Interview with Prof. John Adler

Professor of Neurosurgery & Radiation Oncology, Stanford University, USA

Hi John, tell me please about the beginning of your studies!

In 1985 at Mass General Hospital Raymond Kjellberg had a big clinical practice treating AVMs with proton radiation, the very same location where Tony De Salles kind of started. Although I was just a resident at MGH, mostly spending time in the operating room, I was able to get some exposure to the clinical application of proton irradiation very early in my career. I only got to meet with Kjellberg occasionally, yet I still got to witness him successfully managing the toughest brain AVMs in the world. While Kjellberg's work was rather misunderstood by his MGH neurosurgical colleagues, he was adored by Ray Adams, who by all measures was one of the great neurologists of the 20th century. Adams was a big fan of Kjellberg, and since I was a huge fan of Ray Adams, I indirectly came to respect Kjellberg's work. Nevertheless, during my time at Mass General, I did not fall in love with radiosurgery. In fact, during this stage of my training I thought of specializing in cerebrovascular surgery, which was the main impetus for me to study at Karolinska the following year.

Because at the time the most important thing was AVM, or was it your interest?

In the earliest days of radiosurgery, it was AVM, it was ALL AVM. By the time I showed up at the Karolinska for my fellowship, Lars Leksell's team had only been treating tumors, mostly acoustic neuromas, for a handful of years. Between both acoustic neuroma and pituitary tumors, I bet, by the time I showed up at the Karolinska, they had treated not more than one hundred or one hundred and fifty tumors in the entire history of radiosurgery. AVMs dominated all the thinking and practice.

Upon arriving at the Karolinska in 1985 I got involved with the GammaKnife program, being specifically interested with how radiation affected blood vessels. The biggest project during my fellowship involved collecting and analyzing along with Ladislau Steiner and Christer Lindquist, the hundreds of AVM patients that had previously been treated at the Karolinska. The result was the first big retrospective study of GammaKnife-treated AVMs, which for various reasons would not be published for more than 5 years after I created the first draft of the manuscript. In parallel, I spent a lot of effort treating dozens of rabbits with the GammaKnife, trying to invoke the vascular changes we saw with AVM. In doing so, I learned a little bit of Swedish! Generally speaking all the swedes I would meet spoke such perfect English that it was just natural and easier to simply speak English. However, the young guy, who took care of my rabbits, and incidentally happened to collect poisonous snakes including black Mumbas, could only speak Swedish. By necessity he gave me the only chance to learn a bit of Swedish during my entire year in Stockholm. At the Karolinska I spent sometime in the operating room but most of my energy went into pulling together retrospective AVM series for publication.

Did you perform also a lot of experimental studies, also from a histological point of view?

In the early part of my Stanford career, while I was just starting to build my clinical practice, I out of necessity focused a lot on animal work, and specifically trying to build an animal model for vascular radiosurgery. Ultimately, I totally failed, my animal model going nowhere. Nevertheless the AVM study I did with Steiner eventually proved to be the first big clinical study on AVM radiosurgery.

At the Karolinska I must have spent hundreds and hundreds of hours pulling together the data for our retrospective study, then doing all the analysis and finally writing the first draft of a paper. I made the mistake of giving the manuscript to Prof. Steiner with my name as first author. Steiner's first and only edit was to cross my name off and replace it with his name, saying "Eye moost take reh-spoon-see-bility". Having put in so much effort I was bummed. But ultimately Steiner was a stubborn enigmatic character with a penchant for truth, who when all was said and done took forever to publish "OUR" paper. I mean, I did all the work, all the work was done, yet it took him 3 or 4 years before he finally would agree to submit the manuscript and allow the data to be published.

During my year in Stockholm I fell under the spell of Lars Leksell who was an amazingly charismatic personality. He combined this great mashup of enthusiasm and cynicism. Up to that point in my life, Leksell quickly became the most dazzling neurosurgeon I had ever met. However, Leksell was also at a very senior stage in his career, and by virtue of such his star was in decline within his own neurosurgery department. In fact, I sense that the new head of the department, who in many respects felt overshadowed by Leksell's legacy, wanted him out. Nevertheless, as fate would have it, Leksell's office happened to be right next to my office so I got to spend a lot of time with him alone. It was just the two of us sharing coffee on many mornings. Leksell would talk, I would listen, me captivated by his huge personality. And I boy was so impressed with how he created things - he created medical devices beginning with his stereotactic frame – and before I realized what happened, I was bitten by the stereotaxy bug.

After a few weeks in Stockholm, I became captivated by the idea of a neurosurgeon inventing new technology and determined to figure out some way to follow in Leksell's giant footsteps. I said to myself: "I want to do this too". At first, I did not have a specific idea to pursue, until it dawned on me that while RS was such an amazingly powerful tool in the brain, there was no reason not to treat the entire body with the same radiobiologic principles. So less than 3 months after showing up at the Karolinska, I had come up with the basic technology that would lead to the CyberKnife and image guided radiosurgery. The key technology was x-ray image to image correlation using CT to provide a 3D volumetric map. In 1985, it was unthinkable that a computer would be fast enough to handle the algorithms in question. However, I was confident that it would be only a matter of a few years before computers would have that kind of speed. Absorbing Leksell's entrepreneurial spirit by osmosis, I became totally smitten by neurosurgical entrepreneurship and committed to making a next generation radiosurgical device using image-guidance to target…… it is worth stating that in 1985 there was no such term as image guidance. Ultimately, I took all of my excitement and dreams back with me from Stockholm, as I resumed my final, chief residency year at Harvard.

Did you talk about your idea with Leksell?

Leksell was not the kind of guy who would listen a lot … (laughter).. He talked a lot, and I would listen. I never discussed image-guidance with Leksell….. it was just too futuristic, especially for a man who was mechanically oriented and had almost no experience with computers. While I did have a mechanically oriented idea for a more easily applied stereotactic frame. However, with this, Leksell didn't mince words. He told me my idea was dumb. Hahaha

I knew that my concept for image-guidance was going to take time, if only to allow computer processors to get fast enough. While I vaguely told Leksell about my intention to make a technology to perform radiosurgery for the rest of the body, I did not push my concepts for image guidance too hard on Leksell. Yet ultimately, I regret not doing so because it was during my time in Stockholm

that Lars died quite suddenly. As a result, I never got to share the full extent of my dreams with Leksell. Had Leksell not died when he did, I surely would have told him my plans in greater depth.

You know, when you are a young man you have so many dreams, the odds are they are merely idle passions from which nothing will result. However, since we are now talking about these dreams, it just goes to show that not all dreams are wasted.

Upon returning to the Brigham for my Chief Residency year, it proved to be a uniquely propitious time. The team of neurosurgeon Ken Winston and radiation physicist Wendel Lutz had just assembled the first US based Linac radiosurgical system and were just starting to treat patients, mostly AVM patients. With minimal effort I was able to interject myself into this small team as a junior partner. So as luck would have it, by the time I was finishing my chief residency, I had experienced with protons, GammaKnife and LINAC radiosurgery.

I move to California, with the singular goal of making a device what would later become the CyberKnife. From its inception the goal was to create a device to do radiosurgery anywhere in the body, and to see such procedures replace conventional open surgery whenever possible. However, upon showing up at Stanford I started totally from scratch. I mean, there was literally nothing to work with, other than a distant legacy of innovative radiotherapy. Yet when it came to radiation equipment, there was nothing to work with at the university or medical center. At first I talked to everyone at Stanford who would listen, but truthfully no one inside Stanford gave a damn about my dreams for a whole body radiosurgery machine. But eventually Malcolm Bagshaw, the very senior chairman of Stanford Radiation Oncology became a supporter……Mal was a giant in the field of radiation therapy yet also a kind man, and I suspect his early support for me was more out of pity than belief in my ideas or my ability to execute on them.

Within months of arriving at Stanford I started applying for research funding and succeeded in obtaining only the most modest of grants, the first being only $10K. But through this process I started working with some really smart professors and engineering PhDs in Silicon Valley, the primary focus being x-ray imaging and stereotactic localization; at the heart of the new technology I wanted to build was the need to change the then universal paradigm of frame based stereotactic targeting. Without a new and highly accurate targeting schema there could be no next generation radiosurgical device. After banging on the problem for a couple of years, my team (mostly) and I came up with the notion of x-ray image to image correlation, and in short order, image guided targeting was born.

One of my patients, a delightful fearless guy whose meningioma had been resected by me, and who had a bipolar personality, heard about my efforts to make a radiosurgical system and become captivated by the idea. My patient took it upon himself to find me a smaller LINAC. In short order he discovered this small company in San Jose Calif., Schomberg Radiation, that was making a small X-Band linear accelerator. After explaining to the Schomberg team my research on targeting and concept for a new radiosurgical device, we agreed to collectively investigate the idea. We wrote grants and more government grants, none of which brought in much money. I approached GE (General Electric), Siemens, Phillips for funding, but again no one was interested. So finally when I could raise money in no other way, I put together $600K largely from neurosurgical friends and started Accuray with the Schomberg team, and a smart imaging scientist named Joe Depp. The initial name for the product was the Neurotron 1000. We had laughably little money but I was lucky enough to convince Stanford to buy the first machine, and pay me in advance. As a point of reference, Intuitive Surgical, manufacturer of the Da Vinci operating robot got started shortly after and in the same general neighborhood as Accuray but its earliest rounds of investment involved $50M.

The money I secured for Accuray funds was truthfully only 5% to 10% of what was needed just to get started. Accuray was fortunate to survive only because I was able to sell a number of these machines very early on……I was dumb but also lucky. By sufficiently exciting a handful of influential neurosurgeons and radiation oncologists, who in turn convinced their hospitals to purchase an eventual CyberKnife, all on the basis of some simple schematic drawings, I funded the business. Each hospital would pay a down payments, and then regular progress payments thereafter. Accuray basically got started as a Kickstarter campaign, before there was even a Kickstarter! However, we had so little money that half a year after we started treating patients at Stanford in 1994, Accuray ran out of money. It was really terrible because for 4 years thereafter we had almost no money to keep us alive. No matter how hard I tried, no one would invest in us. It was so very scary and difficult. While the company limped along, delivering a CyberKnife every now and then, we never really had the money to finish the product and it was always breaking on our poor customers. For years I was constantly running around Silicon Valley chasing anybody who had the potential to invest more money in Accuray.

During the early years of the CyberKnife I was also growing a radiosurgical practice involving a more standard frame-based Linac radiosurgery system. Over time my radiosurgical practice got bigger and bigger, even though very few were treated with a constantly breaking CyberKnife. By the mid 1990's I was treating well over a hundred patients a year with standard Linac SRS and in doing so, developing a growing regional reputation for such. But it was always very stressful doing that while in parallel trying to rebuild Accuray and improve the CyberKnife. That is when I got really lucky!

Somehow we got amazingly fast regulatory approval to sell the CyberKnife in Japan, and a couple years later we had sold 10 to 15 machines in Japan, after which the entire business took off.

So the first foreign country was Japan.

Yes, the first five machines went to America, while the next ten machines went to Japan. All of this happening about the time I left Stanford (1999) and became CEO of Accuray. Over the 3 years I lead Accuray as CEO we finally finished the product, we resumed sales in the US. In fact, by 2002 US sales really started to take off again. However early in my tenure as CEO the company faced all kinds of serious challenges. Finding employees then was so difficult because Silicon Valley was in the midst of one of its most historic booms. No matter how hard I tried it seemed impossible to pay engineers enough. Even the least capable were convinced they could work for nearby Cisco or Intel and make a million dollars over a couple of years. Meanwhile, our original supplier of robots (Fanuc) suddenly became concerned with our use of their machines in a medical tool and the Founder/CEO refused to sell us more. Literally overnight my struggling company needed to rework its entire flagship product around an entirely new robot, Kuka. However, one by one the company worked around any number of problems and by the end of 2002 Accuray had lots of orders, and lots of patients were being treated. It was at this time that I decided I would be most useful to the company if a returned to Stanford and pushed the technology in the clinical arena. I made a fateful decision to bring in a new CEO who I helped to select. This decision would ultimately haunt me and lead to my total departure from Accuray 7 years later. However, being back at Stanford lead to some of the most clinically productive years of my life. Back at Stanford I was able to push much harder things like spine radiosurgery (first done by my team in 1996), pancreas SRS, (first done at Stanford in 1998, lung SRS (initially tried at Stanford in 1998) and then prostate SBRT, first done on a neurosurgical friend of mine in 2003. At every step usually in the background, I was there to push, push push. The irony of the first pancreatic and lung cancer patients being treated with the CyberKnife by me, a neurosurgeon, is for many hard to imagine.

Timmerman had a similar experience, as Timmerman, like you, treated for the first time pancreatic or prostatic tumors.

In the early 1990's Lax and Blomgren at the Karolinska developed a targeting scheme for the body and by the late 1990's Timmerman was using it to treat lung cancer with SRS. It was about this time that we started applying the image-guided methodology of the CyberKnife to lung and pancreas cancer. I was oblivious to it, but a lot of Japanese investigators were also doing great work with high dose precision radiation to treat early stage lung cancer. Meanwhile, at the University of Arizona, neurosurgeon Alan Hamilton, a former fellow resident at MGH, began treating a handful of spinal metastasis patients with radiosurgery in the mid 1990's, in his case also using an external frame for targeting. It was truly amazing the lengths to which Alan and team went to attach this enormous stereotactic frame to a patient. The Univ. of Arizona method required a trip to the OR and general anesthesia to both attach and remove the frame. The frame itself provided both a fiducial array for targeting and a means of spinal immobilization. Hamilton's results with a handful of spinal metastases were encouraging but the shear complexity of the procedure convinced me more than ever that image guided radiosurgery, i.e. the CyberKnife solution, was essential if this procedure was to ever become practical. Today I think it is safe to say that Image-guidance, IGRT, is what finally made SBRT and body SRS practical. However, my hat goes off to the many people like Timmerman, Hamilton, Blomgren and Lux who made radiosurgery happen with frames alone and without IGRT.

I was actually referring to hyper-fractionated RT, so the use of hyper-fractions in radiosurgery for the brain. So in terms of hyper-fractionation, you had a similar experience.

I never set out to develop hypofractionated radiotherapy or radiosurgery. Instead from the start the focus of my academic research and clinical practice was the development of image-guided technology itself. From the beginning I saw stereotactic frame-based targeting as a problem to be overcome if radiosurgery was going to have the greatest clinical impact possible……stereotactic frames were just too limiting. Once I had image-guidance, it was a simple step to question the then existing paradigms for both radiosurgery and radiation therapy; fractionation schemes were not based on inherent radiobiology but the limitations of technology and reimbursement. When I left Accuray to go back to Stanford I got to explore clinically these ideas as well as myriad opportunities to treat extracranial lesions. In short order, Steve Chang and I, joined by Iris Gibbs and Scott Soltys in radiation oncology, were soon treating over 600 patients a year, and before long got a second CyberKnife to meet the clinical demand.

Within a couple of years of leaving Accuray I had a serious falling out with the then CEO. I could no longer work with him, or as a result the company to which I had given so much of my life. At about this time I started to reflect on where I had succeeded and where I had failed to make radiosurgery more impactful in the world. It dawned on me that despite my many successes with the CyberKnife, I had failed in many ways. Radiosurgery was so much more powerful than reflected by the number of patients being treated in the world. Frankly I was (and still am) disappointed by the failure of the CyberKnife and competing technologies to reach more patients, even in rich countries like the United States. Too many patients in the world who might benefit just don't have access to radiosurgery once you go outside the real centers of excellence. I have come to believe the numbers of patients who could benefit if radiosurgery were available number in millions each year, and in large part the reason is SRS equipment is too expensive and the technology is so complex. So in this last phase of my career, sometime around 2008 I committed myself to fixing this problem and with that I came up with the ideas behind ZAP.

So in 2008 you were already thinking about a less expensive tool?

Yes, but knowing I could not work with Accuray, I needed to find a technology partner, and in particular a source for a lower energy, high output linear accelerator. This is what lead me to Varian. The CEO of Varian at that time, Tim Guertin, liked the basic project so much I invited me to join the company and develop this yet to be totally defined radiation device inside Varian. Moreover, Tim and the Varian board all said: "We'd like your presence to also help make Varian more entrepreneurial". However, Varian prove to be a very big and not very innovative company; in fact, I felt the powers to be are frankly fearful of disruptive innovation, which is the only type of innovation that ever interested me personally. So after a few years of trying inside Varian the management team and I decided that my Zap device was incompatible with their supposed lack of money and strategic direction, which then was directed towards a machine that would become Halycon. However, my preferred explanation for what happened is that "I was fired" from Varian!! No matter I left the company, taking with me a couple of Varian engineers, and shortly thereafter teamed up with my old startup buddy, Mohan Bodduluri (CTO from Accuray days). Extracting myself from Varian required the better part of a year, but in 2015 we officially started Zap, which is where I have been ever since. Zap's goal is simple. Zap intends to make radiosurgery simpler and cheaper, so that the 2 million brain and head & neck tumor patients every year who today lack access to state-of-the-art precision radiation, can now be treated optimally.

What does Zap stand for?

Zap is an English "onomatopoeia", a word whose meaning aligns with what it sounds like. In English, the word Zap refers to the transfer of energy from one location to another. For example, a common application of the word "zap" might be used to describe what happens when one touches an electric device with faulty wiring and a small jolt of electricity, a little shock is experienced……in English that's a "zap". A lightning strike can also be referred to as a big "zap" of energy. Again the word Zap describes this directed transfer of energy. Zap is not a serious, technical type of word, and that choice is deliberate on my part. I wanted the name to not be too serious, and I especially did not want to use the word radiation, because the term radiation scares the general public (outside of radiation medicine). It is worth noting that the Stanford radiosurgical team also routinely referred to what we did as "zapping tumors" and in the OR, the use of electrocautery is often referenced in the same way; in other words, Zap was common medical slang around Stanford hospital.

Were you the inventor of these names for your machines: Accuray, ZAP…?

My wife named Accuray, I named CyberKnife and Zap, so you can blame me if you don't like them!

Tell me about the people who worked with you, apart from Leksell, who was important in your career development? Were there other people who played a key role in your professional life?

Karolinska: Christer Lindquist and Ladislau Steiner certainly got me started in the field of radiosurgery, as did Ken Winston from Harvard. At Stanford the Chairman of Radiation Oncology (and pioneer in prostate radiation therapy) Mal Bagshaw was a marvelous mentor. Of course I have always had immense admiration for Bob Timmerman for how broadly he impacted the entire field of radiosurgery. When it comes to brain neurosurgery Lunsford, Kondziolka and so many in the Gamma Knife community must be credited with paving the way for people like me. Yet none of my

inventions would have become reality without my lifelong professional business and technology colleague Mohan Bodduluri with whom I worked at both Accuray and Zap.

So the Pittsburgh group was important.

Yes, but now so much of the frontiers of RS are extracranial and in the hands of the CyberKnife world as anybody, because so much radiosurgery is now outside the brain. But I have been inspired by Mal Bagshaw, he was someone I admired immensely. As an entrepreneur, Cardiac Surgeon Tom Fogarty, creator of the Fogarty balloon, one of the most widely used medical devices in medical history, has been a big influence. More recently, Fred Moll, MD, also in Silicon Valley and the entrepreneur behind the Da Vinci surgical robot has been an important advisor.

Are you aware that you changed the life of radiation oncologists? Because with the advent of the CyberKnife, also Varian and Elekta had to start moving in a new direction. Hypofractionation is so important today; it has represented a completely new way of thinking. Are you aware of that? In radiation oncology, in my opinion, you are one of the most important personalities.

Thank you, Laura. I'd like to believe that my ideas have been beneficial for radiation oncology and even more so, for all of our patients. Yet still I am frequently disappointed that the money in Radiation Oncology always seems to be in conventional fractionation, and by virtue of such undermines progress. It takes a special radiation oncologist who is willing to do the right thing, even though it does not pay the most money. It is more than ironic and a little sad that when you do the most sophisticated (and best) treatments for patients, both radiation oncologists and neurosurgeons get penalized financially.

You have to think of a new tool, like Zap, but not just for the brain, but for the whole project.

Who knows, maybe that's going to be my next project; Stay tuned!

So thank you very much John for the interview, a very nice interview, I am so happy to have had this chance to talk to you. Are you coming to Rio?

I'll definitely be there. I am bringing my wife Marilyn and if we drink enough caipirinha I hope to try dancing samba!