The Impact of a Clinical Electron Accelerator on the Advancement of Veterinary Oncology and Translational Cancer Research

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***Abstract*—Cancer is a leading cause of death in veterinary patients. Forms of radiation therapy were used to treat these patients as early as 1896. Dr. Edward Gillette spearheaded veterinary oncology at Colorado State University (CSU). He recognized that a successful program would require well trained personnel together with modern modalities. His motivation presented a dilemma since fiscal realities in veterinary practice are modest compared to clinical practices in humans. In 1981 the CSU College of Veterinary Medicine and Biomedical Sciences commissioned the first clinical linear accelerator dedicated to the treatment of naturally occurring tumors in veterinary patients and translational research. This refurbished Varian Clinac 6 was capable of delivering photon and electron beams generated in an isocentric gantry with flexible beam collimation. Commercially available clinical accelerators are designed exclusively for human medicine. This paper chronicles the adaption of this early electron accelerator to veterinary patients without compromising the accuracy and precision expected in human radiation therapy. Broad challenges were encountered in dosimetry, treatment planning and patient positioning. Dr. Thomas Borak and Mr. Robert Scott formed a team approach to medical physics, engineering and maintenance. Translational research focuses on treatment of pet animals to evaluate novel therapeutics and foster an understanding of mechanisms impacting tumor control. The clinical accelerator, together with scientists, technicians and students at CSU pioneered translational research in radiation oncology. Veterinary oncology today is a mature and thriving discipline, based on modern clinical capabilities for cancer treatment in animals as well as a strong research component that benefits both veterinary and human medicine.**

***Index Terms*—Clinical accelerator, history, translation research, veterinary oncology.**

I. Introduction

CANCER is the second leading cause of death among humans in the United states and a leading cause of death in both dogs and cats. [1]; [2] The treatment of cancer with radiation therapy has followed a similar path for human and veterinary patients, although availability for animal patients has been limited. Shortly after Roentgen discovered the x-ray in 1895, both human and animal skin tumors were treated empirically with radiation, typically separating the total prescribed dose into a series of smaller doses known as "fractions". Despite lack of scientific methodology, encouraging responses to treatment were reported in human and veterinary patients, including dogs and horses, [3]–[5]. Richard Eberlein, considered the Father of Veterinary Radiology, consistently published data regarding the treatment of veterinary patients. His role as Chairman of both the 1st and 2nd Roentgenological Congresses, which primarily was composed of contributions from the human fields of radiology and radiation oncology, demonstrated the early impact of veterinary radiation oncology. [6]. Similarities between normal tissue responses to radiation in human and animal patients were observed and reported.[6]

Despite these early reports of success, radiation therapy, regardless of the species being treated, did not provide an easy or effective treatment for cancer. Serious radiation side effects often occurred, and treatment responses were not durable. [6] A more analytical approach to treatment was taken in the 1920 s and 30 s by Dr. Henri Coutard, a radiation oncologist at the Curie Institute in Paris. [7]; [8] Coutard was an outstanding clinical scientist who approached fractionation schemes in a scientific fashion. He improved basic orthovoltage treatment equipment by adding filtration to provide a reduction in skin dose and modest increase in treatment depth. He carefully evaluated the impact of dose per fraction, total dose, overall treatment time, tumor size and field size on tumor control and on adverse radiation effects. This information did not elucidate an understanding of the underlying radiation biology, but it did provide a fractionation protocol that was tolerated by normal tissues and resulted in long term tumor control for a number of different cancers. Concurrently, Dr. Alois Pommer, a veterinarian at what was then known as the Vienna Veterinary High School, received funding from the Rockefeller Foundation to establish a Roentgen Institute and purchase orthovoltage equipment for therapy. Pommer started a radiation therapy program for animal patients and published extensively on fractionation schedules, tumor control and radiation effects. The protocols developed by these two pioneering radiation oncologists provided a template for safe treatment for future decades. The mechanisms were not understood, but it was recognized that normal tissue were better preserved when radiation therapy was administered in multiple fractions, delivered daily.

The fundamental basis for radiation therapy is to maximize the energy deposition (i.e., dose) to the tumor while minimizing the dose to the surrounding normal tissue. In the 1950 s, technological advances including $^{60}\mathrm{Cobalt}$ machines and linear accelerators greatly expanded the role of radiation therapy. These machines produce photons with energy spectra greater than a million electron volts (designated as MV photons). This

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increase in energy is significant because the distribution of dose to tissues is different than for kV radiations. Megavoltage radiation is more penetrating and thus more accessible for treatment of deeply seated tumors. The dose received by the skin is also diminished significantly. Thus, patients are more comfortable during and following therapy because of decreased radiation effects to skin. Megavoltage radiation is distributed homogenously and predictably through deep seated tissues, permitting the development of computerized treatment planning systems. Radiation therapy was changing, and benefiting both human and veterinary patients.

II. Connecting Particle Accelerators to Veterinary Radiation Oncology–a Case History at Colorado State University

Dr. William Carlson, a veterinarian trained at CSU, acquired distinctive training by completing a Radiology Residency and Ph.D in Radiation Biology at the University of Colorado Medical School. Shortly after his faculty appointment at CSU, he started a program in radiation oncology. CSU was not the first veterinary radiation oncology program in the US; M. A. Emmerson established a program at the University of Pennsylvania in 1938. [9] However, Carlson's program was unique in focusing on outcome based medicine and a direct effort to solicit federal and private funding for a research program in basic radiation biology.[10] Carlson was fortunate to have Edward L. Gillette as his radiology resident and graduate student. Gillette nurtured and advanced the radiation oncology program, assuming responsibility in 1961. [11]–[13] Gillette's vision crystallized during a sabbatical leave at M. D. Anderson, where he worked with Drs. Herman Suit and Rodney Withers, physician scientists who were leaders in integrating radiation biology into clinical radiation oncology. Suit and Withers immediately appreciated the potential of naturally occurring tumors in pet animals as a resource for evaluating radiation biology and tumor treatment response, and they encouraged Gillette to develop clinical trials to help answer important radiobiological questions. Gillette went on to establish a program in clinical and experimental radiation therapy in 1969, which became known as the Comparative Oncology Unit. Gillette mentored many bright and enthusiastic graduate students who helped strengthen his program and went on to establish programs of their own at other universities. Gillette maintained long term collaborations with many of his former students, including Drs. Donald Thrall and Mark Dewhirst who sustained continual multi-institutional collaborations with Gillette until his death in 2006. It should be noted that veterinarians represent a very small market share of medical instrumentation compared to human counterparts. Radiation therapy units used in veterinary medicine were designed for humans and as such, adaptations were always required.

Gillette's early clinical trials, supported by the NCI, relied on a non-isocentric AECL Eldorado 8 Cobalt 60 teletherapy unit. [14]; [15] But the linear accelerator (linac) was emerging as the optimal tool for administering external beam radiation therapy. An important advantage was the capability to use multiple isocentric beams focused on the prescribed treatment volume and thus reducing the dose to surrounding normal tissues. These linacs could also directly produce electron beams in the 4-6 MeV range that only penetrated a few centimeters in tissue. This provided a distinct clinical advantage for treating superficial tumors by dramatically reducing the dose to deep tissues and organs while still providing reduced doses to the skin (Fig. 1)

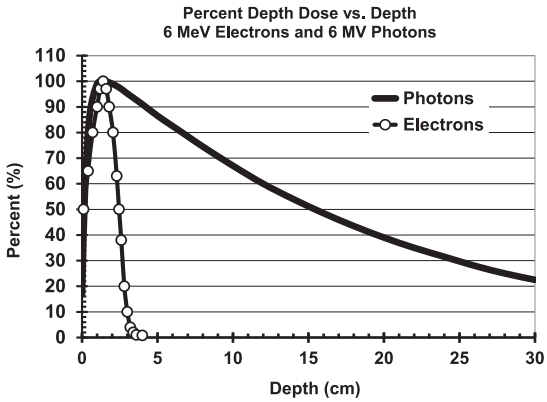

Fig. 1. Dose as a function of depth in tissue for 6 MeV electrons and 6 MV photons generated in a clinical accelerator.

Thus in order to remain technically relevant, Dr. Gillette required an accelerator, specifically with the capability of treating with electrons in addition to photons. The opportunity arose when the Veterinary Teaching Hospital moved from the Glover building on campus, to south campus. A grant to the National Department of Health, Education, and Welfare (HEW) to relocate all of College of Veterinary Medicine and Biomedical Sciences (CVMBS) had been funded. However, the Colorado General Assembly did not approve the matching funds that the HEW grant required. A number of alternatives were considered, including improving existing facilities on campus and reducing the student enrollment from 137 to 100. Eventually a scaled down version relocating only the teaching hospital was approved. Matching money came from Colorado along with contributions from states associated with the Western Interstate Commission for Higher Education (WICHE) program. The ground-breaking ceremony for the new veterinary teaching hospital came on March 8, 1977, but money to alleviate the problem of aging and obsolete equipment was not resolved until final negotiations with the WICHE states to pay a proportional share of the cost of veterinary education. Thus the purchase of a linear accelerator became a reality.[10] The new veterinary teaching hospital on Drake Road had been built with a radiation vault in the northwest corner, with shielding designed for a ^{60}Co therapy unit. Now that vault needed an accelerator.

III. Procurement of the First Linear Accelerator for Veterinary Oncology and Challenges Specific to Animal Dosimetry and Oncology

Choosing an accelerator that would meet the growing needs of his program was the next step. The objectives were to maintain the isocentric and collimation capabilities of photon beams available with current clinical accelerators while taking into

Fig. 2. Dr. Edward Gillette with the Clinac-6 linear accelerator at Colorado State University.

consideration that a deeply penetrating beam was not necessary for most veterinary patients. Intraoperative Radiation therapy (IORT) was emerging as an important cancer treatment modality and Gillette wanted a machine capable of producing electrons as well as photons. In addition, the quality control and reproducibility of beam monitoring electronics could not be compromised under the fiscal constraints mandated in veterinary practice where third party reimbursements were not available for clinical services.

Gillette chose a previously owned 6 MeV linac refurbished by the JM Company from Milpitas CA. (Fig. 2 and Table I) The machine was produced originally by Varian as a Clinac-6. It was one of the first commercially produced medical linacs, and the first to bear the Clinac trademark. The Clinac was also the first model with an isocentrically mounted gantry capable of 360° rotation.

The specific unit was selected because it was possible to produce 6 MeV electrons, which were essential for Gillette's research goals. The system could be converted to electron beam operation for therapy by activating an interlock key at the control desk, and inserting a mechanical key into the X-ray head which translated the photon transmission ionization chamber and flattening filter out of the bean defined by the collimating applicator. It also modified the bending system so that the electrons miss the target and emerge through the vacuum chamber window along the axis of the X-ray beam defining system. A multi-holed beam diffuser, designed to reduce the intensity of the emerging electron beam, was inserted into the head and an assembly, containing the electron transmission beam monitor was attached to the head. This attachment also served as the receptacle for plastic applicators that defined the transverse dimensions of the electron beam at the surface of the patient.

David Taylor, a radiation therapy medical physicist from Presbyterian Hospital in Denver, provided acceptance testing and initial dosimetry tables for the 6 MV photons. Dr. Thomas Borak, a radiation physicist in the Department of Radiology and Radiation Biology, participated in the start-up process including compliance with the State of Colorado, shielding modifications and interlock development.

TABLE I

Characteristics of the CSU Clinac-6	
Vacuum pump	Sputter ion high vacuum
Electron Source	Bombarded cathode electron gun
Modulator	10 kV power supply with solid state rectifiers and hydrogen thyratron switching at 47 kV to magnetron
Injection energy into wave guide	80 kV
Peak power of Magnetron	3,000 Mc/s (S-band) 2 MW: tunable
Length of wave guide	152 cm
Voltage to standing-wave ratio (VSWR)	1.1 over the 8 Mc/s tuning range
RF pulse length	2 μs
Output beam	1.5 μs pulses of 149 mA at 6 MeV
Electron Bend before Target	Dual magnet 90°
Photon Target	Transmission type gold target
Initial Photon Beam collimator	9 cm tungsten primary collimator
Rectangular beam definition	Two motorized pairs of tungsten and lead 12.5 cm thick
Variable beam dimensions	0x0 to 25x30 cm at isocenter
Beam monitor	Transmission parallel plate ionization chamber with digital integrator
Gantry Rotation	360°
Distance of Isocenter from Target	100 cm
Location of Isocenter above floor	117 cm (46")

The absolute accuracy and precision for clinical radiation therapy was constrained to $\pm 2\%$ at the reference location for beam calibration. These criteria were verified routinely for photons using therapy grade ionization chambers with calibrations traceable to NIST. However, one of the initial challenges during commissioning of electron therapy was inconsistent output from the beam monitoring system that was not capable of accommodating the high intensity electron beams emerging from the beam diffuser. Robert Scott, an electromechanical specialist at the Veterinary Teaching Hospital, collaborated with Dr. Borak to design and install an analog to digital charge integrator that provided reproducible calibrations of dose per monitor unit.

Borak and Scott continued to modify the accelerator facility to keep pace with Gillette's emerging research needs, which of course benefited clinical patients as well. Beam defining electron applicators providing well defined collimation and reproducible dosimetry were developed to investigate normal tissue tolerances for a wide variety of organs. [16]; [16]–[20]

A photon treatment planning system originally used for human radiation oncology needed extensive modification and dose verifications to accurately accommodate the shallow depth of tumors often observed in the smaller veterinary patients. The early treatment planners faithfully reproduced axial and transverse beam characteristics at depths beyond 5 centimeters where most human tumors are located. However there were significant differences in the dose distributions in the 5 cm region near the surface where many canine tumors are located. Rather than attempt to revise algorithms in the treatment planner, they adjusted input files from the beam scanning system such that the treatment planner ultimately reproduced beam profiles within ± 3 mm of the actual measurements. An electron treatment planning system was implemented and verified.[22]

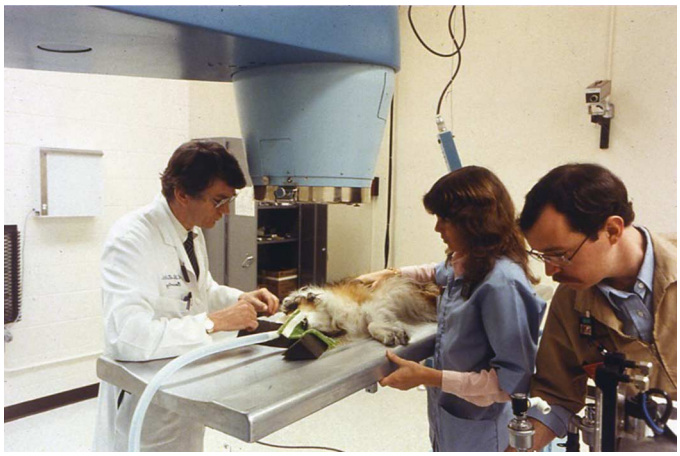

Fig. 3. Dr. Gillette with researearch associate Sharon McChesney-Gillette and anesthetist Ken Crump prepare a patient for therapy. The first trteatment table was adjusted vertically using a gear assembly operated by manually turning a wheel.

Keeping the machine operational was critical with the increasing clinical caseload and diverse research program. A normal maintenance contract was prohibitively expensive for veterinary oncology at that time. Thus Borak and Scott performed necessary preventative maintenance and completed specialized repairs such as replacement of the upstream electron gun and downstream gold target for generating photon beams. Days were spent trouble shooting malfunctions, supplemented by telephone communications with the engineers at JM Inc.

Several accelerator components, (e.g. the electron gun assembly), had a recommended shelf-life. It was not practicable to obtain and store these on-site since the operational lifetime could be longer than the shelf-life. To circumvent this constraint, without the benefit of a service contract, these items were purchased whenever fiscal resources became available through an escrow agreement with JM Corporation. When the failure of a major component was diagnosed, a phone call was made to JM requesting them to send a "fresh" unit, with full life-time expectancy, by overnight express. Borak and Scott made all the necessary preparations to streamline installation once the item arrived the next day. Installation was usually completed late in the evening of the delivery day, followed by beam scanning, dosimetry and quality insurance. They were pleased to greet the therapy team the next morning with the news that all systems were up and running.

Major repairs were intermittent. There was considerable anxiety when they became necessary, because experience gained from frequent repetition was not available at a facility with only one accelerator. The "nail biting" episodes were usually associated with replacing the electron "gun" upstream of the RF cavity or photon target downstream of the RF cavity, both of which were within the high vacuum system. Releasing the vacuum was performed using garbage bags filled with nitrogen to prevent contamination. The squeal and creaking of ageing accelerator components was somewhat terrifying. The canonical "sigh of relief" occurred following the repairs when the sputter-ion high vacuum pump successfully took over from the roughing pump, which did not always happen on the first attempt.

Anesthesia was required for immobilization and reproducible patient positioning for each fractionated treatment. Early studies determined that clinical treatments should be limited to alternate days, i.e., Monday-Wednesday-Friday, because no anesthetic agents, available at that time, could be delivered safely on successive days. The availability of isoflurane in the early 1980 s eliminated this restriction and treatments five days per week were now possible, similar to human protocols.

Sharon McChesney-Gillette served as the first radiation therapist, treating clinical patients (including clinical trial patients) in the morning and then moving on to research dogs in the afternoons. (Fig. 3) She and Scott devised and constructed unique restraining and positioning devices. McChesney-Gillette's dedication and creativity in replicating treatment fields was essential for generating quality data.

IV. Impact on Radiation Oncology

The canine and pet animal models for experimental therapeutics have played an important role in evaluating mechanisms and efficacy of new oncologic treatments.[23]–[26] Medical principles can be studied in dogs and cats and the information can be applied to human subjects. Translational research has become a well-recognized tool and was recently the subject of an Institute of Medicine workshop. [27] Gillette's vision of translational research, encouraged and supported by long term colleagues such as Drs. Herman Suit and Rodney Withers, resulted in the first sustained program of its kind. Gillette's work in intraoperative radiation therapy set the standard for normal tissue tolerances in human and veterinary medicine, and his work evaluating the impact of fraction size and field size helped create data on α/β ratios that are still used by both veterinary and human radiation oncologists. [16]; [18]; [28]–[39] Graduate and post- doctoral students, including Drs. Barbara Powers, Jack Hoopes, McChesney-Gillette, Zeljko Vujaskovic and many others evaluated the impact of IMRT on vasculature, bone, nerves, muscle, ureter, and other abdominal tissues.[17]; [35]; [36]; [40]; [40] This work included the development of extensive endpoints previously not used, including physiological function and analytical histomorphometry. [41]; [42]

Another aspect of the research program evaluated the impact of dose and fractionation on normal tissue structures, including spinal cord, heart, mediastinum, trachea, and lungs.[37]; [37]; [38]; [43]–[47] Thematically, this series of studies evaluated subjects at different time points using multiple endpoints. It still provides a unique catalog of normal tissue response to injury that remains an important radiation oncology resource.

Gillette's early work with naturally occurring canine oral squamous cell carcinomas verified the concept of therapeutic gain and was an important publication in the establishment of naturally occurring tumors as a translational model. [14]; [48] His work with canine sarcomas using the radioprotectant WR2721 foresaw the potential clinical disadvantages of the drug, including nausea and vomiting. [49] Gillette also evaluated a host of other experimental therapeutics using the naturally occurring tumor model, including local and whole body hyperthermia.[50]–[53]

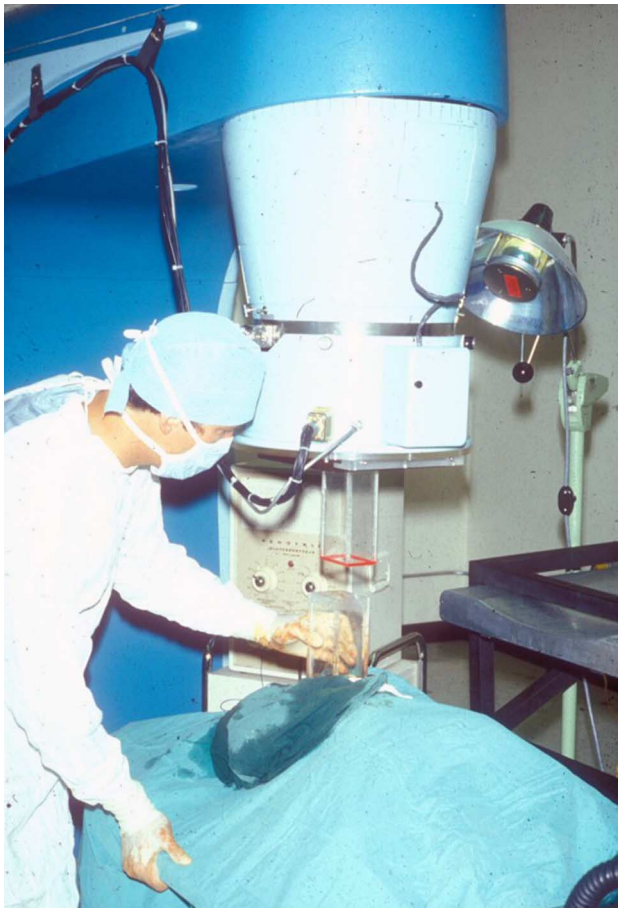

Fig. 4. Dr. Withrow docking an intra-operative electron applicator for the IORT research project. Note the assembly attached to the head of the accelerator that contains the electron beam monitor and plastic extension applicators defining the dimensions of the beam at the surface of the patient.

Gillette's translational work also directly influenced veterinary radiation oncology by establishing dose and fractionation schedules that yielded improved clinical outcome for a variety of tumor types. (14, 48, 49, 51) This increased enthusiasm for radiation oncology and resulted in an influx of new veterinary radiation oncology centers, including facilities in private practice settings. As in human oncology, radiation therapy became the standard of care for many veterinary cancers.

The accelerator was also used for a number of collaborative projects. Of note was work with Dr. Mary Anna Thrall using whole body radiation therapy as a conditioner for bone marrow transplantation on her studies of feline mucopolysaccharidosis as a model of human neuronal storage disorders. An anesthetized cat presented a large irregular and non-reproducible shape for treatment planning. To overcome this obstacle, the patients were placed in a cylindrical plastic tube that slightly compressed them into a consistent configuration during irradiation. The accelerator was rotated to produce a broad horizontal beam and the patient moved 2 meters beyond the normal isocenter. Dosimetry verified that a uniform whole body dose could be achieved with a bilateral exposure by rotating the cylinder laterally 180° without having to change settings on the accelerator.[54]

When Gillette first began treating patients and instituting clinical trials, many clinical faculty members were skeptical and uncomfortable with the concept of treating cancer in animals. Gillette employed veterinary students to roam the wards and identify animals with tumors that could benefit from cancer treatment if enrolled in existing clinical trials. Gillette's work with spontaneous tumors was markedly enhanced when Dr. Stephen J. Withrow became a faculty member in 1978. (Fig. 4) Withrow was a veterinary surgeon with a passion for treating patients with cancer. Together, Gillette and Withrow developed a robust program of projects that helped establish limb sparing surgery as a model for the treatment of osteosarcoma.[51] This important collaboration was a stepping stone to the formation of the Flint Animal Cancer Center at CSU. Dr. Susan LaRue became director of the clinical radiation oncology program when Dr. Gillette became Department Head of Radiological Health Science in 1989. She developed new translational models, continued the long term collaborations with Duke and North Carolina State, and strengthened the clinical radiation oncology program. [55]–[57] LaRue played an important role in transitioning to newer technologies for clinical and translational use, and continued the tradition of educating veterinary radiation oncologists and radiation biologists. [57]–[63]

In 1994 Veterinary Radiation Oncology was recognized as a specialty by the American Board of Veterinary Specialties. Veterinary radiation oncology training programs and an examination process were formalized. Presently there are over 80 veterinary radiation therapy centers and over half are located in private practice settings. In a unique relationship between Veterinary and Human Medical Specialty groups, The American Society for Radiation Oncology (ASTRO), formally recognized the Diplomates of the American College of Veterinary Radiology, Specialty of Radiation Oncology, as colleagues eligible for full membership into ASTRO.

The first accelerator at CSU was decommissioned in 1994 and replaced with a refurbished Siemens Mevatron. This Mevatron was a next generation clinical accelerator that produced flatter photon fields and had turnkey electron capabilities at 5, 6, 7, 8, 10 and 12 MeV. Improved electronics and mechanical capabilities made linacs more conductive to a project evaluating radiation effects to normal lung, heart, and esophagus. Gillette and his team were collaborating with Drs. Joel Tepper and Edward Chaney of the University of North Carolina who provided Gillette access to one of the first 3- dimensional treatment planning systems for the project. [47]; [64]

This generation of clinical accelerators began to implement microprocessors and software for the operating systems. Trouble shooting was based on understanding the software/hardware interfaces which were often proprietary. In effect, a maintenance contract became necessary, and many of the in-house procedures developed for repair of the Clinac 6 were now obsolete.

Interestingly, the original accelerator, after leaving CSU, was again refurbished. It was recommissioned at Yale to replace a Clinac 6 that was used in their long standing total skin electron electron therapy program for the treatment of mycosis fungoides.[65] The machine remained in operation until

2001 when it was destroyed in a flood. It is thought to be the longest commissioned Clinac 6. *(Personal communication, Stan Mansfield).*

V. Other Early Particle Accelerators in Veterinary Medicine

It is important to note that Cambridge School of Veterinary Medicine, under the guidance of Dr. L. N. Owen, was the first veterinary center to regularly treat veterinary patients with a clinical linear accelerator. [66] The program at CSU was designed to benefit companion animals as well as informing the development of clinical protocols in human patients and it could not have been accomplished without exclusive access to a linear accelerator. And while it is clearly the personnel at CSU and affiliated centers that were key to the program's success, the accelerators reliability and flexibility helped provide inspiration.

By the turn of the century, dramatic technological advancements presented scientists with new questions to investigate. The Flint Animal Cancer Center at Colorado State University became the first veterinary facility in the world to obtain a state-of-the-art linear accelerator committed to veterinary clinics and research, in part due to 1 million dollars from the CSU Academic Enhancement Program.

This acquisition of the Varian Trilogy was a significant achievement. The Trilogy was a new and modern clinical accelerator as opposed to the refurbished units obtained previously. It was the first of its kind in Northern Colorado and it provided an important platform for translational research. The Trilogy accellerators are equipped with mechanical features such as a multi-leaf collimator, robotic table, onboard imaging, and respiratory gating to assist in treatment to treatment patient positioning. However the most significant advances have been in the development and implementation of software control of the accelerator during treatment. This automation provides spatial and temporal control of the beam for Intensity Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation Therapy (SBRT), and Image Guided Radiation Therapy (IGRT). Execution of these advanced concepts are made possible with three dimensional imaging and treatment planning capabilities that transfer data directly into a computerized operating system which controls gantry rotation, conformal collimation, and beam intensity during a prescribed therapeutic protocol.

The latest generation of linear accelerators has provided the framework for evaluating the impact of stereotactic radiation therapy on normal tissues, and the clinical outcome of treating naturally occurring tumors, thus continuing the tradition of translational research.[57]; [62]; [67]–[69].

VI. Conclusions

Veterinary Oncology today is a mature and thriving discipline. Its strengths are based on modern clinical capabilities for cancer treatment in animals as well as a strong research component that benefits both veterinary and human medicine. The rapid pace of advances in imaging and clinical accelerators for humans can be applied to radiation therapy for veterinary medicine without significant alterations. Perhaps the most serious obstacle is managing the cost of the wide variety of technological capabilities. The demand and scope of veterinary oncology will never be the primary driver for future accelerator development. However, the input from translational research can provide important information on remission, recurrence, late effects and secondary cancers that will apply directly to technology development for human oncology. These benefits apply to photon, electron and hadron therapy.

This state of affairs would never have been realized without the vision and dedication of the personnel in the College of Veterinary Medicine and Biomedical Sciences at Colorado State University. A "used" 6 MeV electron accelerator might now appear to be an inadequate introduction to radiation therapy. But at the time, it was an unprecedented decision for the veterinary community. This accelerator was capable of providing photons and electrons for pioneering advancements in radiation therapy and could be maintained economically with a conventional tool box and digital volt meter. It was the foundation of a sustained process that slowly generated confidence, experience, and training for the current generation of veterinarians who are capable of transitioning directly to state-of-the-art clinical accelerators.

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