



Maastro and Varian have launched new brachytherapy applicator aiming to have a revolutionary impact on rectal cancer treatment

A new rectal applicator

Many patients with rectal cancer will at some point require surgery – with all the related risks to their quality of life, such as having to live with a stoma¹. However, thanks to a joint innovation by Dutch cancer radiotherapy clinic Maastro and Varian Medical Systems, more radiotherapists can now access a new type of treatment which may substantially lower that risk².

When a patient has rectal cancer and there's a high likelihood of a relapse, the standard procedure is to administer external beam radiotherapy, sometimes in combination with chemotherapy, followed by surgery. "Removing rectal tumors surgically often has a huge impact on a patient's quality of life. It may affect bowel function, sexual health and some patients even have to live with a stoma", says Maaïke Berbée, radiation oncologist at Maastro.

The catch

"Some years ago, several clinical research groups noticed that for a sizeable subgroup of these patients, radiotherapy alone appeared to be sufficient to make the tumor disappear altogether"³, says Berbée's fellow radiation oncologist Evert van Limbergen. "That made us wonder whether it might be possible to treat more patients without the need for surgery." However, there was a catch: "Complete remission through radiotherapy at the time was only observed in 15-20% of patients and it was not possible to predict for which patients this might work. So, the big question was whether we could find a way of boosting this success rate."

Skepticism

Van Limbergen and Berbée started looking for ways of delivering radiation closer to the tumor,



Radiotherapy clinic:
Interviewees:

Maastro
Maaïke Berbée, Evert van Limbergen,
Frank Verhaegen and Marco Laumen
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inside the patient's body. Berbée: "At the time, in 2016, we heard about impressive success rates, of up to 80%, with the Papillon method." This method uses a specialized device to place a low-energy (x-ray) source inside the patient and deliver the radiation directly to a rectal tumor. However, the figures quoted were hard to substantiate, and accordingly were viewed with skepticism by some. "Based on the available data, it was hard to verify the dose delivered to the tumors, or to accurately interpret the outcome data. Anyhow, we felt that the results were credible, and that this would be a valuable treatment strategy for many of our patients."

Specific applicator

Back in Maastricht, they sat down with Professor Frank Verhaegen, Head of Maastricht's Physics Research Division, to discuss the possibilities. Verhaegen: "Investing in a Papillon device was not an option, it's very expensive technology. On the other hand, we already had our own equipment for standard High Dose Rate (HDR) brachytherapy, in which high-

energy radiation from an external source (an afterloader) is delivered directly to the tumor through tubes and catheters. So, it made sense to look for ways to use that existing equipment and see if we could adapt it for treatment of rectal cancer."

This would require designing a very specific applicator, allowing dose delivery with sub-millimeter accuracy. After all, the energy levels used in HDR brachytherapy are seven times higher than those of the Papillon method – perfect for an effective treatment of the tumor, but potentially posing a much higher risk to the surrounding tissue, if not administered accurately.

Collaboration

Verhaegen: "So we had to come up with an applicator containing multiple catheters for the highest possible precision. At the same time, the diameter and the shape of the applicator would have to be suitable for positioning via the anus and as closely as possible to the tumor, whatever its position is in the rectum. Fortunately, our clinic has extensive experience with so-called Monte Carlo simulations, which enable us to run very precise simulation of all kinds of radiation scenarios, helping us to come up with an optimal design."



Very early on in this process, Maastro invited Varian to collaborate on the development of this applicator. "We have been working with Varian equipment and applicators for years. And while we registered the original patent application ourselves, developing this idea into a commercially feasible applicator that meets all regulatory requirements and can be manufactured at scale, requires specific expertise. After all, an innovation such as this one is only going to be worthwhile if the technology can be used by radiotherapists in as many clinics as possible."

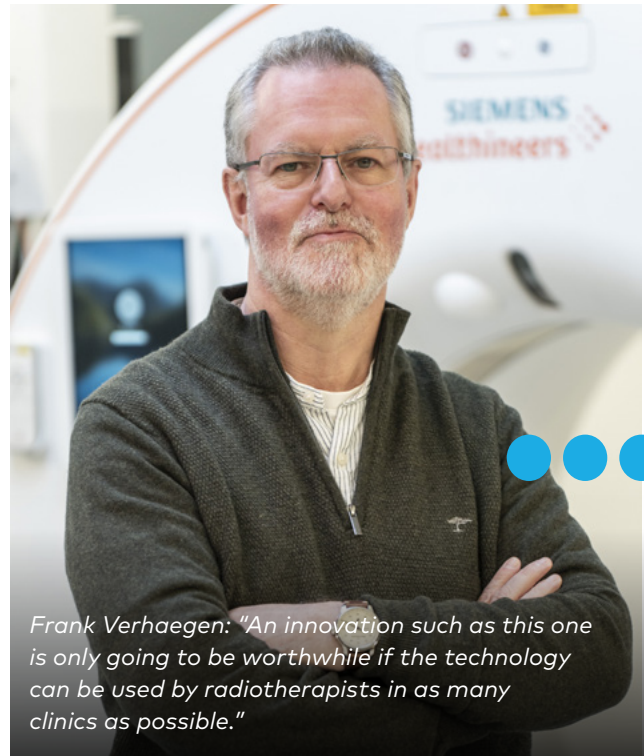
Many more patients

Varian quickly recognized the potential benefits of this initiative, says Marco Laumen, Manager Advanced Applicator Development. "It would open up a completely new kind of treatment to many more patients. Instead of requiring an expensive device exclusively designed for treatment of rectal cancer, this applicator could work with our standard afterloader technology, which is used by clinics all over the world."

Over several years, Maastro and Varian collaborated to refine the applicator's design, going through various iterations. The result is Varian's first 3D-printed applicator, designed to ensure the largest possible contact area with the tumor and a uniform dose distribution, without blind spots. In terms of dose profile (the spatial distribution of radiation), the applicator can match x-ray brachytherapy ⁴. The device is also fitted with a shield that protects the surrounding tissue from radiation and can be used with a proctoscope for visual positioning.

Ready for clinical use

On a personal level, Laumen also enjoyed the opportunity to be involved with the development of this applicator. "It's not



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every day that you get the opportunity to work so closely on addressing an unmet clinical need, and with such a direct impact on patient well-being. We came across all kinds of challenges, some technical, some regulatory or logistical, but we managed to overcome them all, resulting in an applicator that has recently been CE certified and is ready for clinical use."

Crucially, this milestone follows the recent publication of the OPERA randomized trial ⁵, which has demonstrated that the results of localized x-ray brachytherapy are superior to those of external beam radiation. In other words, the uncertainty that surrounded this approach back in 2016, no longer exists. Berbée: "And that means that we can limit the scope of our own clinical trial, scheduled to start in 2024, to demonstrate that our applicator can be used to provide a clinically feasible treatment that is similar to the Papillon method."

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Evert van Limbergen: "It's really a textbook example of successful cooperation."

More clinical benefits

Berbée and Van Limbergen are convinced that equaling the OPERA study results will only be a first step, and there is plenty of scope for achieving even more clinical benefits. "We'll be looking into ways to tailor dose delivery to individual tumors and broadening the indication area, using this treatment for (much) larger

tumors and coming up with even more effective and individualized treatment strategies, perhaps in combination with external beam radiotherapy or chemotherapy."

The response from the global radiotherapy community so far has been enthusiastic. Berbee: "People are really waiting for this type of innovation. If you look at current research on rectal cancer treatment, the focus currently is very much on strategies enabling organ preservation. So, every treatment option that helps to avoid the need for surgery is very welcome."

Career highlight

All in all, it has been a hugely rewarding experience for all those involved, says Van Limbergen: "I really enjoyed the collaboration with Varian and we're really proud of the results. This was the first time that we designed something from scratch and took it further, step by step. It's really a textbook example of successful cooperation. Getting this product to the market, at a time when the clinical benefits of localized radiation for this group of patients have so clearly been demonstrated, is very special. I'm pretty sure that we'll always look back on it as one of the major highlights of our careers."

Disclaimer: the information captured here represents the genuine experience of the attributed individuals and may not represent the views of Varian. Your results may vary.

1. 'The impact on health-related quality of a stoma or poor functional outcomes after rectal cancer surgery in Dutch patients: A prospective cohort study', European journal of surgical oncology, 2023 Sep;49(9):106914
2. 'Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial', Lancet Gastroenterol Hepatol. 2023 Apr;8(4):356-367.
3. This was recently confirmed by the study referenced under 2.
4. In terms of biological equivalent dose absorption, the applicator can boost to an astonishing dose ranging from 60 Gy to a total of over 200 Gy EQD2, depending on the thickness of the tumor,
5. See the study referenced under 2.