More than Pretty Pictures: 3-D Treatment Planning and Conformal Therapy

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/mp.16117.

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The 1980s saw a major revolution in the field of radiation oncology. Early in the decade, people began to explore the ability to image internal anatomy with the then-newly developed CT scanners. By the end of the decade, the field was using 3-D anatomy based on CT and MR imaging to perform sophisticated conformal therapy treatments developed using fully 3-D treatment planning and beginning to explore automated optimization and intensity modulated radiation therapy (IMRT) techniques. Many people and institutions across the US and Europe contributed to these huge advances in what could be done with radiotherapy, a revolution that we were lucky enough to be part of.

Our part of this story began in mid-1984 when we all arrived at the University of Michigan to start the newly independent Department of Radiation Oncology, led by the Allen Lichter, MD, the first department chair. We had no choice but to start developing a new treatment planning system, as the highest-tech device available when we walked in the door was an HP-45 calculator. Within a couple months, we had a "super mini-computer" VAX 750 (8 MB memory! huge 456 MB disk drives!) that would be used for multiple treatment planning stations, and for all the other departmental functions as well. Within another month or two we pulled together a 2.5D CT-based treatment planning system based on work from our earlier institutions. However, one of the reasons we had all come to Ann Arbor was to contribute to the on-going technological revolution that was happening in the field, so we immediately began designing and developing a "3-D Planning System", in which all the basic data structures, algorithms, and functionality were designed to make use of the 3-D volumetric data that was available from CT (and developing MR and PET) scanners. The effort was supercharged by the submission deadline for contract proposals for the NCI 3-D Electron Treatment Planning Working Group, due January 5, 1985. Our 3-D Hogstrom-type pencil beam dose calculation algorithm and 3-D display code worked together for the first time on January 4, 1985. If there was a holiday season that winter, we don't remember it.

The late 80s were a time of concerted efforts to develop 3-D planning by many academic groups, driven by many factors, including 1) the availability (and desire to use) the 3-D imaging data finally becoming available with CT, MR and PET, 2) reasonable cost minicomputers with enough memory (~8 MB) to allow functional graphics displays, 3) evolving graphics standards (X-windows), 4) ethernet and networks, and many other factors. Most evolving systems were research systems, used for particular cases and situations. As for us, our old friend the deadline helped again. We moved our entire department into the new UM hospital in early 1986, equipped with 3 new accelerators. Deciding to switch clinical treatment planning completely to the new 3-D planning system was made much easier by just deciding not to commission the new machines in the old planning system: the new 3-D system had to be used for all planning in the new department.

There were several keys to the successful development, implementation, and use of the 3-D system. First, we had a weekly treatment planning conference that reviewed treatment plans (and the planning capabilities that had been used) with all the physician, physicist, and dosimetry staff. Since the person "driving" the planning system during the early conferences was typically one of the developers, we could easily see what features were useful to help the discussion, what new capabilities were needed, and what ideas needed more work. Planning conference discussions also led to new treatment techniques, protocols, and eventually studies. The 6-field conformal plan for the prostate, which was one of the first standardized conformal treatment techniques (ref 1), was developed during one of the early planning conferences. A second and just as vital component in the development was that the physicians continually pushed for new capabilities and always had a patient plan which needed this or that new functionality. Having the physician push for a given feature that is needed for a specific patient was a powerful motivator! A third reason for the successful implementation of the system was its obvious utility and superiority. Once we were planning in the 3-D world there was clearly no going back! For example, we attempted to develop a very early trial to evaluate the benefit of the new "beam's eye view" (BEV) capability of the 3-D system for designing field shapes compared to the old simulator-based 2-D method of field design. However, it turned out to be impossible to get anyone to do the comparisons as the new capability was just too powerful compared to the old method.

Of course, many other groups were developing 3-D planning during the same years. During the summer of 1987, the every-three-years International Conference on Computers in Radiotherapy (ICCR) occurred in Scheveningen, the Netherlands, and hosted talks from virtually everyone in the field of 3-D planning, as illustrated in Figure 2. There has rarely been such a well-timed meeting, small enough that everyone could talk, involving all the people in the field, with the added benefit of meetings at beach-side cafes. The published proceedings of that conference (ref 2) document virtually all the work going on in the field of treatment planning in the latter half of the 1980s, along with the early work which led toward the development of intensity modulated radiation therapy (IMRT).

The big issues with 3-D treatment planning, once the basic systems were developed, were to figure out how to use the 3-D tools, and then to determine whether the new capabilities were actually useful and made real improvements in patient outcomes. The ability to create 3-D anatomical descriptions made it necessary to learn how to contour all the structures of interest to the planner and physician, forcing everyone to learn CT-anatomy, and to find efficient ways to outline all those structures on 20 or 50 or 100 CT slices. Learning how to contour using a trackball (mouse and graphical user interfaces were not available on most computers) was not easy, and thus it was important to develop automated contouring tools. We also developed a big screen digitizer using a projection TV and transparent digitizer tablet (see Figure 3) to allow point and click type contouring (i.e., the kind of contouring that you do now with your mouse and a normal computer display).

This issue points out one of the interesting facts involved with the exploding development of 3-D treatment planning: all sorts of technologies were also exploding at the same time. During the 1980s, CT scanners evolved from single slice rotate/translate systems (30 sec per slice) to the 1989 invention of the slip ring which enables helical scanning, leading to major increases in CT scanning capabilities. Computer CPU speeds went up and memory costs went down, dramatically increasing the computer power available to support improved calculation algorithms, more sophisticated graphics, and eventually graphical user interfaces with a mouse. If your treatment planning software could survive the operating system upgrades that happened often as new hardware capabilities were added to the system, sometimes untenable features became possible just by utilizing a new version of the hardware/software (at least if the system was based on a well-designed operating

system, which is why most systems at this time were developed using Digital's VMS operating system).

The display of anatomy in 3-D, plus the ability to visualize beam geometry and field shaping in 3-D led to the use of much more complex beam arrangements than the typical AP/PA (anterior/posterior pair of fields), 3-field, and 4-field plans from the 2-D era. Now planners could plan 3-D arrangements, with non-axial beams and complex field shaping formed with focused Cerrobend blocks. All of these new capabilities were harnessed to make plans more "conformal", i.e. to shape the high dose volume to the target, and minimize dose to normal tissues. With the effort to improve conformality, all sorts of issues became more important: daily treatment localization (driving the development of flat panel imagers and eventually cone-beam CT), improved calculation algorithm accuracy (now that there was enough calculational power to use improved algorithms), multileaf collimators (initially so the therapists didn't need to lift 40 lb block trays), computer-automated delivery (to make delivery of these many field conformal plans more efficient), and motion management (the smaller margins and imaging available forced the consideration of how to manage respiratory and other motion during treatment), among other things. The parallel and exciting developments of magnetic resonance imaging (MRI) and positron emission tomography (PET) made integration of both MRI and PET into the new 3-D treatment planning capabilities also necessary. Understanding and then managing all these issues would be enough to keep the radiotherapy community busy for a decade (or two).

During the first few years of our work in 3-D planning, the new capabilities were often derided by others as "pretty pictures" with no real benefits. The question, as is often the case with a new technology, is whether the new technology is worth the additional effort and cost: does it improve patient outcomes? New technologies, for example CT scanning for radiotherapy, are often implemented without specific studies documenting the improvements that accrue when the new technology is used. As mentioned earlier, a randomized comparison of simulator-drawn blocking versus BEV-designed blocks using a 3-D planning system cannot be performed if no one will use the old standard technique (in this case, drawing blocks on simulator films). So how did we determine if 3-D planning, and all the additional technologies that were driven into the field by the use of 3-D planning, are actually more than pretty pictures?

Answers to that question came about in those weekly treatment planning conference presentations and discussions. Comparisons of the dose distributions used in the 2-D world, compared to the new 3-D conformal dose distributions, demonstrated significant decreases in the dose to normal tissues (now "organs-at-risk" or OARs). Since it has been known for generations that radiotherapy depends on giving enough dose to the tumor to sterilize it while keeping the dose to normal tissues low so that toxicity is acceptable, it became clear that conformal plans might allow us to change the then-current tradeoff, either by decreasing toxicity due to the smaller dose to OARs, or by increasing the dose to the tumor to improve the control rate. Historically, the dose accepted for most types of tumors had been determined by experience and was mainly limited by the potential for unacceptable toxicity which could occur with the standard "2-D" types of plans that were used. As described later by Allen Lichter (ref 3), if the normal tissue doses were substantially decreased by conformal treatments, then it would be possible to escalate the tumor dose, thereby increasing control rate, while keeping the toxicity as low or lower than the standard expectations. This kind of tumor dose escalation would quantitatively document the value of the new technology while also scientifically determining the tumor dose which was best, rather than relying simply on experience. We followed through on that philosophy: in 1986, a few months after the first conformal prostate treatment plan was created, a prostate dose escalation trial was started, eventually taking the dose from 60 Gy to 80.4 Gy in controlled escalation steps. Other trials in partial liver (start in 1987, 30 to 90 Gy eventually), Glioblastoma (start in 1989, 60 to 90 Gy eventually), and lung (start in 1991, 60 to 102.9 Gy eventually) all helped to determine appropriate target doses to use when conformal therapy was employed.

Of course, the situation is much more complicated than the simple picture just described. Even for the prostate, which is perhaps the most straightforward site to think about, the rectum, bladder, femoral heads, and other anatomical structures all contribute to the toxicity, and each has its own dose-volume-toxicity dependency. To do any of these dose escalation trials, it is important to understand the dose-volume-toxicity dependences so the normal tissue doses can be limited appropriately. There was just no choice but to look critically at all the important OARs around each target site and to find a way to determine the dose-volume-toxicity relationships for those organs, so that we could safely perform the conformal plans and especially the dose escalation studies. This work has been crucial to the field, as it lies at the heart not only of the dose escalation studies and conformal therapy, but is a critical requirement for all IMRT/VMAT plan optimization (used for the majority of all radiotherapy treatments currently).

There is one more important component which had to be dealt with to perform some of the conformal therapy dose escalation studies. For tumors of the liver and the lung, for example, it had long been known what the limiting dose was for irradiating large parts of the organ. Now, with conformal techniques, it was possible to consider just irradiating the involved part of the liver (for example): but the tolerance for partial irradiation of the liver was unknown. For the liver escalation trial, a real leap was required: how could we determine what dose could safely be delivered to part of the liver? To start to understand this dose-volume relationship, a simple dose escalation trial was developed, using the newly developed dose-volume-histogram (DVH) capability of the 3-D planning system (DVHs were first published by several groups a couple years earlier) to enable a careful (but still "brave") escalation of the dose to partial liver volumes (ref 4). The first liver studies, along with parallel experimental and theoretical work in radiobiology, led to the concept of volume-effect organs in which parts of the organ could be irradiated to very high doses without causing complete organ failure or toxicity. Safe trials of dose escalation for these volume-effect organs could not occur unless the dose-volume-toxicity relationships were understood and incorporated into the trial design. To deal with this complicated situation, a new kind of escalation trial had to be designed: for this kind of trial, the structure driving the escalation strategy was the normal tissue complication probability, based on data obtained from dose-volume-toxicity data of other trials (ref 5). Eventually, understanding liver and lung behavior required a series of trials in each site, taking most of 20 years to achieve real clarity on the behavior of these organs.

In the end, those early "pretty pictures" have led to a complete revolution in how radiotherapy is practiced. The early 3-D planning capabilities demonstrated (see Fig. 4) that we needed all sorts of new technologies: better localization imaging (flat panel imagers for MV and then KV imaging, CBCT, and image guided radiotherapy (IGRT)), motion management (fiducials, 4-D imaging, respiratory motion management), DVHs, models for normal tissue complication probabilities, clinical dose-volume-toxicity data for all relevant organs, MLCs and computer-controlled treatments to make complex treatments efficient, and careful application and understanding of the needs for target volumes, margins, and handling uncertainties. All these capabilities, plus the continued improvement in computer resources and development of optimization strategies which made use of those capabilities, finally led to the development and widespread implementation of intensity modulated radiation therapy (IMRT) which brought sophisticated conformal therapy to clinics throughout the world.

Acknowledgements

The authors would like to thank the large number of people at the UM (and in institutions throughout the world) that made this work possible, exciting, and gratifying.

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Figures

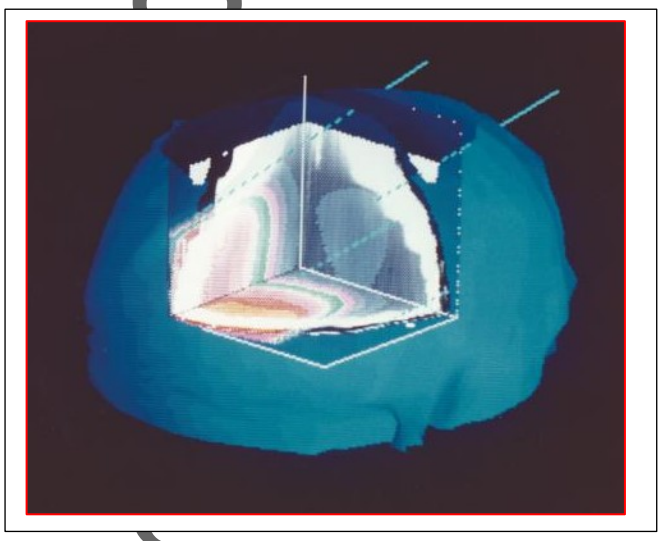

Fig. 1. 3-D Pencil Beam dose calculation and 3-D anatomical display – together (January 1985)!

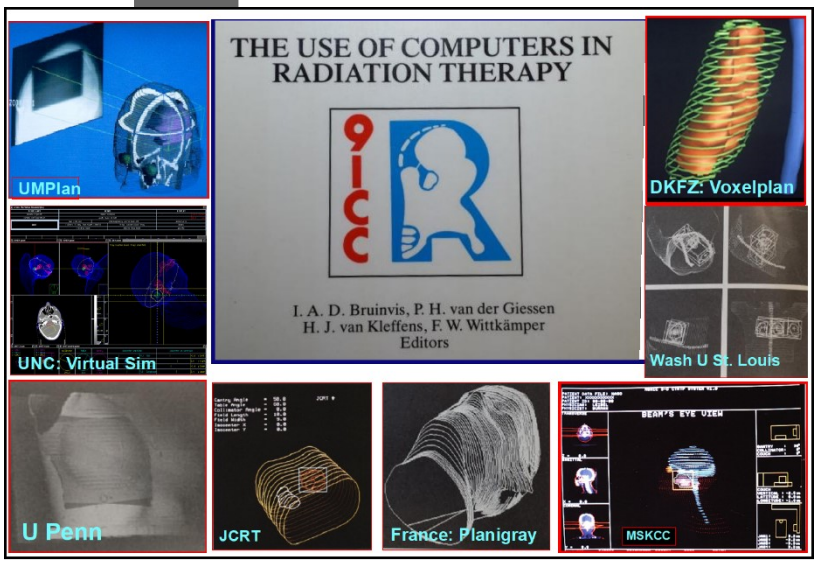

Fig. 2. Some of the 3-D treatment planning developments shown at the 9th ICCR meeting in Scheveningen (ref 2) in 1987. Counterclockwise from the top left: UMPlan (University of Michigan), Virtual Simulation (University of North Carolina), University of Pennsylvania, Joint Center for Radiation Therapy (Boston), Planigray (France), Memorial Sloan Kettering Cancer Center, Washington University St. Louis, and Voxelplan (DKFZ, the German Cancer Research Center).

Fig,3, Large screen digitizer system, built into the wall of the treatment planning room, circa 1989.

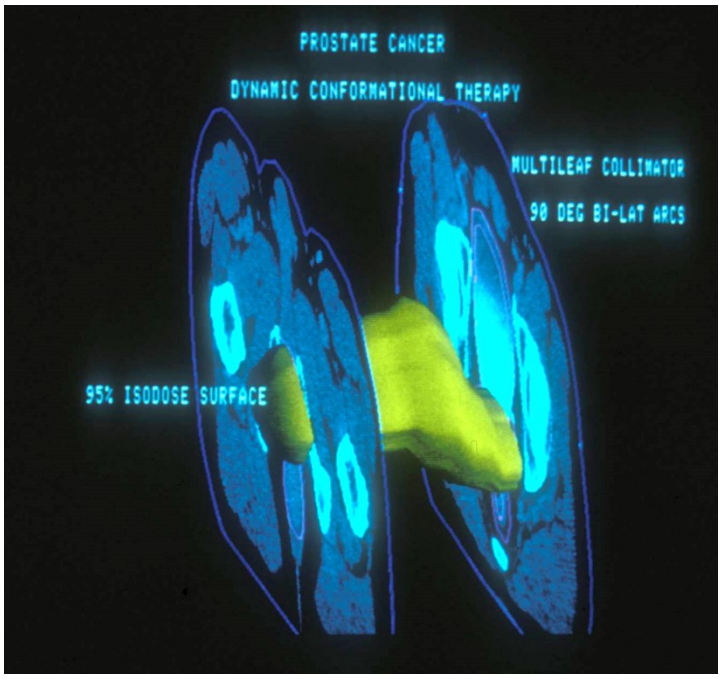

Fig. 4. “Dynamic Conformational Therapy”, which these days would be called DCA (Dynamic Conformal Arc). This is a demonstration of what would be possible with an MLC-equipped machine, presented at the 1987 ASTRO meeting. Now, most prostate patients are treated with MLC-shaped arc (VMAT) treatments which look very much like this.