



DEVELOPING CYBERKNIFE AND THE ERA OF ETHICS IN ENGINEERING

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Based on an interview with Accuray Chief Marketing Officer Ms. Birgit Fleurent

TechNews Extra by: Dr. Jesse A. Stoff



By now, most people recognize the name 'CyberKnife' from 20+ years of local radio commercials or an occasional news article about Radiotherapy (RT) for cancer care. But to understand its impact on the war against cancer, we also need to view the many ways that such inventions have shaped the direction of future medical technologies.

Since the introduction of the x-ray in 1895 [1], European and American scientists [2] have flocked to the study of radiation for its therapeutic potential. The "race for a cure" brought us into the fast track with many new devices and technological advancements from non-invasive cellular

imaging to the use of surgical robotics and the many integrated applications of AI (Artificial Intelligence) in computerized micro-treatment solutions.

Our tech review series brought us on a tour of Accuray Incorporated – one of the top names in the development of cutting edge radiotherapy systems for the treatment of cancer. Accuray has introduced innovations to the market that include the CyberKnife®, TomoTherapy® and Radixact® Systems. The Accuray headquarters in Sunnyvale, California directed us off shore to one of the company's top educators about these products for an exclusive interview with Chief Marketing Officer Ms. Birgit Fleurent in Morges, Switzerland.

HARNESSING RADIATION: THE 100-YEAR ROAD TO "PATIENT FIRST"

We have truly come a long way since the early days of clinical application of the x-ray (electromagnetic radiation) by Marie Curie in the late 1890's. From the discovery of radioactive isotopes in the 1920's to the use of the radium-based interstitial irradiation called brachytherapy and stereotactic radiosurgery (SRS) in the 50's to the introduction of early devices that delivered the first proton beam in the 1970's.

By the early 1990's, a revolutionary form of treatment classified as SBRT or Stereotactic Body Radiation Therapy was launched in Stockholm, Sweden. SBRT was defined as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using

either a single dose or a small number of fractions.” The multiple radiation beams intersect to deliver an accurate, high dose of radiation to a carefully defined location. [7] This may result in a significant reduction in side effects from radiation exposure that patients typically experience from the wide un-focused beam of conventional RT.



Image L- The CyberKnife System enables stereotactic targeting without a stereotactic frame. Simple immobilization devices such as thermoplastic masks, a foam cradle or vacuum bags keep the patient comfortably in treatment position and prevent large displacements that cannot be compensated for by the robotic arm.

The CyberKnife System became the next advancement of SBRT, earning FDA acceptance in 1999 as the first robotic image-guided radiosurgery treatment. Its unique architecture is comprised of a linear accelerator delivering a dose rate of 1000

MU/minute, mounted on a 6 axis robotic manipulator (arm developed by KUKA) and orthogonal kV imaging system. The system represented a trend in treatment technology designed to attack (and target) tumors more accurately without irradiating the surrounding healthy tissue. Today, there are over 930 Accuray radiotherapy systems installed globally. The CyberKnife System is in use at hospitals worldwide, reflecting its success and standardized acceptance in the medical community.

The ability to accurately target the photon-based x-ray beam to exact coordinates in the body enables clinicians to deliver SBRT and SRS. For the patient, these treatment methods may provide a safer alternative (and potential replacement) to invasive surgery by eliminating the many hazards that come with the 'scalpel-to-body' paradigm. These considerations and the CyberKnife System's ability to track, detect and automatically synchronize the radiation beam to target motion, make it a true game-changer. Clinicians can confidently treat most tumors in the body including the brain or the spine, where invasive surgery may bring long-term injury to the body and risks to the patient.

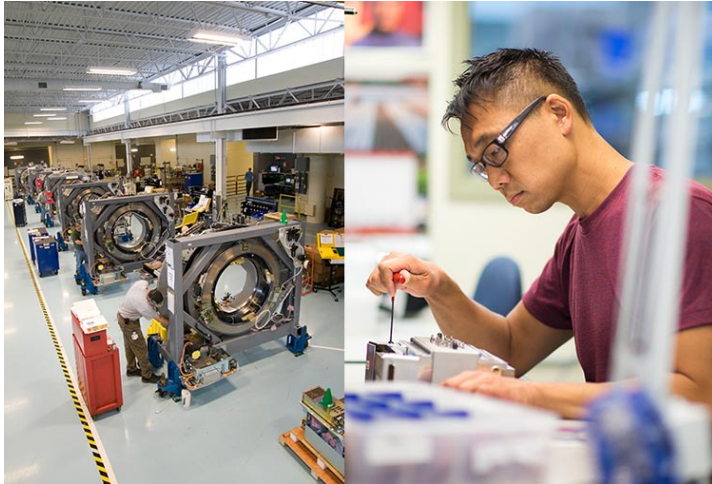
TECHNOETHICS

Today's engineering and medical technology (from the late 1980s) show significant evidence of ethical standards and major consideration for patient response. Ethics in treatment engineering covers all angles considered about the innovation including: the way it is built, the materials applied, the engagement of the operator and the aftermath of the patient. [11]

Each year, Accuray presents at the American Society for Radiation Oncology (ASTRO) with the flagship tagline "Patient-First" underscoring the design philosophy of their team's prime directive.[8] "Historically, radiation CAUSED cancer, but that's because you didn't have precision then. You were basically irradiating healthy tissue. That's what you want to avoid at all costs. So the more precise you can be, the better - and we (Accuray) pride ourselves on exquisite and unparalleled precision," says Ms. Fleurent.

THE ORGANIC NATURE OF UPGRADES

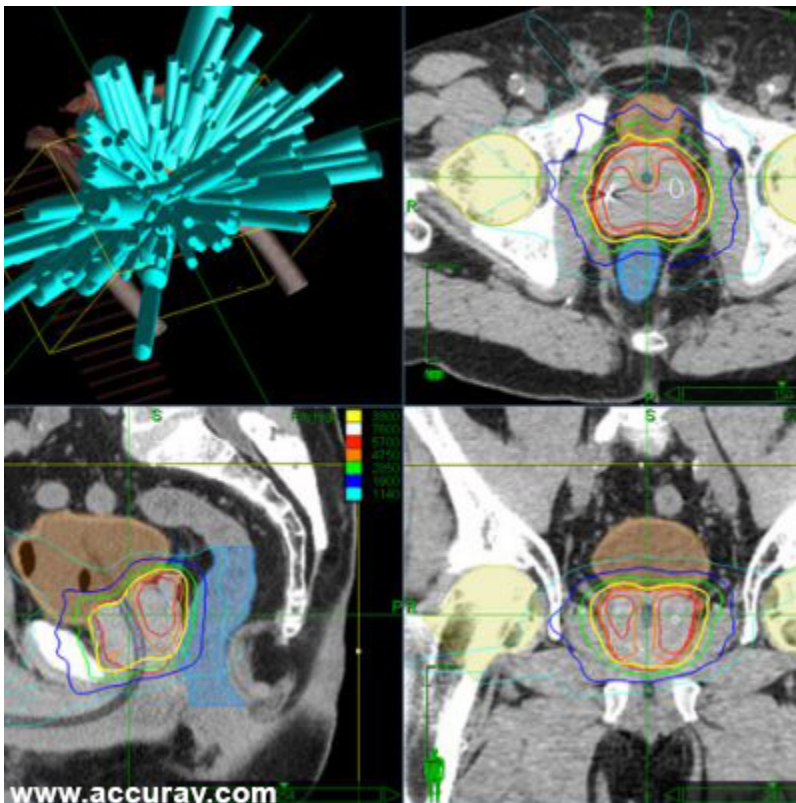
A virtual tour of the Accuray manufacturing plant in Madison Wisconsin would illustrate an impressive portion of the development flow of each CyberKnife System assembly. From the component designers to the hardware and software engineers to the army of expert assemblers, each device and model has (seemingly) countless parts dedicated to responding as one intelligent beam of light.



TomoTherapy System gantry in the Accuray Madison manufacturing facility

But even deeper behind the scenes are the concept people - what is regarded as the solutionists. This includes the product strategy teams that take on the voice of the customers sourced on a regular basis. In other words, a vast amount of information is gathered from end users that steer the next set of upgrades cast by the engineering team.

Next is the development of a prototype to conduct an extensive amount of beta-testing on phantom cases. "We're not going to give a System to a customer unless we feel it's absolutely ready to treat a patient. And they, in advance of that, will do all of their pre-qualification. In addition, when we introduce a significant product upgrade, both Accuray and our customers will conduct extensive QC testing prior to the initiation of any patient treatments."



The CyberKnife System uses proprietary anatomy-specific algorithms to track tumor motion. These specialized image guidance algorithms enable sub-millimeter precision and accuracy without the need for an invasive and cumbersome stereotactic frame.

REAL-TIME MOTION SYNCHRONIZATION

In its lifetime, Accuray developers have designed various upgrade models to the CyberKnife line. This includes the G3, G4, VSI (2009) and M6 (2012). Recently, the company introduced the Accuray Precision® Treatment Planning System (TPS) with the CyberKnife VOLO™ Optimizer (2018) which enables clinicians to reduce both the time to create high quality treatment plans and the time it

takes to deliver patient treatments. “With this software upgrade clinicians can create optimal treatment plans up to 90 percent faster than before and deliver the treatment up to an estimated 50 percent faster than before.”

Each model reflected a set of specific feature upgrades that were designed based on user demand and the company’s continued innovations in R&D. One remarkable feature advancement was over 15 years ago with the development of Synchrony® Respiratory Tracking System. This real-time motion synchronization technology enables treatment of a lung tumor while the patient is breathing normally -- uncomfortable patient restraints or breath-hold techniques are not required, nor does the clinician need to turn the radiation beam on and off as the tumor moves in and out of the specified treatment window.



Accuray originally designed and patented Synchrony, its ‘adaptive delivery’ software, to track, detect and automatically adapt the radiation beam for tumors that moved with respiration. The technology expands on the CyberKnife System’s unique motion synchronization capabilities that are inherently part of the system architecture. It is comprised of a unique image guidance system that locks the radiation beam onto the tumor while calculating, self-adjusting and moving it in sync with the patient’s chest movement while breathing. This unique feature adds major advantages to the success of the treatment process and is available only with Accuray products like the CyberKnife and now the Radixact Systems. According to Ms. Fleurent, “...our future is really moving on an increasing basis to treatment planning and treatment delivery adapted in real time. You have to create a plan, then you have to deliver the plan. The more you can automate that, and the more you can do it while the patient is on the treatment table, the better.

The other focus is in the direction of adaptive therapy in a way that is efficient --with exceptional imaging capabilities -- and to the extent that we can automate (including the software and the integrated system) . . . that is a priority to help ensure patient-first treatment. We are focused on providing clinicians with confidence in delivering safe, hypofractionated radiation therapy with unparalleled precision. Precision is especially important with hypofractionated radiation therapy, which involves the delivery of higher doses of radiation over a smaller number of treatment sessions compared to conventional radiation therapy.”

THERE IS MORE THAN ONE ANSWER TO CANCER

Part of the necessary education for cancer patients and doctors is staying on top of all the available treatment options and their respective benefits. From a “quality of life” perspective, the CyberKnife System was designed and has been recognized to be so much more patient-friendly. Also, the reduction in the number of treatment sessions provides the economic benefit of reduced work days lost and increased productivity.

Radiation therapy is often done in conjunction with another type of therapy. Between 50 and 60% of cancer patients would benefit from having radiation therapy, and not even close to that number of patients are getting access to or realize that they have this option. Sometimes, surgery is followed by radiation therapy while other cases call on chemotherapy with radiation therapy. There’s some data that suggests immunotherapy works more effectively when done in conjunction with radiotherapy.

THE NON-INVASIVE OPTIONS

The CyberKnife System was developed by Dr. John Adler, neurosurgeon, with the intended use for intracranial and spine treatment. Where tumors in the brain or the spine once called for some of the highest surgical risks and complexity, targeted image-guided radiation delivery has become a true game-changer for disorders in

these areas of the body. CyberKnife has numerous applications from brain to liver to lung to pancreas and prostate tumors. You can treat most indications with the CyberKnife System.

Accuray manufactures other cancer radiation therapy treatment solutions like the TomoTherapy System and the latest evolution called Radixact, a device with different architecture (from CyberKnife), designed to treat via IG-IMRT or Image-Guided, Intensity-Modulated Radiation Therapy. It also does SBRT. There are some indications that could be treated by both Systems, so there is some overlap, but they're not competing. These options are made available depending on the type of cancer center, the types of cases you treat, and whether you're a community or an academic teaching hospital.

TechNews Extra

Dr. Jesse Stoff is a renowned cancer immunologist and the medical director of the Integrative Medicine of New York in Garden City, NY (located minutes from NYU/Winthrop Hospital- one of the top CyberKnife facilities in the country). In this separate report, Dr. Stoff shares his experiences with cancer patients, professional insights and statements about the CyberKnife system from the perspective of a referring practitioner.

WHY ONE CANCER SPECIALIST SENDS PATIENTS FOR CYBERKNIFE?

By Dr. Jesse Stoff

On occasion, I send patients for CyberKnife treatment to receive focused and highly precise radiation therapy- including a recent one with mets (metastases) to the brain. A PET scan and her last blood test basically said she's in remission, but I want to see what still lights up because if there's several little spots here or there, CyberKnife could potentially target her and finish the cure.

Another use for CyberKnife is that it has a minimal negative impact on the immune system and it's a much shorter treatment course while giving you a big release of dead cancer proteins into the bloodstream in a very short period of time. Those proteins are antigens, which means the immune system can recognize them and react against them.

I time my CyberKnife referrals to a specific point during the patient's immunotherapy treatments where it makes the best sense. As I up-regulate the immune system and get it looking for targets, CyberKnife is one of several therapies that gives you antigen shedding or a sudden spike of antigens. The therapies that do that are things that are very focal- like radio frequency ablation, cryotherapy and CyberKnife. Everything else is more broad-based and you don't get that big spike. Hyperthermia gives you a spike but not as good. Timing the



immunotherapy with CyberKnife gives me a much better response to the overall treatment of the patient than just the local spot that they're targeting.

Now when you get that sort of radiation amplification of an immune response, that's called the abscopal effect. That's something I try to get because if you can do that, then immunotherapy plus focused radiation can equal a positive response in terms of the immune response and people going into remission. If you can get the abscopal response going, what can happen is that tumor(s) may shrink that have nothing to do with what they shot with the CyberKnife or the RFA or the cryo(therapy) because now you have a generalized immune response against this antigen spike. This is one of the main reasons why I like CyberKnife. The abscopal effect is when you're doing something that causes a rapid die off of cancer cells. You don't normally get this with chemotherapy because it usually takes too long to respond.

I've done this with a number of patients where I've gotten them into remission. On the flip side, if you don't have one good target for CyberKnife, but you have a zillion mets in the liver (as an example) and you have an area with a lot of bulky tumors, then I send them for what's called a hypofractionated SBRT- which is low dose regular radiation therapy, a low enough dose that is not designed to kill the cancer during zapping. It's designed to stimulate the tumor infiltrating lymphocytes that are infiltrating into that bulky tumor and raise their level of activity. That's another way of generating an abscopal effect. So, there's two ways of doing it. One is with CyberKnife or RFA or cryotherapy. The other is with low dose hypofractionated SBRT.

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