cancer Institute decided to join forces with HollandPTC. Following the Ministry’s decision to grant licenses to no fewer than four of these centres, there was a great deal of discussion involving the radiotherapy community, health insurers, banks, the government and others. Emotions ran high on occasion, with statements such as: ‘proton therapy is healthcare’s new white elephant’; or, on the other hand: ‘denying patients proton therapy would be unethical’.

We have very effective and specific regulations regarding proton therapy in the Netherlands.[6,7] The number of patients who can be treated is currently limited to 2,200 per year by the four centres. In the revised report by the Health Council, the estimate is that around 5,800 patients will require proton therapy in 2020. There are two clear indications for proton therapy: the standard indications, on which there is international consensus regarding the added value of proton therapy over photon therapy, such as childhood tumours, eye tumours and skull base tumours. The second concerns indications based on models that can predict side effects. These models are validated using data from Dutch databases and checked by an independent methodological centre. If, using these models, the risk of side effects for a patient would be considerably lower using proton therapy, then the green light for proton therapy is given. In 2012, the National Healthcare Institute ruled that proton therapy for the model-based care indications is ‘consistent with current science and practice’. This is an important finding. It means that proton therapy is part of the basic package of insured healthcare. Using the nationwide tumour-specific indication protocols, the entire radiotherapy community decides which indications the model comparison should take place for. The National Healthcare Institute then decides on whether to make treatment available. Currently, treatment for head and neck cancer, breast cancer, lung cancer and brain tumours are all covered under healthcare insurance. National protocols for various other types of tumour are under development. Tables for the uniform recording of side effects and other relevant variables are also being added to the national indication protocols. The models used will therefore be validated prospectively and can be adjusted if necessary. The validation process will be repeated regularly using ‘rapid learning’ techniques. This will help us to determine the added value of proton therapy.[8]

In conclusion then, we have already developed extensive regulations and a national system of indications for proton therapy. This system has received praise, both nationally and internationally. A national database, ProTraiT, is also being developed for proton therapy. The database contains data for all patients treated using proton therapy in the Netherlands. It has been agreed that photon therapy data will also be added to this database. Ideally, other innovative therapies would also be added, such as the MRI accelerator or extreme hypofractionation, for which the same tables would of course need to be used for registration purposes. This would allow us to generate cyclical reports and possibly to compare a number of new healthcare products in a uniform manner. Another option is to form cohorts, share FAIR data and new forms of data collection. With the help of these cohorts, new forms of research would be possible so that smart comparisons could be made between innovations and they could be tracked over time.[9] The Netherlands Comprehensive Cancer Organisation (IKNL) could play an important role in this.

So proton therapy is an officially recommended treatment for certain groups of patients and is therefore covered by health insurance. Proton therapy should be discussed routinely with patients who exhibit the relevant indications, and they should be referred to a proton therapy centre. However, as things currently stand, this is hardly happening. This is often used as an argument that the value of proton therapy has not yet been proven. But this is not the case. After all, its value has already been determined through a rigorous process at the national level. Official tumour-specific working groups have reached a consensus on this at the national level with respect to various types of tumour, for instance. After approval by the Ministry of Health, Welfare and Sport, there ought not to be any further discussion about this. It is true that the *added* value of proton therapy still needs to be determined, but this is a separate process which we will return to discuss later. A number of practical objections are also cited. These objections that are easily resolved, however. This leaves me wondering how it can be that after extensive lobbying for the introduction of proton therapy by the radiotherapy community in the Netherlands, now that proton therapy has been introduced in a responsible and prudent manner, the enthusiasm for proton therapy seems to have fallen away fairly rapidly. The only conclusion I can draw is that, unfortunately, we are back to thinking in terms of vertical columns and silos. Market forces are also mentioned – the process of one treatment centre transferring its patients, and therefore also its income – to another treatment centre. But this makes no sense: the number of cancer patients in the Netherlands continues to rise every year due to our growing and ageing population. The number of patients who are eligible for proton therapy, which is estimated at 4.4%, is a drop in the ocean compared to the rise in the number of patients treated by the average radiotherapy ward in the Netherlands every year. And besides that: shouldn't doctors want the best for their patients? What difference does it make if one treatment centre treats fewer patients while another (affiliated treatment centre) treats more? Another factor that is mentioned is competition for the purchase of new equipment, such as MRI accelerators. But surely this objection cannot be a justified either. An MRI accelerator is used to treat small, moving tumours using MRI. There is hardly any overlap with patients who are eligible for proton therapy. There may be some overlap in terms of indications, but that would not be a sensible place from which to start. And yet currently, it seems that the radiotherapy community is not accepting its fair share of societal responsibility; it is failing to make the step from broad support for the introduction of proton therapy to its implementation in clinical practice. Whether we are talking about treatment centres or about individual radiotherapists. If the number of referrals continues to grow at such a glacial pace, radiotherapy in the Netherlands – including individual radiation oncologists – will have a lot of explaining to do to patients and financers alike. The funding required – some two hundred and fifty million euros – has been asked for and provided by society, on the say-so of the radiotherapy community, and now we are failing to refer patients to those facilities.

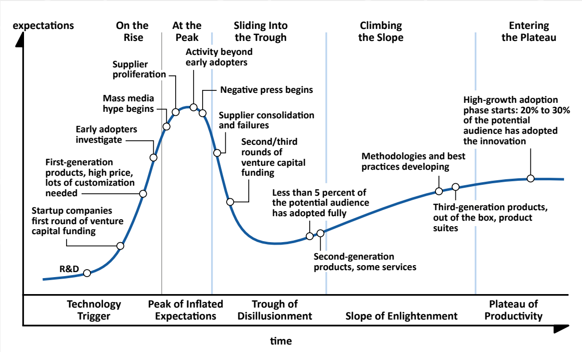
The clinical (added) value of innovative treatments

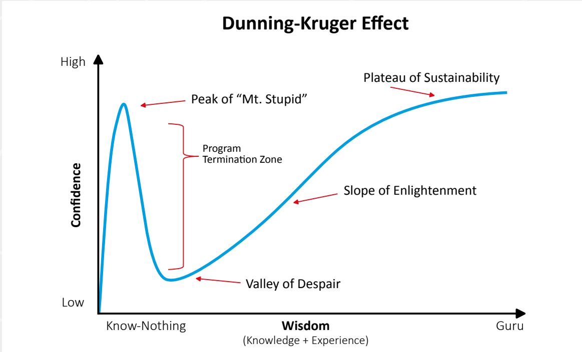
Although it is not yet clear why this clinical innovation is not being embraced, there are several examples of other innovative treatments that have gone through a similar process in the past. It appears that change management is often the key. Here is an example. A new operating facility is built for a large sum of money at the urgent request of medical specialists, because good care will no longer be possible without this operating facility. However, once it has been built, the new operating facility is hardly used. After the passage of a few years, however, the operating facility becomes a successful part of the care services at that hospital. A similar example from within the discipline of radiotherapy was the introduction of IMRT – intensity-modulated radiotherapy. IMRT was introduced around two decades ago but despite significantly better radiation plans, it was not implemented immediately. The requirement of randomised studies and concerns about safety and cost were mentioned frequently during the years of discussions that followed. Now, IMRT forms the basis of radiotherapy.

On the internet you can find numerous advice websites, books and courses on how to implement innovations successfully. Exactly how long it might take for an innovation to be fully implemented is more difficult to say. But in any event, the estimate is many years. Five to ten years does not seem exceptional. The introduction of new technology therefore requires change management. People are naturally averse to change. A good measure of patience is required. Perhaps our new proton centres have become entangled in overambitious multi-year budgets. This figure, a Gartner Hype cycle, shows the evolution from 'good idea' through to 'clinical acceptance'.[10] After reaching a 'peak of inflated expectations' and 'mass hype', the reality proves disappointing and enthusiasm wanes. There is then a period of reflection during which expectations are adjusted to reflect the reality and the innovation finally comes to occupy a stable and productive place in the healthcare system. It seems that my job is safe for the time being. This universally applicable figure has many other interpretations, including the Dunning Kruger effect, whereby the same graph is used to chart self-confidence and wisdom.[11] In this case, it features the peak of 'mount stupid' and the 'valley of despair'. The question is whether society, collectively, has the resources and the required degree of insight to wait for this process to unfold.

Current care practices demand evidence-based medicine, which means that there must be scientific and/or clinical evidence for every treatment and operation. Unfortunately, this is not usually available. The majority of our treatments have developed empirically. This often makes discussions about 'value' and 'added value' difficult. New forms of therapy must be based on evidence of added value with respect to existing forms of therapy for which there is no actual 'evidence'. This means that risk is inevitable. Existing therapies are usually a result of procedures that have evolved over many years. Optimisation has only involved a particular component of that therapy, not the therapy as a whole. But if nobody looks at the therapy as a whole, and only starts with choices that have already been made, there is a real risk that better solutions will be wrongfully rejected. Developments over time are just as important. We currently look at a development at one single point in time, and we often forget that in 10 years the care landscape will look very different.

In the fields of oncology and radiotherapy, too, guidelines do not appear to be wholly 'evidence-based'. One study in the United States looked at the scientific evidence that forms the basis of the national guidelines for oncological

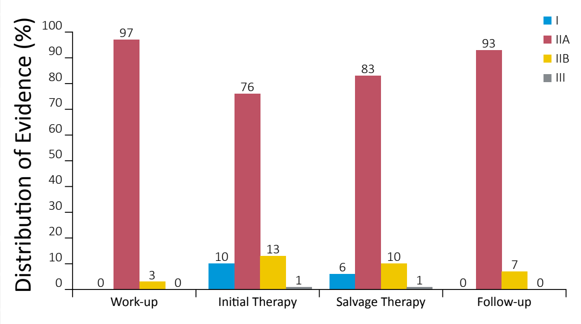


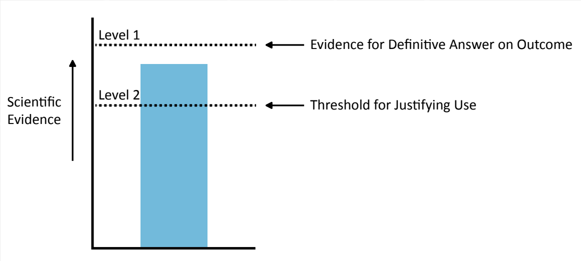


care.[12] Of the 1,023 recommendations for ten different types of tumours, the National Comprehensive Cancer Network (NCCN) found that on average only six percent of the recommendations make it to level I evidence. Level I is generally seen as the minimum level of evidence required that a new treatment is better than the standard treatment. In other words, the guidelines do not incorporate this level of evidence. The research showed that weaker level II evidence is widely used when formulating guideline recommendations. Well, we have plenty of level II evidence for proton therapy. Based on the NCCN benchmark, then, there is sufficient evidence for proton therapy.

The proton therapy licenses state that our proton centres must demonstrate the added value of proton therapy in relation to photon therapy. The proton centres are doing their level best in this regard, and are in the process of quantifying this added value in several ways. This is proving difficult, however. For example, can you still demonstrate a difference between protons and photons in a treatment programme that also involves surgery, chemotherapy and radiation? After all, the other therapies can all lead to side effects too. In addition, these other therapies can vary considerably between treatment centres, while the proton therapy is always administered in the same way. And finally, we need a large number of patients before we can draw any meaningful conclusions. As I mentioned earlier, the ultimate goal in radiotherapy is ALARA: the radiation that surrounding healthy tissues are exposed to must be 'as low as reasonably achievable'. If we take this principle alone, the added value of protons seems clear.

The societal (added) value of innovative treatments
Society also applies the 'as low as reasonably achievable' principle, but in this instance it is applied to cost. So there are multiple ways of looking at value: financial value, scientific value, clinical value and value for professionals. In





healthcare, value is often described in terms of efficiency: the ratio between costs and returns.[13] The effectiveness of new medical products plays an important role in national decision-making about what will be covered in the basic health insurance package. After all, healthcare is very expensive, and costs continue to rise. Determining value for money, or efficiency, is always done by comparing different types of therapy. For new treatments, the additional cost is divided by the added health benefit. The QALY, or quality-adjusted life year, is used as a universal outcome measure for the clinical benefit of any new healthcare product. In the National Health Service (NHS) in England, a consensus has been reached that one QALY is worth thirteen thousand pounds. This is also known as 'willingness to pay' (WTP). How much are we in the Netherlands willing to pay for a new treatment? This is not yet clear. At present, the sum of eighty thousand euros per one QALY gained is used as an indicative limit for cost-effectiveness.

In 2018, the Dutch National Healthcare Institute published a report on therapy displacement within hospital care, also called repression.[14] We can look at the total budget for care as a big box full of care products: if you want to add a new product to the box, you also need to decide what you will take out of the box to make room for it. There is only a limited amount of space in the box. This is a complex problem. Who should get to decide which care will no longer be covered? And how is this decision to be made? First, we need to examine the new healthcare product: for all new therapies, we now require a calculation of their value. For instance, let's suppose that one QALY is gained if we use a new therapy costing one hundred thousand euros. If adding that product to the box means that ten other therapies need to be removed, the logical question is how many QALYs we will lose as a result. The problem is that, generally, those ten therapies will not have been evaluated in terms of QALYs. Maybe you will lose six QALYs while gaining only one. After some discussion about this, it became clear to me that actually we have a well-funded healthcare system in this country, and we even apply a much more generous limit than is the case in England, for example. A further issue is that the process of therapy displacement is not transparent. This means that healthcare professionals can continue to push for new developments without necessarily feeling a sense of responsibility for the therapies that will need be removed from the healthcare package as a result. It would be better to include healthcare professionals and patients in the discussion regarding therapy displacement. But this is not a tradition that we have.

Another important point was mentioned at a symposium of the Council for Public Health and Society (RVS) regarding healthcare for the 21st century.[15] There, Marcel Levi explained that we need to realise that our healthcare system is actually full of pointless healthcare, duplication and unproductive methods. It would be remiss of us if we, in our clean-up of traditional care, were simply to allow every innovation to co-exist alongside existing therapies. Levi told us about calculations which indicate that a rigorous 'clean-up' of the system could free up enough funds to finance the growth in healthcare costs in the United States for several years. This all sounds great, but if it is so easy to make these savings, why are we not doing this already? I fear that such statements especially have significant political implications. But at the same time, I realise that a major change in culture and organisation is needed if we are actually to embark on this type of discussion and to follow through with the required steps. It could potentially pave the way for the easier introduction of innovative new therapies. We can liken it tidying up our wardrobe – it's the only way to make space for that new pair of jeans which fit you much better than the ones you bought 10 years ago.

Generally speaking, we doctors are not motivated primarily by money and costs.[13] This is hardly surprising. If someone says that proton therapy is costly, all kinds of different costs might be lumped in together. There are the investment costs for a cyclotron-based proton therapy centre – around ninety million euros. For this, you get two or three treatment rooms, known as gantries. You can write off the cost of a proton therapy centre with three gantries over a period of 30 years. A photon gantry costs around ten million euros, but it can be written off over ten years. In short, proton therapy may seem expensive, but over time there is not a major difference between the cost of investing in proton therapy and investing in photon therapy. Photon therapy currently costs around fifteen thousand euros per patient, and proton therapy costs about one and a half to two and a half times as much. That's a fairly small difference when you compare this with certain systemic therapies. So the additional cost of proton therapy is manageable, particularly since the price of treatment will fall over time. It is fairly realistic to assume that in the future there will be no difference at all between the cost of proton therapy and that of photon therapy.

And while doctors may say that certain new therapies are costly, there are several examples that show that doctors may not be the best people to be watching over our purse strings. Here it seems pertinent to mention the introduction of the DaVinci surgical robot,[16] and I think what this example shows above all is the enormous influence that doctors have. The DaVinci robot involves high investment costs as well as high annual maintenance costs. But when this robot was introduced, there was no evidence of any added value compared to normal surgery. Now, years later and after a number of extensive studies, the conclusion is that there is indeed no evidence of added value. Nevertheless, any hospital was allowed to purchase such a robot- no special license is required- and they still can. And indeed, they still do – complete with a slick marketing story for their patients. It is a case of competition and market forces getting the upper hand over the need to reduce escalating healthcare costs. At the same time, this zero-added-value robot has led to a sense of mistrust in relation to other new healthcare products. And that mistrust has played a role in the introduction of proton therapy. But for precisely this reason, I am pleased that the introduction of proton therapy is being subject to a critical examination, and that I have been given the task of rolling out this innovation in a responsible manner.

Market forces or cooperation in healthcare: a crucial dilemma

The introduction of the DaVinci robot is an example of market forces leading to undesirable consequences. The robot is often used as an excuse for differentiating a treatment centre as a centre of expertise with multidisciplinary collaboration. After all, collaboration and innovation are buzzwords in today's healthcare. Our colleague Mr van Rijn, when he was the Secretary of State, demonstrated this clearly when he referred to cooperation as 'the new competition'. But how can cooperation be more than just another buzzword that leads to its polar opposite – in other words more competition? And how do market forces relate to cooperation? Hugo de Jonge, the Minister of Health, Welfare and Sport, recently stated in an interview with the *Algemeen Dagblad*: 'The healthcare sector needs less market and more cooperation. Otherwise we can't carry on. Cooperation will not just happen of its own accord; it needs to be baked into the way in which we organise healthcare together.' In my opinion, HollandPTC has been set up to achieve exactly this; but more about that later.

It is important to reflect on how we should be working together. The postgraduate programme in Care Chain Management at the Erasmus Academy has the following to say on this subject:[17] 'Cooperation emphasises what is shared and focuses less on differences'. The slogans of cooperation that we often hear include: 'We are all working towards the same thing', 'Put the patient first' and 'We must all work together'. In other words, the emphasis is on what all the parties have in common. However, it is every bit as important to emphasise the differences between the actors involved, and to highlight the added value that each actor contributes. It is also useful to emphasise the individuality of each player and to highlight the value of each actor within the cooperation process. This helps to minimise strategic behaviour, and it also reinforces ambassadorship within the relevant organisation and among those who rely on it. In short, good cooperation means highlighting and appreciating differences.

One statement from a PhD dissertation from a few years ago has always stayed with me: 'The Hippocratic Oath should have been revised when market forces were introduced into the healthcare sector.' Common sense should always prevail in the consultation room. When market forces are not functioning as they should, we run the risk that patient care will deteriorate and cooperation will be jeopardised. Market forces work well for regular established care procedures, where there is a mature body of evidence and a balanced market, as in the case of cataracts or hernia for instance. Market forces improve patients' freedom of choice and help optimise the way in which care is provided. But when it comes to advanced and innovative treatments, collaboration works better. We still need the pressure of market forces – in order to find the right balance between cost and efficiency, for instance. But at the same time, market forces create incentives that make cooperation harder. However, these can be overcome. So let us now turn to consider the way in which HollandPTC has been designed.

The Holland Proton Therapy Centre

HollandPTC is an initiative of Erasmus MC, LUMC and TU Delft. It is located by the A13 motorway on the TU Delft campus, and provides a unique opportunity to introduce technological innovations into our healthcare system. HollandPTC is a focus clinic for proton therapy, but an individual patient can receive every aspect of his or her care at HollandPTC. The vertical silos that we mentioned earlier have indeed been rotated through ninety degrees. So the centre actually looks something like a regular radiology department. HollandPTC is equipped with an extensive imaging block with a Dual Energy CT scanner, a 3 Tesla MRI and a PET/CT scanner. There is also a section devoted to chemotherapy and other interventions. In addition to two treatment rooms, there is an eye bundle for patients with eye melanoma and there is an experimental bunker for science. HollandPTC also has laboratories for biology, chemistry and physics.

In a riposte to those 'everyone-for-themselves' tendencies, HollandPTC is designed as a cooperative platform for a range of parties; there is a shared space to work on improving quality, collect evidence and build up our experience together. I refer to this as an 'open workplace'. A percentage of radiation oncologists, but also laboratory technicians and medical physicists, are seconded to HollandPTC from affiliated treatment centres. So HollandPTC is an integral part of our partners' care pathways, and proton therapy is not a 'stand-alone' phenomenon. I am very proud that our open workplace design at HollandPTC has been such a success. Currently, HollandPTC employs 21 medical doctors, mostly from large hospitals, and the HollandPTC medical staff are also employed in part by those other treatment centres. The rotation of our healthcare structure through ninety degrees, which I described in my previous inaugural lecture, has begun. Ultimately, the integration process will also need to extend to business operations, but that is proving to be more of a challenge.

The open workplace sounds wonderful, but bringing it about has been a complex exercise. Multiple cultures under one roof, making joint decisions about patient care as well as matters such as quality and safety – it might seem like an impossible task. But actually it has gone better than expected. Apparently there is something in this set-up that motivates people and makes them more inclined to learn. For everyone involved, it requires a substantial investment of time and a concerted effort to look beyond the boundaries of their own discipline and organisation. I am enormously proud of everyone who has contributed to this. And I am also convinced that this design results in better healthcare, particularly for patients. Patients are accompanied by their radiation oncologist to the new treatment centre, HollandPTC, provided with high-quality care there, and then the patient and radiation oncologist return to their original treatment centre.

HollandPTC is enhancing the added value that proton therapy can bring to patients and to society. This is our goal and what we stand for. To achieve this, the open workplace is being realised for care, scientific research and in other areas. In addition, all HollandPTC patients are being asked to participate in a cohort for data-collection purposes, and new forms of research will be applied, such as new types of randomised studies.[9]

The added value of HollandPTC is being further enhanced by a secondment from Erasmus University's Department of Health Economics. Medical Delta, the partnership between the three universities and Erasmus MC and LUMC have rewarded this workplace design by assigning two PhD students; one will investigate the cost structure of HollandPTC, while the second will create models for the cost-effectiveness of proton therapy for head and neck cancer and the brain cancer that I mentioned earlier. This will include using data from HollandPTC, data from the national proton therapy database, the Dutch Cancer Registry (NKR) and the Netherlands Comprehensive Cancer Organisation (IKNL).

HollandPTC's open workplace concept will go even further. We are also making agreements with the Dutch Health Insurers (ZN) and the National Healthcare Institute (ZiN) about their participation in our workplace. For example, we intend to hold discussions with radiation oncologists and other medical specialties about therapy displacement: which care products would they remove in order to make room for a new product? Patient associations, too, may take part in our open workplace, and HollandPTC's client council will also be actively involved in developing these new concepts in healthcare.

This same open workplace has also been put in place for HollandPTC's scientific research. To achieve this, a consortium has been set up that extends from HollandPTC to the three universities that have provided direction to the research programme through the Programme Council. With a starting budget of over ten million euros provided by a number of private-sector partners, such as Varian, RaySearch, Siemens and Philips, a scientific research programme has been established that will involve between fifty and sixty PhD students over a three-year period, spread across the three universities. Other universities have already indicated that they would also like to participate in this consortium. The research is divided between clinical, physical and biological research. The three universities involved have leading, internationally recognised researchers who have contributed to HollandPTC's R&D Programme. Thanks to them and to the quality and innovative strength of the research consortium, this is also expected to attract considerable external financing. The added value of cooperation in HollandPTC's open workplace can already be seen clearly in our R&D. And cooperation between departments and universities is, of course, a precondition for participation in the open workplace.

To provide a framework for HollandPTC's R&D programme, a master plan has been developed that includes six roadmaps. These roadmaps include technical developments, developments in imaging, the clinical implementation of innovations, biological studies, modelling, big data and cost-effectiveness and, finally, clinical studies. As I mentioned, LUMC, Erasmus MC and TU Delft all have outstanding reputations for robust and innovative research, and they are internationally renowned institutions. Their respective focuses are clearly complementary. I have heard from international colleagues that the HollandPTC R&D consortium is now seen as a giant stirring from a long slumber.

I would briefly like to mention a few of the existing research groups within our consortium. Our renowned ophthalmology departments are playing an international role in the introduction of proton therapy for eye melanoma. What makes HollandPTC special is that we are the only centre in the Netherlands that is able to treat eye tumours using proton therapy. Chordoma and chondrosarcoma are very rare and destructive bone tumours. LUMC is an international centre for these types of tumour, and has a highly effective multidisciplinary team. By including proton therapy in their range of treatment options, we expect to be working with even more international parties and to be able to make progress in this rare form of therapy. Other areas in which our universities excel include neurology, head and neck cancer, breast cancer, lung cancer, gynaecological tumours, lymphomas, urological tumours and colon, liver and pancreatic cancer. The possible addition of proton therapy for all these tumours will be investigated. Large, well-known groups from biology are involved in research into DNA repair, cell and tissue response and genetic research, among other things. Supplemented by research into big data, we are expecting significant results that may have wider applications than in proton therapy alone.

Turning to imaging, we have a Dual-Energy CT scan at our disposal. This type of scanner is only available at a few locations in the world and one of its advantages is that it enables us to estimate the precise depth of the proton depth charge more accurately. We also have a PET/CT scanner which is used for studies into response modelling, for instance. Our 3 Tesla MRI scanner is used not only for sequencing studies but also for other purposes such as Diffusion-Weighted MRI optimisation. Our close collaboration with radiology departments in both houses means that we are fully utilising all the opportunities that this equipment brings us.

Our radiation therapy equipment is also quite special. For example, we have a cone-beam CT at our disposal, which is a CT scanner mounted in the gantry. We also have an excellent separate CT scanner in the bunker. Hardly any comparisons have been carried out between cone-beam and conventional scanners, for instance. In the gantry, it is possible, in principle, to measure the depth of the protons in the body using, for example, Prompt Gamma imaging, which also enables the biological effects to be modelled. And then there is the new imaging system based on x-rays which would be used while administering proton therapy in order to monitor any movement of the tumour, and to make adjustments accordingly. This would be a huge breakthrough if it can be implemented in clinical practice.[18] Several faculties from TU Delft are actively participating in the HollandPTC consortium. They include Applied Physics, Industrial Design, Mechanical Engineering, Mathematics and Computer Science. In the last two days, we have been holding the 'HollandPTC Collaboration and Innovation Hub', at which we discussed our joint research programme. If you would like any more information about HollandPTC and our consortium R&D programme, feel free to raise your hand now. And I would like to invite you to participate in our open workplace too.

There are so many opportunities for making improvements in radiotherapy, but they will require some out-of-the-box thinking. There are also some concerns. In radiotherapy, there is a tendency to administer ever higher doses with tighter margins and in ever fewer radiation fractions. Over time, this increases the risk of serious side effects. However, we radiation oncologists do not have the knowledge or expertise to treat those serious side effects, and we cannot usually take on our own patients. And because we are struggling with the pillars that we mentioned earlier, this can sometimes lead to considerable tensions in the care chain. The future of radiotherapy can only be guaranteed through wider cooperation with other medical specialists and scientists who are willing and able to facilitate this aspect of care. We need to re-evaluate the position of radiotherapy within the care chain.

But radiotherapy is not standing still, as you will have noticed. There is a continuous stream of new improvements. But those improvements are usually new iterations of existing radiotherapy processes or equipment; and because radiotherapy is rather inward-focused, major breakthroughs are not expected in the immediate future. Innovations in radiotherapy therefore also tend to receive very little attention from the outside world. But with a different way of thinking and a more outward focus, radiotherapy could bring us some breakthroughs – for example by increasing the options for successful chemotherapy by adapting radiotherapy so that the bone marrow receives a lower dose of radiation, or none at all. Proton therapy will, of course, bring countless opportunities for achieving such breakthroughs. The same is true of surgery. By not irradiating the location of the surgery, either before or after an operation, surgeons expect fewer side effects and to achieve better results from their operations.[19] Could we see radiation therapy decisions that are determined in part by medical oncologists or surgeons? Thumbs down or thumbs up to that? I think the latter.

As for me, I am struck by the following hypothesis. In traditional photon therapy, radiation always reaches a large part of the surrounding tissue and the many blood vessels that this contains. It is estimated that a patient's entire blood volume is irradiated about three times in a six to seven-week treatment programme. Even though this is spread out over longer period and the dose is low, there is a high chance that this affects the immune system and the body's own resilience in some way. By deliberately avoiding blood vessels and areas with high blood flow, we may be able to spare the immune system some of this stress. It is becoming increasingly clear that the body's own immune system plays an important role in its fight against cancer. Experiments involving the immune trigger have revealed an excellent cancer response when the primary tumour is irradiated with a high dose and the metastases are not irradiated, or only at a much lower dose. With proton therapy and practices to reduce the volume of blood that is irradiated, I believe that major breakthroughs and advances in oncology are possible.

Another novel technique is FLASH therapy. This involves a very high dose rate, between forty and one hundred Gy per second. Initial experiments show a considerable decrease in side effects and an increased chance of successful treatment. At the moment, FLASH is only possible at proton centres that have a cyclotron. By applying this high dose rate and considerably fewer irradiation fractions, the blood is exposed to less and less radiation, possibly strengthening the patient's own immune system response.

Critical mass

The critical mass that I have been describing to you takes many forms. A proton is a particle with mass, meaning that the precise dosage and location play a more critical role than with photons. HollandPTC is located on the site of the Delft Reactor Institute: for them, a critical mass is the minimum amount of fissile material that is required to sustain a nuclear chain reaction, as well as the basis of a nuclear bomb. A critical mass is also the number of patients who need to be referred to proton therapy centres in order to make them viable. Radiation oncologists also form a critical mass in this story, just like patients, health insurers, the Ministry of Health, Welfare and Sport, Executive Boards, Deans, Supervisory Boards, overseas treatment centres and, ultimately, society as a whole. And it is very important that we understand that it is very difficult to achieve critical mass when there is fragmentation. The introduction of a new technology therefore requires a “critical mass”. This is always the foundation of any good product. Without critical mass, there is nothing and there will be no proton therapy.

Acknowledgements

HollandPTC is a marvellous organisation. I take great pride in being able to contribute to its realisation. I would like to thank all of HollandPTC’s employees for your courage in joining HollandPTC and for all the extra effort that each of you has made over recent years. It is important to mention that I include in this every seconded doctor, physicist, MBB employee, controller, lawyer, and so on. There is no ‘us and them’ in an open workplace. HollandPTC would not exist now without the efforts of all these committed individuals. Together, we have lived through the first stages of HollandPTC’s inception and those memories will always stay with us. HollandPTC includes so many people that it is not possible to thank each one of them by name in the time we have available. I apologise for this – everyone deserves to be mentioned. I am well aware of that.

My special thanks go to the radiotherapy departments that are involved. Erasmus MC, LUMC and the Haaglanden Medical Centre, in particular, are turning HollandPTC into an integrated department. This requires exceptional leadership skills from the heads of departments and management teams. My thanks to all of you.

Our current contacts with Amsterdam UMC, the NKI/AvL, UMC Utrecht, ZRTI, NWZ, Haga, Instituut Verbeeten and others are so good that I expect to be able to proceed with their further integration into HollandPTC in the near future.

Of course, many other people are also involved with HollandPTC. I owe a great debt to the members of the Supervisory Board, the shareholders, the various other boards and the Executive Board, the members of the Programme Board for our R&D Programme and to many, many others. I would like to specifically mention the R&D core team members and the R&D Programme Board members. Making strategic choices and defending them is no easy task. I want to thank all of you.

HollandPTC was established long before I became involved. At least ten years before I was appointed, various people were working hard to get HollandPTC off the ground. The fact that HollandPTC has come about at all is due to their perseverance and idealism. I hope that you can all sense the determination of today’s HollandPTC and see that your commitment and dedication is now heading towards a great future. Thank you all.

Then there are the many people from all the affiliated institutions who want to work with HollandPTC on research, clinical care or education. There are so many enthusiastic people! Unfortunately, there are not enough hours in the day or week to give everyone the attention that they actually deserve. I hope you can forgive me for this. I am very happy with all your work and dedication.

Every two weeks I meet my colleagues from DUPROTON, representing all of the Netherlands’ proton therapy centres. We have a uniquely cooperative and productive relationship. My thanks to all of you – it is only in this way that proton therapy centres can work together to make proton therapy a success.

To the members of the NVRO (the Dutch Society of Radiotherapy and Oncology), I have deliberately sought to grab your attention on several occasions- not least when I announced the end of radiotherapy for instance, but also by exaggerating our divisions. I hope that this has led to an improvement in our position within healthcare. I am grateful and proud to be a member of the radiotherapy guild.

And I would like to express my sincere thanks to all those

oncology departments that have committed so unequivocally to HollandPTC. Departments such as medical oncology, oncological surgery, ENT, ophthalmology, GE, lung diseases and many other departments are all investing in proton therapy because they are convinced of its added value. Thank you for your support.

I would like to express my pride for the way in which HollandPTC has become integrated so closely with TU Delft. It has been a little strange to set up a hospital on the campus of a technical university, but also very exciting and, above all, a very smart decision.

My thanks go to the Faculty of Health Economics at Erasmus University Rotterdam. How much I have learned from you, and how wonderful it is to have you on board. And I'm not planning to let go of you, just so you know!

I would like to thank my parents. Your unconditional dedication and trust are the foundation on which this address is built. Jan-Willem, Justus and Jasmine, you are my own critical mass, not least because of your highly original initials. And of course, thank you Mees! You are a diamond.

And finally I would also like to thank Johannes Vermeer. His games with light encapsulate what HollandPTC stands for. The girl with the pearl earring has become so popular that we are launching a webshop to sell wallpaper and cycling shirts, among other things.

And... if in the future you should ever be driving past HollandPTC on the A13 in the evening, please look out for the glowing Bragg peak on the front of our building.

Final word

I am grateful that in my position as a professor at TU Delft, Erasmus MC and LUMC I am able to contribute to the introduction of proton therapy in the Netherlands. This really is my dream job and a wonderful challenge. HollandPTC is maximising the added value that proton therapy can bring to patients and to society. This is our mission. This is what we stand for. And my personal mission is to transform the vertical columns of our radiotherapy departments into a patient-centred open workplace.

I have said my piece.

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