REG001-09

Evaluation Tracking Project: A Prospective Chart Review of Patients Treated with Radiation Therapy

Study Chair Carlos E. Vargas, MD 5777 East Mayo Blvd Phoenix, AZ 85054 480-342-1262 carlos2002@gmail.com	**Co-Chair** Sameer Keole, MD 5777 East Mayo Blvd Phoenix, AZ 85054 480-342-1262 keole.sameer@mayo.edu
Co-Chair/Radiation Oncology William Hartsell, MD CDH Proton Center 4455 Weaver Parkway Warrenville, IL 60555 877-887-5807 william.hartsell@cadencehealth.org	**Co-Chair/Radiation Oncology** Gary Larson, MD ProCure Proton Therapy Center 5901 West Memorial Road Oklahoma City, OK 73142 888-847-2640 gary.larson@okc.procure.com
Co-Chair/Radiation Oncology Henry Tsai, MD ProCure Proton Therapy Center 103 Cedar Grove Lane Somerset, NJ 08873 877-967-7628 henry.tsai@nj.procure.com	**Co-Chair/Radiation Oncology** George Laramore, MD SCCA Proton Therapy-A ProCure Center 1570 North 115th Street Seattle, WA 98133 877-897-7628 georgel@u.washington.edu
Co-Chair/Radiation Oncology Jin-Shei Lai, Ph.D., OTR/L Northwestern University 710 North Lake Shore Drive, Suite 724 Chicago, Illinois 60611 312-503-3370 js-lai@northwestern.edu	

Amendment #4: March 5, 2015
Amendment #3 Date: May 9, 2013
Amendment #2 Date: March 09, 2011
Amendment #1 Date: February 04, 2011
Activation Date: July 01, 2009
Original Version Date: May 16, 2009

PROTOCOL SIGNATURE PAGE

REG001-09

Evaluation Tracking Project: A Prospective Chart Review of Patients Treated with Radiation Therapy

Protocol Version March 5, 2015

I certify that I have read the protocol. I agree to conduct the protocol according to ethical principles stated in the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations, whichever provides the greatest protection of the individual. I will accept the monitor's oversight of the study.

_____ _____

Signature of the Site Principal Investigator Date

_____

Principal Investigator's Printed Name

_____

Name of Facility

_____

Location of Facility (City, State)

PLEASE COMPLETE AND SEND TO THE PROTON COLLABORATIVE GROUP OFFICE VIA EMAIL: HQ@PCGRESEARCH.ORG

INDEX

SCHEMA

Stratify

Modality

Proton Therapy, Photon Therapy and other forms of radiation and non-proton radiation

Sex

- Male
- Female

Age

- <18 yrs of age
- 18 to <50 yrs
- 50 to <70 yrs
- ≥70 yrs

Patient population:

- Patients who will be treated with radiation therapy at participating centers
- Patients over the age of 18 who are able to understand and sign an IRB approved consent including HIPAA authorization form.
- Patients under the age of 18 whose legal guardian is able to understand and sign an IRB approved consent including HIPAA authorization form.

Executive summary: The tracking program allows the collection and analysis of patient information to evaluate the disease process and treatment related outcome thus defining strengths and weaknesses of our program ultimately leading to better patient care. The Evaluation Tracking Program (ETP) consists of prospective enrollment and collection of information from the date of the ETP approval and patient consent.

1.0 INTRODUCTION

Optimal patient care requires an understanding of the outcome of treatment. It is not accurate to assume that one can extrapolate results from one doctor's practice, or one healthcare setting, to another. Every situation has its own individual factors that may affect the results of medical therapies. Ideally, all healthcare providers would systematically analyze the outcome of their management in a way that allows them to identify the practices that are working well, as well as those that should be modified to improve healthcare delivery. This is true for both large organizations and individual doctors.

Proton therapy is offered at a number of centers throughout the United States. While this type of radiation therapy is in no way experimental, it is relatively new in the context of its use (versus conventional photon radiation therapy). We feel strongly that we should make every effort to collect and report data on our outcomes with protons for 2 major reasons:

- With the rare privilege of access to a proton center comes an important social and academic responsibility. This cutting edge technology comes at a significant financial price (over $100 million), and in many ways, the future of this radiation modality depends on whether or not a substantial benefit can be obtained with proton radiation therapy.
- With all treatment modalities, we believe it is the best practice to provide the patient with actual outcome data from our own practice when obtaining an informed consent for treatment from a patient. Not only does this data serve us as the best source of information on probable outcomes for the patient, but it also provides us with the best tool for continuous quality assurance and improvement.
    - More specifically, clarification of prognostic variables will help to identify the subgroups of patients who are likely to benefit from different management strategies in the future.
    - Also, comparing outcome with different treatments that are used over time, either here at our center, or with published results from other centers, will allow us to identify the programs that are, and are not, working optimally.

1.1 Background Information Regarding Proton Radiation Therapy

"Conventional" radiation therapy (RT) refers to treatment with X-rays (also called photons). William Roentgen is credited with the discovery of photons (for medical use) in 1895.[1] He created the first known X-ray image when he accidentally exposed his wife's hand. A few months later, in January 1896, Emil Grubbe became the first person to use photons in a therapeutic fashion when he treated a woman with recurrent breast cancer in a palliative setting.[2] Today nearly 50% of patients with cancer in the United States receive radiation therapy. Linear accelerators are the most common source of photons for radiation therapy.

Conventional photon RT is very effective, but cannot be targeted for a specific depth range. Photons follow simple rules of physics. For a 6 Megavolt (MV) photon radiation beam, its greatest energy deposition will be 1.5 cm beyond its impact with tissue and it will lose about 4% of its energy for each centimeter of tissue it passes through.[3,43] For a single photon beam, the greatest energy is not necessarily near the target structure and the beam always travels past the target structure. For photon RT, the radiation side effects are directly related to the tissue through which the beam passes.

Proton RT differs from photon RT in that it uses charged particles. For this reason, protons can be targeted for a specific depth range. Charged particle RT has better physical characteristics than photons, resulting in lower radiation in the healthy tissues prior to the target volume. Past the target zone, there is almost an immediate fall-off of radiation dose. This sharp peak of radiation dose deposition is referred to as the "Bragg peak" and is unique to charged particle radiation, and in terms of this protocol, proton radiation. [5]

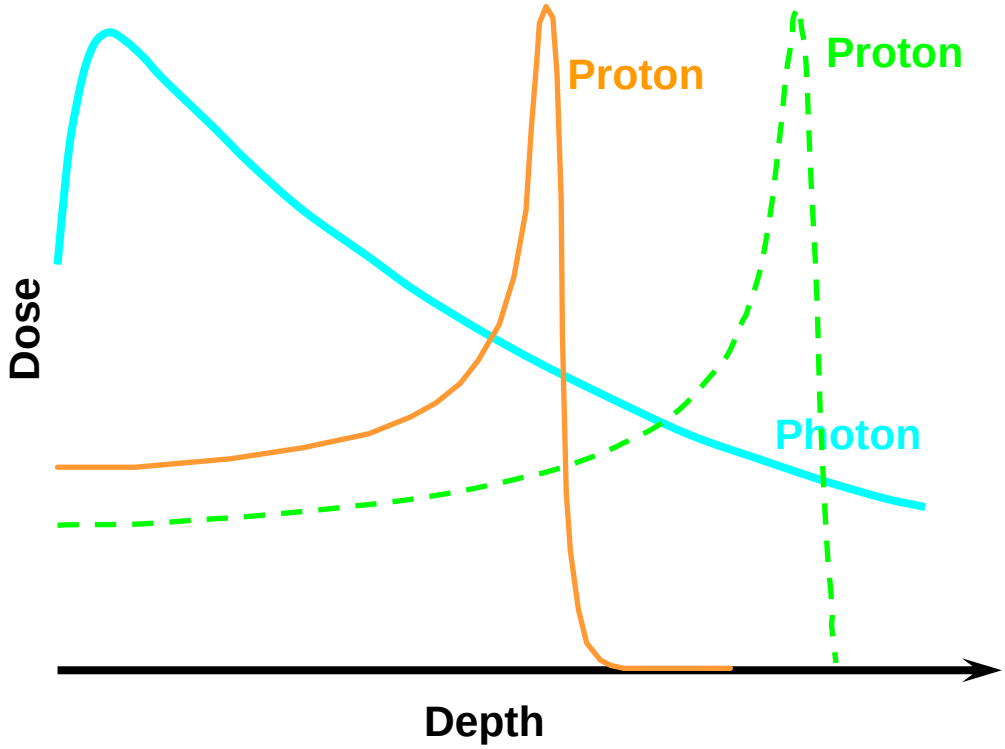
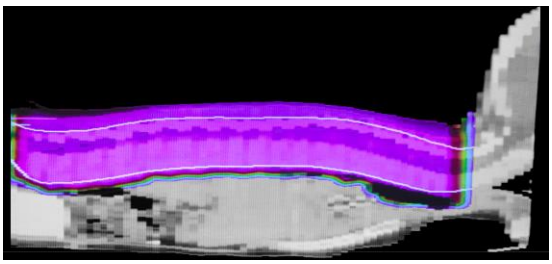
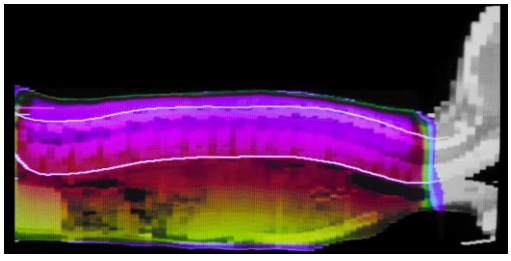


Diagram 1: Depth-Dose diagram demonstrating the "Bragg peak" of protons. Electrons and photons deposit their greatest dose close to the surface of the patient. Protons deposit their greatest dose in the Bragg peak, which can be adjusted for individual patients and their specific target area by adjusting the energy imparted to the proton particles.

As a result of the Bragg peak, side effects due to proton RT can be limited (versus photon RT), since there is less dose to non-target tissues. Below is the dose reconstruction of a child receiving radiation therapy to the spine for a brain tumor. The diagram on the left depicts dose fall-off using proton RT. The diagram on the right depicts continued "exit dose" using photon RT.





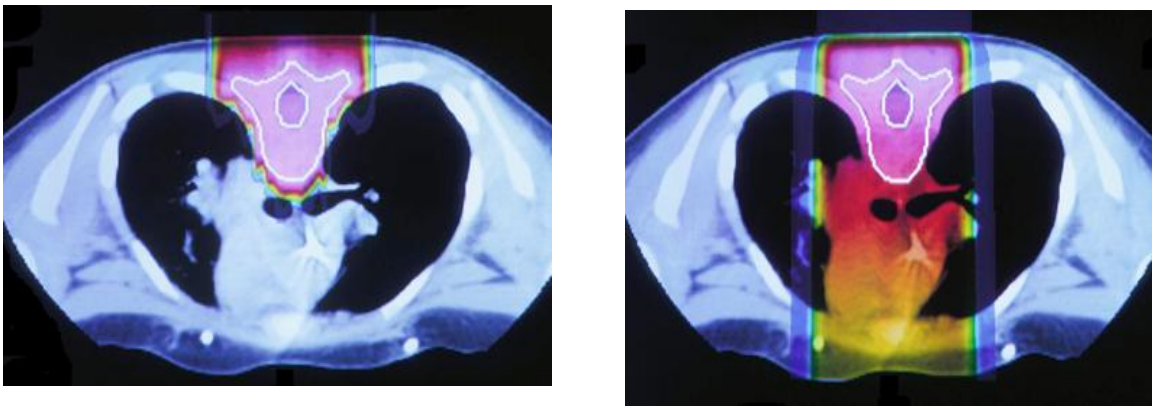


Diagram 2: The sagittal and axial views on the left are from a CSI (craniospinal irradiation) plan using protons. The sagittal and axial views on the right are from a CSI plan using photons. The proton CSI plan is able to avoid distal fall-off to visceral organs, including the heart.[6]

Therapeutic gain (TG) refers to an increase in the ratio of tumor control probability (TCP) to normal tissue complications (NTC).

$$TG = TCP/NTC$$

A TG can be achieved by either an increase in TCP relative to NTC or a decrease in NTC relative to TCP. Protons allow for a TG using both.

Protons allow for increased TCP since more of the dose can be delivered safely (versus photons). An example of this is using proton RT in the setting of base of skull chondrosarcoma or unresectable osteosarcoma. In these cases, the TCP is driven up with higher doses.

Protons allow for decreased NTC by better dose distribution. By having decreased dose delivered to the build-up (pre-target volume) regions and almost immediate dose fall-off past the target volume, the integral dose (total dose under the curve) is decreased. Lower integral dose means decreased radiation dose to the patients' normal tissues, allowing for decreased acute and chronic side effects. In the case of the child receiving CSI-craniospinal irradiation (as shown above), the improved TG is a result of decreased NTC, since there is minimal risk of radiation injury to the visceral organs (heart, lungs, etc) anterior to the target volume. This can be seen in diagram 2.

Protons have potential for significant improvement over conventional photons in that dose escalation is easier to achieve and normal tissue toxicity is easier to avoid. This is the case even when comparing intensity-modulated radiation therapy (IMRT) with protons. IMRT is a treatment technique which uses photons in a complicated treatment pattern, utilizing multiple field arrangements and varying photon intensities. While conformality to a treatment volume is improved (versus a standard photon treatment plan), the additional fields require additional radiation to be given and as a result, the patient's overall radiation exposure (defined as integral dose) actually increases. [7] Integral dose, in simple terms, is the total amount of irradiation being delivered to the entire body. This accounts for not just the radiation dose being delivered to the target site, but also the radiation dose delivered along the direction of the photon beam as it travels to and past this site. A high integral dose means excessive radiation in non-targeted tissues. IMRT, since it uses many additional beams to improve conformality, also results in an increase in integral dose. Thus, when using photons, the cost for improved conformality is increased integral dose.

Protons will achieve a higher degree of dose conformality than even the best IMRT plans while keeping integral doses far lower than even the best standard photon plan. In the example of pediatric patients being treated with craniospinal irradiation, protons match the conformality of IMRT, while significantly decreasing the dose to normal structures.

In short, while photon RT delivery has improved significantly in the past 50 years, we are reaching the end of meaningful improvements. To see significant progress in RT, a different modality needs to be used. Protons are an improved radiation modality over photons, due to their physical characteristics. Protons, even when delivered with the simplest planning, will provide a superior radiation dose distribution compared to the best delivered photon RT, such as IMRT, because of reduced integral dose.

To better compare results between different radiation modalities it is necessary to have similar data sets of patients treated with either modality. The registry will include patients treated with photons, brachytherapy, radiopharmaceuticals, protons or other forms of radiation. The inclusion of patients treated with different radiation modalities will allow us to compare treatments and do comparative effectiveness research between modalities and better evaluate the role of proton therapy.

Dose distributions to the target volume and critical structures are listed in diagram 3 for a standard photon plan, an IMRT plan, and a proton plan. (Figures and data from Massachusetts General Hospital). [6]

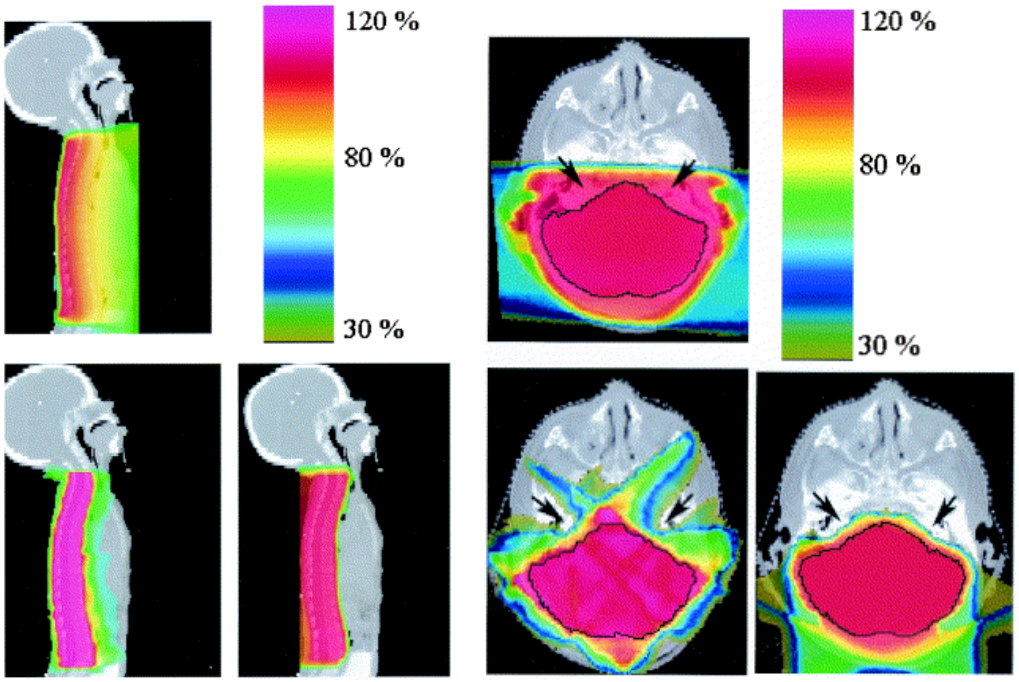


Diagram 3a. The above diagrams depict a pediatric patient receiving craniospinal irradiation (CSI) with a posterior fossa boost. The sagittal body images and axial cranial images, in order, graphically show the radiation dose distributions of a conventional photon radiation plan, intensity modulated photon radiation plan, and a proton plan. The proton plan has a much lower dose distribution outside of the target areas.

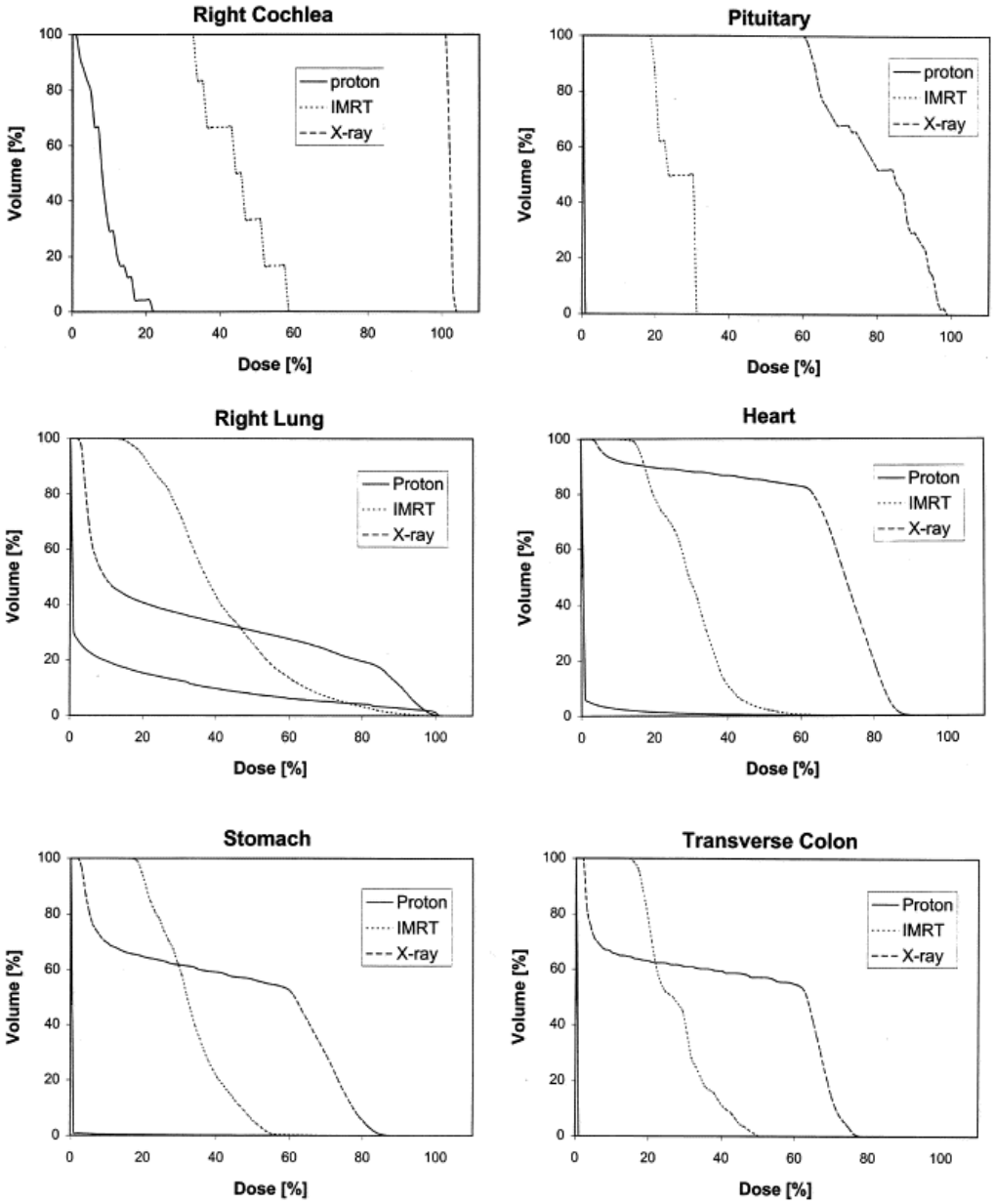


Diagram 3b. The above dose volume histograms (DVH) represent the amount of radiation dose an organ system receives with the different types of radiation used. Note the significantly lower dose to all of the organs with proton radiation. For the pituitary, stomach, and transverse colon, the dose to these organs is so negligible that a graph line cannot be demonstrated.[6]

Modalities of Radiation Therapy

- External-beam RT with photons
- External-beam RT with protons
- External-beam RT with electrons
- Brachytherapy using low-dose irradiation
- Brachytherapy using high-dose irradiation
- Radioisotope administration
- Proton therapy pencil beam or passive scatter

2.0 OVERALL OBJECTIVES

2.1 Define outcomes for patients treated at participating institutions.

2.2 Determine strategies necessary to improve patients outcome and decrease toxicities related to treatments and procedures.

2.3 Improve patient care by an adequate understanding of the results and patient population at participating institutions.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Patients who will be treated with radiation therapy at participating centers.

3.1.2 Patients over the age of 18 who are able to understand and sign an IRB approved consent including HIPAA authorization form.

3.1.3 Patients under the age of 18 whose legal guardian is able to understand and sign an IRB approved consent including HIPAA authorization form.

3.2 Inclusion of International Subjects

Patients from outside of the United States may participate in the study. Enrollment and treatment must be completed at an approved PCG member institution in the United States.

4.0 REGISTRATION

4.1 PCG headquarters must have documentation of each institution's IRB approval of the protocol on file prior to prospectively registering patients.

4.2 Obtain written informed consent from the participant prior to registration.

4.3 Verify the patient meets the eligibility criteria prior to enrolling the patient.

4.4 Patients must be registered through the PCG Electronic Data Capture (EDC) system. Patients can be registered only after eligibility criteria are met.

5.0 STUDY METHODS

5.1 Study Interventions

No additional interventions will be done for the purpose of this study. The only intervention involved in the ETP is the collection of the information and its analysis.

5.2 Data Collection

The information collected includes the following: socioeconomic, clinical data, treatment parameters, physics or dosimetric information, imaging studies required for staging, follow up or simulation of the patients; Pathologic evaluation of the tissue sampled for diagnosis or as part of the standard treatment process; Blood work pertinent to the disease process. Information related to treatment as surgery, chemotherapy, radiation or other modalities employed as treatment, or the management of the complications. Information will be collected from patient visits, via the medical record. Only information related to the patient's cancer disease that is being treated at the research site will be collected.

Different physics or dosimetric parameters will be calculated or derived from previously collected information.

Evaluation of this information may include the creation of different databases for statistical analysis of the information or the generation of physics/dosimetric parameters from the gathered information for analysis.

No additional interventions will be done for the purpose of this protocol. Only the information that is part of routine care will be collected for protocol purposes. Participating sites will be required to provide follow up information for each subject enrolled on at least an annual basis. More frequent follow up and data collection are highly recommended. If site staff is unable to obtain follow up information on a subject, sponsor level assistance in contacting the patient, or obtaining outside medical records, is permitted.

Databases will be used to collect the information necessary for the analysis. The information will be collected electronically in compliance with 21 CFR Part 11. Only patients consented with an IRB approved consent form will have their data collected for this study.

6.0 DATA ANALYSIS

The data generated will be analyzed employing different statistical packages or graphical representations. A wide range of analyses will be used depending on the nature of the data being evaluated. In some cases, the outcome analysis will be limited to a qualitative description of tumor status, survival, toxicity, treatment parameters, or dosimetric/physics related information. In other cases, statistical comparisons will be made between different groups of patients or treatment modalities.

6.1 Study Duration

This study will begin upon receipt of IRB approval. There is no expected termination date as this is an ongoing effort to record long-term information for patients.

6.2 Number of Subjects

At any point in time, the ETP database will contain information on tumor status and long-term toxicity on several thousand patients who have signed consent for the collection and analysis of their information.

7.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

This study will be conducted in full compliance with the Institutional Review Board regulations in 21 CFR 56. This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. Only staff members who have completed human subject protection training will obtain informed consent from the study participants.

Written informed consent and authorization of use and disclosure of PHI (as applicable in the US) must be obtained from each patient before performing any Screening/Baseline evaluations that are specifically study related (outside the scope of routine care). A copy of the signed informed consent document and HIPPA authorization will be given to the patient, and the investigative site will retain either the original *or* an exact copy electronically. The consent document must contain the 20 elements of informed consent described in ICH E6 4.8. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations.

7.1 Potential Risks to Subjects

The risk of participation in the ETP is minimal. Consideration is given to loss of confidentiality, but this risk will be minimized to the fullest extent possible.

7.2 Potential Benefits to Subjects

The primary objective of the ETP is to improve the care of future patients. Therefore, the patients may receive no direct benefit from enrollment.

However, continued analysis will benefit future patients as they themselves benefit today from knowledge generated from years of previous patient care.

A secondary objective of the initiative is to provide the best possible medical care to the patients that have received radiotherapy. Radiation Oncology is a specialized field with expertise about the management of long-term effects from radiotherapy. In many cases the patient is followed outside our department in the years following radiotherapy. In the past, when conducting retrospective research projects, we have been able to identify medical issues during the process. In these situations, we encourage the patient to seek follow up for this condition, either with us or a health care provider that they are more comfortable seeing. For this reason a potential benefit of the study is that it will enable us to identify patients who are likely to benefit from therapy that they are not currently receiving.

7.3 Withdrawal from Participation in the ETP

Patients have the right to prohibit the use of their health information for research purposes. Patients who withdraw or refuse participation in the ETP will not have their medical records reviewed or analyzed for the purpose of this study. However, if a patient withdraws consent during the study, any information collected previous to withdraw of consent cannot be withdrawn.

7.4 Study Data Storage and Confidentiality

Raw and collected research data will be stored in locked cabinets at all times. If electronic forms are used they will be kept in a password protected form. Electronic data will be in compliance with FDA CFR Title 21 Part 11.

No study documents will be destroyed or moved to a new location without prior written approval from the sponsor. If the site investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator or the institution where the study was conducted.

All information regarding the nature of the proposed investigation provided to the study chair by the site investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the investigator.

The anonymity of participating patients must be maintained. Patients will be identified by their initials and assigned patient numbers in CRFs and other documents submitted off site. Documents that will not be submitted off site and that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the CRA, or sponsor representatives.

REFERENCES

[1] Mould RF: A Century of X-rays and Radioactivity in Medicine. Bristol, England, Institute of Physics Publishing, 1993
[2] Grubbe E. Priority in the therapeutic use of x-rays. Radiology 1933;21:156-162.
[3] Depth dose tables for use in radiotherapy. A survey, prepared by the Scientific Sub-Committee of the Hospital Physicist's Association, of central axis depth-dose data measured in water or equivalent media. Br J Radiol 1961;10 Suppl:1-96.
[4] Cohen M. Central axis depth dose data for use in radiotherapy. General introduction. Br J Radiol 1972;11:Suppl-17.
[5] Schulz-Ertner D, Jakel O, Schlegel W. Radiation therapy with charged particles. Semin Radiat Oncol 2006;16:249-259.
[6] St Clair WH, Adams JA, Bues M et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Oncol Biol Phys 2004;58:727-734.
[7] Verellen D, Vanhavere F. Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region. Radiother Oncol 1999;53:199-203.