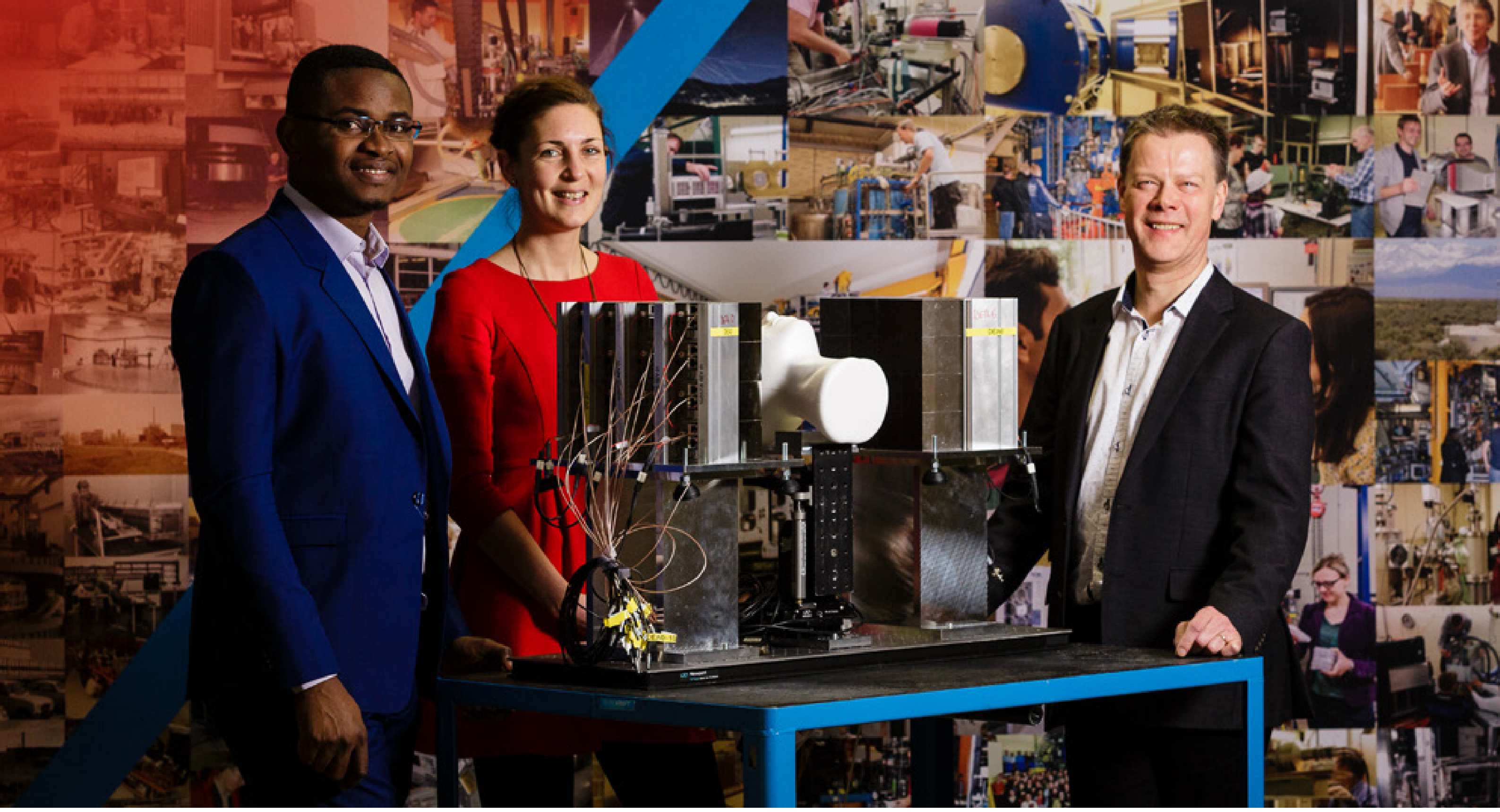


Ikechi Ozoelam, Antje Knopf and Peter Dendooven

Research at KVI-CART could make proton therapy even more accurate:

Short-lived isotopes give real-time feedback on proton therapy

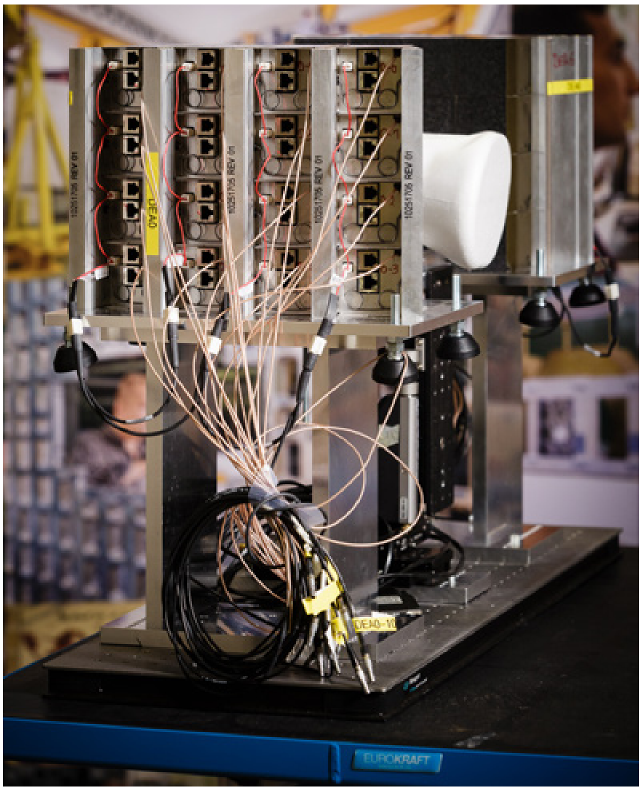
Proton therapy is a more effective and accurate method for treating certain cancer patients. The Groningen KVI-Center for Advanced Radiation Technology (KVI-CART) is looking for ways to monitor this treatment more efficiently and even to make real-time adjustments.

In early 2018 the UMCG in Groningen became the first place in the Netherlands where cancer patients could be treated using proton therapy. The previous two years saw the construction of a proton therapy center where, by means of a particle accelerator, the proton beam necessary for this treatment would be generated.

“Proton therapy is a fractionated treatment” says Antje Knopf, researcher at the UMCG proton therapy center. “That means that patients undergo daily treatment sessions for about thirty days in a row. Patients used to have to go abroad for this proton treatment, and the time period involved meant that could be a real strain. Especially when you consider that this proton treatment is often used to treat children.”

More accurate

The advantage proton therapy offers over conventional radiotherapy is the accuracy with which a dose can be administered to a tumor. Knopf continues: “With radiotherapy, which is the usual option in the Netherlands, we use photons. And the energy this releases decreases exponentially the further the particles enter the body. In this form of therapy much of the energy is lost to surrounding healthy tissue. With protons the release of energy follows a different pattern: their maximal energy is released at a specific point, the so-called Bragg peak. By varying the energy of the protons, it is possible to position this Bragg peak inside the tumor. This limits the amount of radiation



The test set-up used by Peter Dendooven and Ikechi Ozoemelam in the laboratory: two PET ring elements surround a (polystyrene) model of a human head.

in surrounding healthy tissue. This is why proton therapy is especially used to treat children or patients who have tumors close to critical organs, such as eye tumors or tumors located in the head or neck area." "So, as you can see, it's great technology, but we are still not using it to its full potential" states Peter Dendooven, associate professor of Medical Physics at KVI-CART, part of the University of Groningen. KVI-CART has its own cyclotron, a particle accelerator which accelerates protons and heavier ions to a specific energy level.

Real-time adjustments

Dendooven and his group are researching whether it is possible to monitor proton therapy as it happens, which in turn would make it possible to make real-time adjustments to the planned therapy. There are a number of uncertain factors. "The position of the patient's body in relation to the beam, for example. But especially the question of where exactly the peak of the proton beam lies. That is not 100% certain. Because it is necessary to radiate the entire tumor this uncertainty is compensated for by having a safety margin around the tumor. This margin can be quite large, in which case affecting surrounding healthy tissue is unavoidable. This means the protons cannot be used to their full advantage." Expanded by Knopf: "And not only that: some cases can be especially difficult to treat, for example when a tumor moves as a patient breathes."

Smaller margin

According to Dendooven "The road ahead is made up of two different paths. On the one hand we will try to reduce the number of uncertainties involved in the treatment as much as possible, for example by having excellent imaging to guide us. On the other hand, we want to examine how we can more accurately measure exactly where the protons stop during treatment." How exactly that can be done is the research question that Dendooven and his group are working on. "Putting a detector inside the patient just can't be done in a really practical way. Because the proton beam stops in the patient, in contrast to radiotherapy, you have to look for another option. The proton beam collides with atoms in the body. In the reactions that then take place meta-stables isotopes are formed which transition to its ground state by releasing gamma radiation-is released: photons with a high energy value which can be detected outside of the patient. By measuring

Peter Dendooven, associate professor of Medical Physics at the KVI-Center for Advanced Radiation Technology (KVI-CART), part of the University of Groningen

Antje Knopf, associate professor, Department of Radiation Oncology, UMCG

this secondary radiation, it is possible to determine where the protons are releasing their energy.

Capturing isotopes

"By measuring secondary radiation, you are bring, as it were,ing the isotopeswhich are emittingthatradiation into the picture, and theyisotostopes which are formed by the collision ofthe protons against (for example) carbon atoms," continues Dendooven. Those isotopes are formed along the entire path of the protons. Depending on the composition of the tissue there are differing quantities of carbon, oxygen, calcium or phosphorus and therefore different isotopes in differing quantities.
Positron Eemission Ttomography (PET) can be used to measure these photons released during the decay of these positron emitting Isotopes and generatee an image of the isotope locations, and therefore indirectly form an image of the proton beam. "This is already being done in a number of places around the world," says Dendooven. "But all these cases involve PET detection of isotopes with a relatively long half-life of between 2 and 20 minutes. Isotopes such as ^{15}O, ^{11}C or ^{30}P (see box). This means that scanning times are long and, because you need to wait for the isotopes to decay, there is a delay in producing the required information." And that is where the technology falls short: there is still no real-time feedback for the treatment in progress. "You have to take the half-life of the isotopes into account. That delay is a problem" explains Dendooven. "Such isotopes also diffuse within the body, in what is known as the biological wash-out. This is a normal biological process, but it clouds the picture."

Short-lived isotopes

Dendooven's group think they have found a solution to the long-lived isotope conundrum. "Now we are focusing particularly on short-lived isotopes," explains Ikechi Ozoemelam, a PhD student in the KVI-CART's Medical Physics department. "This kind of isotope decays relatively quickly, and this shorter time frame gives them less opportunity to move around. In addition, the time delay is minimal. Our group has previously examined which short-lived positron emitters are produced in sufficient quantities by proton therapy to be useful in monitoring the therapy."
Detecting short-lived isotopes during proton therapy is in itself a challenge. This led to Dendooven getting in touch with the R&D department of Siemens Healthineers in Knoxville (USA). "Their PET detectors could be the answer to detecting these signals," explains Ozoemelam. "We've constructed a set-up with two

Short- and long-lived isotopes

^{15}O, ^{11}C and ^{30}P are relatively long-lived isotopes with a half-life of between 2 and 20 minutes:

Oxygen-15 (^{15}O) is formed by the reaction of protons on stable oxygen (^{16}O) and has a half-life of slightly more than 2 minutes, after which it decays with a positron emission to more stable nitrogen-15. **Phosphorus-30** is formed by the reaction of protons on stable phosphorus (^{31}P) and decays to ^{30}Si (half-life 150 seconds). **Carbon-11** (^{11}C) is formed by the reaction of protons on both stable carbon (^{12}C) and oxygen (^{16}O), has a half-life of 20 minutes and thereby decays to boron-11.
Nitrogen-12 (^{12}N) on the other hand has an extremely short half-life of just 11 milliseconds. The unstable nitrogen isotope results from proton capture in stable carbon, and decays through positron emission to ^{12}C.

(partial) PET detector bankss." Dendooven: "The detectors which would usually be installed in a clinical PET scanner have been modified so they can be quickly turned on and off. That is a necessary step to protect the detector, because otherwise theyit would effectively be 'blinded' by the high level of prompt radiation (not from delayed positron decay) when the proton beam is turned on. When the proton beam is disabled the detector has to be turned on again immediately in order to register the signal of the short-lived positron emitting isotopes. As the proton beam is transmitted in pulses, it is vital that the PET detector can be turned on and off extremely quickly, so it can take measurements between the pulses of the beam."

Looking for a signal

"Our focus is now on ^{12}N, a short-lived isotope of nitrogen which is formed by the proton beam coming into contact with carbon. It has a half-life of 11 milliseconds," says Ozoemelam. "We are not looking for the best image, but the best correlation between the image and the position of the Bragg peak. In other words: we want to demonstrate that the isotope signal we detect is an accurate indication of the location of the proton beam and in particular the Bragg peak." If that correlation can be clearly demonstrated it will have several implications for clinical practice, continue Knopf and Dendooven. "The therapy can then focus on a smaller area, which means less tissue damage and fewer side effects," Knopf explains. "It could also be used to treat tumors which currently can't be treated using proton therapy because they are even closer to vital organs." Dendooven can already picture the next step: "Real-time adjustments. In other words, if you see that the beam is going too deep, you can adjust the energy and thereby the position of the Bragg peak during a treatment session. This would allow us to make treatment even more precise." Dendooven thinks that this method could be fast enough for this kind of real-time feedback.

From graphite to patient

At the moment Ozoemelam is carrying out studies on graphite (which is 100% carbon) and Plexiglas, which is a more complex material, consisting of a polymer containing carbon, nitrogen and oxygen atoms. "That should enable us to determine the proof of concept", says Dendooven. But this research doesn't stop there. "We also want to examine the possibilities for further development, using more complex physical models, or phantoms, to create an even more realistic picture of the secondary radiation:. From less homogeneous materials to, ultimately, real tissue. Another future step would be to set up semi-clinical studies, involving taking measurements in patients undergoing proton therapy – not yet with a view to adaptive treatment, but in order to assess the concept of real-time monitoring."

Ikechi Ozoemelam, PhD student in the Medical Physics group at KVI-CART.

The competition

There is also the competition. Dendooven: "There are definitely other groups who are doing similar research. But we are the first, and up until now the only ones, who are working with short-lived isotopes. Most detectors are not up to the job, because the radiation needs to be measured as soon as the proton beam is turned off."

When patients will be able to benefit fromreap the benefits of this will entirely in practice depends entirely on the further progress of the research. Knopf: "Even if the first tests which are carried out on a handful of patients are positive, it will still take a couple of years to develop the necessary equipment, with all the required validations and approvals. But it could be a first step towards a broader application of proton therapy."