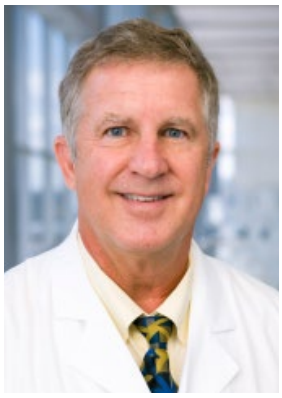
PULSAR-integrated Radiotherapy—A new approach for treating patients

By Tammy McCausland

Conventional radiotherapy treatment offers a standardized approach to treatment, typically 30 minutes a day over several weeks. The duration of treatment can vary according to the patient's type of cancer and responsiveness to treatment. By contrast, stereotactic ablative radiotherapy (SABR) is a very focused and potent radiation treatment that generally comprises three to five treatments over a period of five days.



Dr. Robert Timmerman

Adaptive radiotherapy is changing the treatment paradigm yet again. It's defined as "changing the radiation treatment plan delivered to a patient during a course of radiotherapy to account for temporal changes in anatomy (e.g., tumor shrinkage, weight loss or internal motion) and changes in tumor biology/function (e.g., hypoxia)." [1] Personalized Ultrafractionated Stereotactic Adaptive Radiotherapy (PULSAR) is an application of SABR, developed by Robert Timmerman, M.D., and his colleagues at UT Southwestern Medical Center. PULSAR entails giving patients "only a few large dose 'pulses,' delivered with sophisticated, image-guided precision, at least a week, perhaps even months, apart. These 'split treatments' are a radical break from the daily, long-course, conventional radiation treatments lasting six to nine weeks."[2] For patients with large tumors, the PULSAR treatments are given two weeks apart to try to get the tumors to change more quickly. If the tumor is less threatening, patients are treated once a month. PULSAR is mostly used in Stage IV, but it's also been used in Stage I. "It's better to treat a big tumor once when it's big, then once when it's medium, and once when it's small," said Dr. Timmerman, professor of radiation oncology and neurological surgery, and member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center.

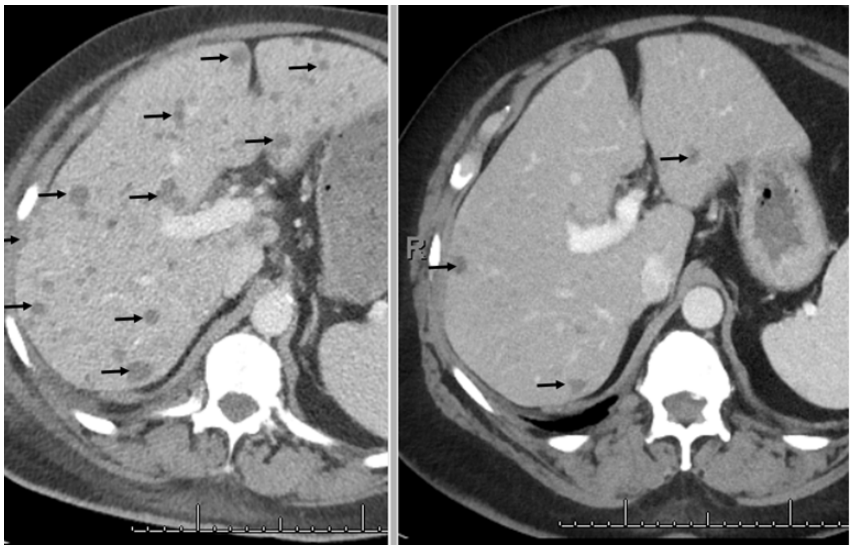
As Dr. Timmerman explained, the primary objective of using PULSAR was to see if they could get the tumors to shrink, so that they could treat smaller fields with the next treatment. He differentiates "pulses" from fractions. "We want people to not get fractions anymore. We want them to switch to pulses, and pulses are independent treatments. They're replanned every time," he said. "It's almost like you're approaching a new patient in a new circumstance. We realized that besides just reducing toxicity, which is the first attribute of PULSAR, it also gave more opportunities to adapt beyond just the shrinkage of the tumor."

Researchers have found that PULSAR treatments are less toxic and also provide oncologists with the opportunity "to fine-tune treatment after the new machines' imaging shows the tumor's changed shape, size, position, and its reaction to radiation." [2] "It turns out that if you give a SABR treatment and split it with a long period in between, it's very unlikely that the tumor would ever grow. It's just going to be in remission, maybe even shrinking, maybe even falling back, so there's really not a penalty to separate SABR treatments," he said.

A tumor will sometimes change its whole character from one pulse to another. After one pulse treatment, several things may be observed:

- The tumor itself might necrose, or it might become more or less hypoxic.

- The tumor might change its signaling, using different ways to try to invade the immune system, for example.
- The tumor microenvironment might change where new cells, ones that weren't there before, are infiltrating, which may or may not help.
- Clinicians may be able to check if the treatment's effective, to determine if there's a decline in the number of circulating tumor cells in the blood, for example.
- Clinicians can assess how well the patient is tolerating the treatment.



Left panel: Liver CT scan of patient with metastatic melanoma originally responding but now rapidly progressing despite standard therapy using dual agent ipilimumab and nivolumab immunotherapy (arrows to several of the larger lesions); Right panel: Same patient 3 months after PULSAR treatment combined with single agent nivolumab showing dramatic tumor reduction both in number and size of lesions. Along with the immunotherapy, the PULSAR provided a "vaccination" effect separately treating one liver metastasis, a single spinal bone metastasis, and a single skin tumor each separated by several weeks. (©2021 Dr. Robert Timmerman, UT Southwestern Medical Center)

"All of these are called features, and all of the features could be prognostic and help guide the therapy as it's going along, so this is a more effective adaptation than people had postulated just with shrinkage of the tumor as the only feature," said Dr. Timmerman.

Another advantage, Dr. Timmerman explained, is that "PULSAR might work better in concert with the immune system—especially with immunotherapies that are now quite exciting—in that the PULSAR acts almost like a vaccine. Vaccines are not given daily, they're given monthly, like the COVID-19 shot followed by the booster a month later. If the pulse is acting like a vaccine, then you shouldn't give it daily." They did experiments in animals that confirmed their hypothesis; now, they're planning clinical trials to try to understand the phenomenon better. A study[3] published in August 2021 in the International Journal of Radiation Oncology, Biology, Physics, showed that PULSAR "achieved better tumor control by giving a-PD-L1 therapy during or after radiation, and spacing fractions 10 days apart rather than traditional daily fractions." The study researchers found that when the pulses are 10 days apart, the drug therapy is helpful.

"Adapting to different features that change over time is what we're interested in now, to see how we can exploit this," said Dr. Timmerman. He explained that if they can determine Patient A is having a certain change in their features that would predict the possibility of recurrence, then a clinician might add therapies or intensified therapies. In comparison, treatment of another patient with the same tumor might go really well, and there's no need to intensify the treatment. "We're looking to see if we could get to the point where we're giving no more or no less treatment than a specific patient needs. In other words, avoid a one-size-fits-all therapy, which is what cancer therapy is now," he said.

The researchers are also hoping that with PULSAR, they can achieve the elusive abscopal effect, which occurs, for example, if a tumor treated in the leg somehow shrinks or changes a tumor in the lung. "That adaptive immunity is the only thing that could explain the abscopal effect. We rarely see it. It's exciting when we do, but we rarely see it with conventional radiotherapy," said Dr. Timmerman. "What we're trying to do in the research is to see it all the time, figure out the circumstances in which it becomes a common outcome, rather than a rare outcome, so it's a systemic effect."

PULSAR is an approach, not a technology, but it requires an MR-Linac or the RefleXion X1 because of the need to image and replan a treatment quickly. It also requires an infrastructure to collect, store and analyze features, to provide a directive of what to do next. The features include blood and tumor markers; noting weight to see if the patient's gaining or losing weight; repeat imaging to see if the tumor is changing its blood flow and/or shrinking; and repeat biopsies to tell whether a patient's on a path to success or failure. Collecting features for a specific patient's tumor along the way enables personalization of the therapy. Interrogating all these features requires an analytic process to determine what to do next.

Dr. Timmerman and his research team plan to collect and publish data to show what PULSAR can achieve. With SABR, they presented at meetings and published results with long-term follow-up that showed it's more effective and less toxic than conventional radiotherapy. "We've got to do the same thing with PULSAR, and just like SABR was an approach using existing technology, PULSAR's an approach using existing

technology. In Texas, practically every center does SABR. That was not the case 10 years ago," he said. He hopes to achieve the same with PULSAR.

Radiation devices have broad scope applications for their FDA approval. SABR is five or fewer treatments for a whole course of therapy, but the CPT codes don't specify the frequency of treatments, so they could be separated by an hour, a day or a month. The radiation oncologist decides. Dr. Timmerman said they can readily justify reimbursement for the radiation, but he's not sure currently about reimbursement for the other elements, such as mining imaging, frequent imaging during treatment and repeat biopsies. "None of this is commonly used, so I don't know how that will play out. We're doing clinical trials now where we try to get external funding to pay the other elements," he said. "SABR, which is the root of PULSAR, is one of the most cost-effective treatments there is. A course of SABR for prostate cancer is absolutely one of the cheapest and most effective treatments that a patient can get. We're not trying to be the cheapest. We're trying to be the best."

Dr. Timmerman said radiation oncology is a traditional and cautious field. "It's good to be cautious because radiation can be dangerous. The downside is that the modality never reaches its potential if we're so cautious," he said. "We still make progress in the field. PULSAR is an example of one of the coolest concepts and most effective potential treatments there can be, and it's radiotherapy."

PULSAR aligns well with the trend toward hypofractionation. It also aligns with precision medicine's goal of making treatment unique to each patient. "PULSAR takes personalized medicine to another level. Most personalized medicine is only up front. The tumor is sequenced upfront to find what mutations it has and then a drug is selected that is useful with that mutation. In some patients it works, and in some patients it doesn't, whereas PULSAR keeps interrogating, even during the treatment, not just at the beginning but even during the treatment," he said. "I would love to get to the point where we're giving no more or no less therapy than the patient absolutely needs. If we could get there, then we would not only be more effective at curing cancer, treatments would be way less toxic."

References:

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