

Interview with Robert D. Timmerman

Professor of Radiation Oncology and Neurosurgery, Effie Marie Cain Distinguished Chair in Cancer Therapy Research at the University of Texas Southwestern Medical Center in Dallas, Texas, USA.

LF: Professor Timmerman, shall I start by asking you how it all began?

RT: I decided to attend the first course ever offered on extra-cranial stereotactic radiotherapy in Sweden. Ingmar Lax and Henric Blomgren from Karolinska were the pioneers. None of the senior faculty at Indiana University wanted to go to Sweden in middle of winter because it was cold and dark, but I went. And I was amazed by the people, the country and the doses they used for this new, “crazy” treatment.

We thought the treatment needed to be more formalized. To start, we needed a clinical model and dosing schemes that would be logically escalated to understand tolerance boundaries. So in the US, we performed a phase I study, using motion control and management, improving immobilization, but no image guidance, and did a treatment that was biologically different from the typical treatment for a lung cancer. We picked lung cancer as the clinical model over the previous clinical indications, like unresectable hepatomas and metastases used in Sweden and in some other countries. The trouble with hepatomas and metastases was that most patients died too quickly, prior to when late toxicity would manifest. So, in an era when we had no idea what doses to give, picking a model where patients would live long enough to experience late toxicity was critical. With unresectable hepatomas, or other inoperable conditions, the likelihood of a 1-year patient survival is pretty low. Administering, say, 14 Gy per fraction to a liver tumor does not allow determining whether that dose is tolerable or not, as most patients die at approximately six months. Early stage lung cancer at the time had control rates ranging from 30% to 50%, yet, half of those patients survived two to three years, so we thought that early stage lung cancer would be a good clinical model to test this new therapy, hence we proceeded with the protocols and the dose escalating studies. According to the United States’ billing codes, you could give between 1 and 5 treatments, so we just picked the middle, 3, and wrote the clinical trials escalating the dose. This was on a US NIH grant.

LF: You have been one of the first radiation oncologists to perform radiation oncology on extra-cranial disease; you are one of the founders of stereotactic body radiation.

Our team had plenty of experience treating intracranial tumors with radiosurgery. The early focus outside the brain was lung cancer. And yet, I am not a professional lung cancer doctor. But we used lung cancer to establish some clinical formalism to test the therapy. We are proud that we performed systematic testing with a logical treatment approach. Instead of just picking a dose and treating everybody with that, we tried to determine what was the best dose to use.

Most of the centers performing the treatment early on did not perform a phase 1 clinical study, though. Phase I study means you escalate the dose systematically until you reach toxicity. There had not been many phase I studies in radiation oncology at the time. When we first designed the lung protocol in 1998, we started out at 24Gy in 3 fractions, which today sounds sort of weak, but at that time it was a potent dose. We treated a number of patients with that dose, then we escalated to 30Gy in 3 fractions, 36Gy in 3 fractions... When we reached 42Gy in 3 fractions, we were getting quite nervous because these were higher doses than ever experienced, so I called the people who ran the grants for the Government here in the US and said that I wanted to stop the dose escalation. But in most medical oncology drug trials, when they escalate the dose, they keep going until they hit the maximum tolerated dose (MTD), and

then back off one step. In the grant we said we'd escalate until we found the maximum tolerated dose, so the answer was: "We paid you to find the MTD, so go ahead and find it".

So we kept on escalating all the way to 72 Gy in 3 fractions, which I suppose is the highest dose anyone has ever delivered. And it turned out it was too toxic. So we backed off 2 levels, down to 60Gy in 3 fractions, which ended up being the dose we used in our RTOG trials.

LF: What about your colleagues, the other radiation oncologists, were they interested and supported you or were they too scared of toxicity?

We were in a horrible position, n. 1 because in our training you are taught to avoid hypofractionation, n. 2 because this is a very cautious field, and when they heard about the doses we were delivering, the reaction in the radiation oncology community was mostly very negative. We were unable to publish our reports in American journals. Although they were well-conducted phase I prospective trials, they were rejected many times, because, even though the science was valid and what we were doing was reasonable in terms of patient protection, the field was very bothered by this, to a degree that is still disappointing. But finally, we got them published, and then we decided that we had to perform a phase II study on a larger scale, and that's when we starting our RTOG trials.

LF: Nowadays your studies are among the most cited, because you have a lot of experience in this field. Today it is totally different. Your experience, in my opinion, is at the basis of radiobiology and clinical decision-making for a variety of conditions and hypofractionation.

You're kind to say that... People eventually started being more willing to consider hypofractionation. Initially the reaction was very negative, but younger doctors started to give it a chance and fortunately, even though slowly, we were able to enroll to the RTOG trials. The first trial was a big surprise, because the control rates at 60Gy in 3 fractions were phenomenal. We had control rates that were never heard of before. At three years, only 7% of the patients had a failure. Secondly, despite the dose, there was no high-grade toxicity, as long as you did not treat tumors in the central part of the chest.

LF: Did you treat these patients with Elekta instruments, or other machines?

In the RTOG trials, any equipment could be used to do the treatment: "This is not about the machine, it's about the treatment".

LF: True, although in my opinion, machines play a role. CyberKnife, for instance, is a safe instrument for hypo-fractionation, as it enables monitoring the tumor, the tumor site, and be sure about the real dose to PTV. Also Varian now...

I don't disagree with you, I have a CyberKnife here too. Nonetheless I still think that it's not so much the equipment, it's the approach, in particular with hypo-fractionation. Proton therapy, when it was first introduced, was wisely used by neurosurgeons to perform hypofractionation. Lars Leksell used protons to do the early hypofractionated radiosurgery in the brain as early work in eventually developing the Gamma Knife. In contrast, radiation oncologists used protons to give the same old conventional fractionation in the body without regard to proton's higher quality. Hypofractionated radiosurgery in the brain has evolved to one of the most important and successful therapies. But for using conventional fractionation in the body the scientific community is wondering whether protons are valuable or not, particularly to treat organs like breast, prostate, lung... I personally think that there was a rather dramatic mistake made by radiation oncologists when they got better technology - protons are better technology, CyberKnife is better technology, image-guidance is better

technology - the question is: "What are you going to do with that technology: are you going to go on performing the same treatments that you have been performing for years, maybe to a little higher dose, or are you going to do something totally different, like hypo-fractionation?" When you have better equipment, like the CyberKnife or protons, you need to do something special with that. In the early days, we did not have any image-guidance, all we had was this body frame. I am glad now, that I have more technology that I can harness to do more sophisticated treatments. Yet, things like 4DCT make your life so much easier, because you can see the residual tumor motion. So, I love the technology, but the conduct is still more important. You could have used all this technology to give more treatments at 2Gy per fraction, but I think that would have been a fundamental mistake. So we hypofractionated.

LF: What is, in your opinion, the future of hypo-fractionation?

It is mostly the treatment of metastasis. We picked a primary early stage lung cancer as our initial clinical model, and then we moved on to treat primary prostate, pancreas, breast etc., but I still think that the future of radiotherapy is metastatic cancer beyond palliation.

LF: For oligometastatic patients, or to delay the fatal event?

I think there is a good rationale for treating metastatic disease. People die of cancer, because tumor cells get so invasive in the organ system that the organ system fails. You can look at it in different ways, you could say: "I am going to debulk the tumor in the most critical organ system, so that the patient stays below the threshold that would be deadly". Or you can say: "I am going to treat oligometastatic cancers to eliminate every bit of gross disease in the body." Or you can say: "I am going to treat some tumors, hoping to stimulate the immune system, and then give a systemic therapy that would bolster the immune response to achieve an abscopal effect." But the point is, we can find a rationale and be systematic. When we first started doing hypo-fractionation nobody would believe us, we could not publish our papers, but when they finally saw that these were well-conducted clinical trials, they had to publish them. Same thing with metastatic disease. The biggest mistake we could make, is to just treat people off clinical trial. Instead we need to implement clinical trials and show the benefits, whether it's a survival benefit, a progression-free survival benefit, or improved quality of life.

When you first built your team, were physicists interested in this new type of fractionation, in the possibility to offer different types of solutions? What was their attitude?

In terms of quality assurance, physicists have improved the testing they perform to make sure that everything is right, so physicists are integral to making sure that the delivery of hypo-fractionation is at a high level. The trouble with conventional fractionation - which I call forgiving radiation, as it forgives mistakes, inappropriate fields, poor QA, and even improper dose. Hypo-fractionation is a more effective treatment, but it is also potentially very toxic, therefore everything has to be exact. It is not forgiving.

The other thing is the biology. In the past physicists described the biology of radiation - the linear quadratic modelling and different normal tissue complications probability formalism physicists developed. They used rather crude estimations in modeling. I think that this therapy has really called that into question. Even with DNA damage not different from conventional fractionation, with hypo-fractionation there are many other biological effects occurring after a threshold dose. In the past we thought that radiation effect was always related to the DNA damage, but there are many other effects that radiation causes in tissues, that have nothing to do with DNA damage in the tumor. And many of these do not occur until a threshold dose. Let's say the threshold dose is 1Gy, then you'll see it when you give conventional fractionation, because conventional fractionation is at 2Gy. What if one of these

effects occurs only at 6Gy or 10Gy? There are many biological effects that have been recognized since we started performing SRS - many related to the tumor vasculature, to apoptosis, to the immune stimulation - you just don't see them at 2Gy. So the old models, like the Lyman-Kutcher model of normal tissue toxicity in the liver, are totally inadequate to describe the effects of SRS. This is a wonderful opportunity for biologists to get involved and for physicists to rethink their approach. For example, linear quadratic modeling is not so useful as it might have been for conventional radiation. A lot of people are offended when I say that, but I think that young investigators will come up with new ideas. Hypo-fractionation gives a degree of freedom to explore new opportunities that we would have never been able to explore in an era of poor technology, where all you could do was conventional fractionation. Instead, in an era of image-guidance, protons, carbon, the degree of freedom in stimulating these threshold effects goes dramatically up. I find this very interesting and fascinating and hope that more smart young people get involved, because I think we are just scratching the surface of what could be accomplished in radiation. The potential of radiation, to kill cancer without hurting patients, is so dramatically better than any other therapy, we just need to fully exploit it.

LF: You have opened a new era...

I'm proud that our team insisted in using a strict conduct. We picked the clinical models and tested them with prospective trials. In an era where people are skeptical, you have to be a clinical scientist first.

LF: Thank you very much for spending time with us and for your insights, we really appreciate your time.

Thanks for having me Laura.