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Protocol Title: A Phase II Trial of Proton Radiation for the Treatment of Pediatric Rhabdomyosarcoma

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I. BACKGROUND AND SIGNIFICANCE:

Rhabdomyosarcomas account for 3.8% of solid malignancies in children under the age of 19 years. There are 320 cases per year in the United States[1]. It is a curable disease in most children with localized disease who receive combined modality therapy, with more than 70% surviving 5 years after diagnosis[2-4]. The most common primary sites for rhabdomyosarcoma are the head and neck (e.g., parameningeal, orbit, pharyngeal, etc.), the genitourinary tract, and the extremities[2,4] Other less common primary sites include the trunk, chest wall, the abdomen (including the retroperitoneum and biliary tract), and the perineal/anal region. Most cases of rhabdomyosarcoma occur sporadically with no recognized predisposing factor or risk factor[5], although a small proportion are associated with genetic conditions.

In the 1970's, a combined modality approach of radiation, chemotherapy and surgery when possible for rhabdomyosarcoma (RMS) was introduced and refined over the past three decades by the Intergroup Rhabdomyosarcoma Study (IRS) group who are on their fifth generation of trials IRS V (protocol D9803, D9602, D9501).

The prognosis for a child or adolescent with rhabdomyosarcoma is related to the site of origin, resectability, presence of metastases, number of metastatic sites, and histopathology[4-7]. Embryonal histology is more favorable than alveolar or undifferentiated. Certain areas are considered favorable sites such as the orbit, non-parameningeal head and neck, non-bladder/prostate GU. All other sites such as trunk, parameningeal, bladder/prostate and extremity are considered unfavorable.

Pediatric patients with RMS are categorized by stage and group. Staging helps determine what risk category patients are in and grouping helps determine the need and dose for radiation therapy.

Grouping: The IRS Grouping System (5 yr OS from IRS III)

Group I: Localized disease, completely resected (93%)
- a. Confined to muscle or organ of origin
- b. Infiltration outside the muscle or organ of origin

Group II: Total Gross Resection with: (81%)
- a. Microscopic residual disease
- b. Regional lymphatic spread, resected
- c. Both

Group III: Incomplete Resection with Gross Residual Disease (73%)
- a. After Bx only
- b. After major resection (>50%)

Group IV: Distant metastatic disease present at onset. (30%) (If bone metastases are present at diagnosis, then there is only 10% chance of cure.[8])

TNM Pretreatment Staging Classification:

Stage	Sites	T (confined?)	T size	N	M	5 yr OS
I	Orbit, H and N, GU-non bladder/prostate	Either	A or B	**Any**	0	89%
II	Bladder/Prostate, Extremity, Parameningeal, (Other, trunk, retroperitoneal)	Either	A (≤5 cm)	N0, Nx	0	86%
III	Same as II but either large or node +.	Either	A B	N1 N0-1	0	69%
IV	All				1	30%

T1: confined to anatomic site of origin, T2: extension beyond anatomic site
A: ≤5 cm, B> 5cm

Most of the pediatric patients treated in the United States are treated in major academic centers that participate in the IRS protocols. Chemotherapy and radiation therapy is dictated by the protocol upon which the patient is treated (currently IRS V). If a patient is not on-protocol already they will be treated according to the guidelines of either IRS IV or IRS V. IRS IV was the last completed trial that showed further gains in tumor control compared with previous trials (IRS I-III). The use of radiation therapy to attain the highest rates of local control for patients with microscopic residual disease, gross unresectable disease, or fully resected tumors with alveolar histology is now the standard of care in the United States and based upon these IRS I-IV studies.

However, radiation therapy in the pediatric population can be associated with long-term and short-term morbidity, depending upon the volume treated and the dose delivered. In order to sterilize a tumor with radiation, normal tissues invariably are treated in the process. The normal tissue irradiated in the process of treating tumor directly causes morbidity. Organs and tissue growth and development are impaired with increasing doses of radiation. The younger a patient is at the time of treatment the greater the clinical effect of the developmental impairment[9-11].

Acute toxicity and long-term complications from radiation therapy depend on the site being treated, since sarcomas may occur at almost any site in the body. In general, most sarcomas treated with radiation require doses, which may cause acute toxicity necessitating treatment breaks, aggressive symptom management or long-term complications that require medical management as well.

Since the advent of the CT scanner and magnetic resonance (MR) imaging techniques, radiation oncologists have been able to more exactly target tumor within a body by better visualizing it. Furthermore, the CT scanner has become an integral part of treatment planning in radiation therapy. Currently the standard of care widely available in the United States is 3-D CT planned conformal radiation therapy. A further step has been taken to improve the dose to the tumor but reduce dose to surrounding structures called

intensity modulated radiation therapy (IMRT), where blocks are moved in and out of a field in order to better shape the dose distribution around the tumor. IMRT is available in a limited number of centers around the country.

However, both 3-D conformal therapy and IMRT still entail both an entrance dose to normal tissue as it penetrates to reach a tumor at depth in tissue, and an exit dose as it exits the body in a straight path beyond the tumor. Typically, multiple fields are used coming in at different angles all converging on the tumor to spread out the dose to normal tissue, while bringing the tumor to higher, curative doses.

Proton radiation differs from standard radiation (photons) in that the radiation can be stopped at a defined depth in tissue. Therefore, there is no exit radiation dose, sparing all the normal tissues beyond the tumor. Using proton irradiation, more normal tissue can be spared irradiation, resulting in less short-term and long-term morbidity.

Protons have a similar biologic effect to photons against tumors. Their clinical advantage over standard radiation results from the more favorable dose distributions achievable with their particular physical properties. The rapid increase in energy loss at the end of the range of protons results in a rapid increase in dose absorbed and is known as the Bragg peak. By modulating the beam, this Bragg peak can be spread out over the entire target volume to produce a nearly uniform dose distribution. The other advantage of protons is the lack of exit dose beyond the Bragg peak. The accuracy of delivering proton therapy is further enhanced by advancements in treatment planning and delivery technology. The advantage of protons has been demonstrated for medulloblastoma, and comparative treatment planning using protons versus photons have shown a clear advantage to protons in terms of dose distribution [12-20]

The acute toxicity seen with radiation therapy depends on the location of the tumor and the area and volume of tissue necessitating treatment. If a large portion of the vertebral spine or pelvis is being treated, or if combined with chemotherapy, bone marrow suppression can occur. Fatigue and general malaise can occur from treatment involving any part of the body but is usually worse with increasing dose. Treatment to the head and neck area can cause alopecia, dermatitis, folliculitis, irritative conjunctivitis, otitis externa, otitis media, laryngitis and pharyngitis. Acute toxicities from radiation to the thorax include esophagitis, dysphagia, heartburn, pneumonitis, or pericarditis. Radiation to the abdomen and pelvis can cause anorexia, weight loss, nausea, vomiting, gastritis, enteritis, cystitis, nephritis, and /or hepatitis. Any neurologic symptoms produced by the tumor can worsen acutely with treatment but this is usually temporary. Acute symptoms from radiotherapy to tumors in the extremities are usually limited to skin reactions. Acute symptoms may be worse when concurrent chemotherapy is administered.

Long-term complications can start to manifest after about 3 months following completion of radiation therapy and are also specific to the normal tissues irradiated in the process of treating the tumor. Tissues such as muscle, bone, and organs irradiated in a growing child often fail to develop normally which can result in asymmetries and significant cosmetic and/or functional abnormalities.

Complications for cranial irradiation include permanent hair loss, the increased risk of radiation-induced secondary malignancy, neuro-endocrine dysfunction, neurocognitive dysfunction, brain necrosis, neuronal atrophy, persistent edema and vascular abnormalities. Late complications from irradiation in the head and neck region may include: permanent dry mouth or dry eye, cataract formation, retinopathy, chronic otitis media, permanent dysphagia and facial asymmetry. Complications from irradiation to the chest/abdomen or pelvis can result in stunting of growth, asymmetric growth (scoliosis, kyphosis) or restrictive air movement from lung irradiation, primary hypothyroidism, cardiac disease, pneumonitis, peptic ulcer disease, permanent enteritis, gonadal failure or decreased bone marrow reserve.

The proposed treatment regimen of replacing fractionated photon therapy with fractionated proton therapy takes advantage of the superior dose distribution of protons. It is expected that the therapeutic gain will be the greatest in children whose development and tissue maturation can be significantly retarded by the effects of radiation. The risk of induction of second malignancies due to radiation should also be reduced as a result of less normal tissue irradiated.

Patients enrolled on this protocol are often already enrolled on other national pediatric sarcoma protocols such as those testing chemotherapy regimens but also requiring radiation as part of the treatment regimen. Children's Oncology Group (COG) is the body overseeing the IRS studies and has agreed to allow the substitution of proton radiation for photon radiation in the rhabdomyosarcoma protocols. The same radiation treatment parameters such as dose, fraction size, and scheduling will be used as specified in the national protocol in which the patient is participating.

II. SPECIFIC AIMS (RESEARCH OBJECTIVES)

1. To assess late complications from irradiation using proton beam therapy in place of conventional photon beam therapy in pediatric patients with rhabdomyosarcomas.

2. To assess acute side effects from irradiation using proton beam therapy in place of conventional photon beam therapy in pediatric patients with rhabdomyosarcomas.

3. To compare the dose distribution to tumor and surrounding normal structures using DVH's (Dose Volume Histograms) generated from the proton plan used to treat the patient and the photon plan generated for comparison purposes. Photon plans for comparison purposes will be completed for the first 79 patients.

4. To monitor the rates of event-free survival, overall survival and local control using proton radiotherapy.

III. SUBJECT SELECTION

Inclusion criteria:

1. Patients with biopsy proven newly diagnosed rhabdomyosarcoma.

2. Patients less than or equal to 30 years of age.
3. Patients must be treated with a standard accepted chemotherapy regimen for rhabdomyosarcoma (for example, according to IRS-IV, IRS-V, or future IRS study).
4. Patients may not have metastatic disease, unless aged 2-10 with embryonal histology.
5. Patients must be willing to receive follow-up care for a minimum of five years after treatment at the treating institution, including annual follow up visits. In the event that the patient is not from the local area and returning to the treating institution for follow up visits is too difficult, they must be willing to have their outside medical information (i.e. imaging studies, laboratory results and doctor or other health professional notes) released to the treating institution to track the results of treatment.
6. The patient or their legal guardian must give their informed consent.
7. Timing of radiation must be according to the IRS protocol upon which the patient is treated within either 35 days of last chemotherapy or surgery. (The clinical characteristics dictate the need for or/and timing of surgery and radiotherapy in relation to the chemotherapy.)

Exclusion criteria:

1. Patients with a life expectancy of less than 2 years.
2. Patients with co-morbidities that would make the use of radiation too toxic to deliver safely, such as serious local injury or collagen vascular disease.
3. Patients who are pregnant.
4. Patients who have previously received radiation therapy.

Source of subjects and recruitment methods:

Approximately 320 cases of pediatric rhabdomyosarcoma are diagnosed in the US per year[1]. Patients have been coming to MGH from all over the United States to be treated with proton irradiation and this trend is likely to continue. Patients will be recruited from MGH, BWH, Boston Children's Hospital, DFCI and MD Anderson Cancer Center. We estimate an annual accrual of 10 pediatric sarcoma patients across all participating sites, for a total accrual of 80 patients. Proton radiotherapy will be listed on the MGH Proton Center web site as a formal protocol and information of its availability will be made known to treating professionals through group (COG) meetings.

IV. SUBJECT ENROLLMENT

Methods of enrollment: Registration Procedures

REGISTRATION PROCEDURES

General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Coordinating Center by the Multi-center Coordinator. All sites should contact the Multi-center Coordinator to verify dose level availabilities prior to consent.

Following registration, participants should begin protocol therapy within 5 weeks. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Multi-center Coordinator should be notified of cancellations as soon as possible.

Procedure for obtaining informed consent:
The PI or Co-investigators will obtain informed consent from patient or the patient's parent or guardian after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study to the parent or guardian (and the patient if appropriate). If the patients, guardians and/or patient are non-English speaking, an interpreter will be made available to them and the enrolling site's IRB-approved process for obtaining informed consent from non-English speaking subjects will be followed. The patient or parent or guardian will be given a copy of the signed informed consent. The original signed informed consent will be retained per institutional policy.

Treatment assignment:
Treatment specifics such as dose and volume of radiation will be decided based on the national protocol, which is being followed for the patient's treatment and/or the clinical situation including histology and tumor site.

Study Visits and Measured Parameters

Baseline staging requirements:

1. Complete history and physical by a radiation oncologist, medical oncologist or surgeon.
2. Other baseline laboratories or evaluations necessary to evaluate function of organs that the tumor effects or that the treatment is likely to effect. For example, if the thyroid gland will be irradiated or compromised by tumor a TSH and thyroid function tests are indicated for a baseline test. Likewise, if the tumor is located in the orbit, full vision testing to the extent that it is possible should be achieved prior to irradiation. (Please refer to Studies at Baseline section for additional details).
3. CT or MRI scan (preferably with contrast or gadolinium if not contraindicated in the patient) of the original tumor or tumor site at the time of diagnosis.
4. CT scan of the chest to rule out lung metastases at time of diagnosis
5. Bone marrow biopsy to rule out bone marrow involvement at time of diagnosis for patients with intermediate or high-risk disease (in general, alveolar histology, unfavorable sites with gross residual disease and/or metastatic disease). Refer to the COG protocol breakdown of risk if there is a question. Bone marrow biopsy is not required for low-risk patients.

6. PET or bone scan at time of diagnosis.
7. Pathology review at treating institution.

Schedule of Assessments:

Data Set	**Completed prior to enrollment or within 35 days after enrollment**	**Weekly Visit During RT**	**At least 1 visit after RT within 3 months (suggested = 6 weeks after RT)**	**Yearly Follow-Up (+/- 6 months)**
Age	x			x
Sex	x			
Hx and P	x	x	x	x
Acute Toxicity Assessment		x	x	

Bone Marrow Biopsy at diagnosis for intermediate and high-risk patients	x			
PET or Bone scan	x			
Chest CT at diagnosis	x			
CT or MRI of the original site of disease (plain film if it is an extremity), at diagnosis	x			x (per IRS guidelines)
Brain MRI or CT if parameningeal, at diagnosis	x			
Late Toxicity Assessment				x
Site related tests that will be repeated at yearly f/u (see below).	x			x

Note: Many patients have received surgery and chemotherapy prior to being referred for radiation therapy. The timing of the radiation therapy is dictated by the treatment protocol or by best clinical judgment. Some patients who are very young at diagnosis (such as <1 year old) are treated off-protocol and given the full 48 weeks of chemotherapy prior to their radiation therapy in order to allow maximal growth and development before radiation therapy.

Studies at baseline:

1. History and Physical exam
2. Baseline weight and height

Head and Neck:

- Neuro-psychiatric evaluation at baseline (+/- 6 months) if >20% of the whole brain received 10% of the prescribed dose as determined by the radiation oncologist evaluating the treatment plan.
- Baseline panel of endocrine labs recommended within 6 weeks of the radiation start date if the dose to the pituitary or hypothalamus received 20 Gy RBE or more, or if the whole thyroid was included in the radiation port. Labs include TSH, Free T4, Cortisol (AM value), IGF-1, IGF-BP3, LH, FSH, prolactin, estradiol (females) or testosterone (males).
- For patients who received any dose to oral structures (as deemed necessary by the PI) a routine dental evaluation is recommended to screen for any major dental deficiencies.

Orbit:

- Baseline ophthalmologic exam to be completed (+/- 6 months) if the orbit is in the involved field.

Ear or middle ear involvement (Performed within the first three weeks of treatment):

Audiometric exams with word recognition must be completed up to 6 weeks before or within 10 weeks after the start of radiation if the mean radiation dose to the cochlea received 20 Gy RBE or more, or for patients in which the tumor involved one or both of the 8th cranial nerves. The word recognition portion of the exam will be administered to age and developmentally appropriate children, generally age 4 and over.

Criteria for Removal from Study:

If a patient develops recurrent disease, he/she will be taken off treatment and followed per standard of care. All patients will continue to be followed for survival status.

Acute Toxicity:

Acute toxicity will be scored at weekly status check visits by the radiation oncology nurse or doctor. In addition, acute toxicity will be scored at least one time within the 3 months following completion of radiation therapy. This may be scored by the local pediatric oncologist if the patient does not return to the treating institution for a follow-up visit during this time frame. The recommended evaluation time for acute toxicity after radiotherapy is 6 weeks following completion, but may be at any time during the 3 months after treatment. In addition, any event requiring admission must be recorded. Acute toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

All toxicities and adverse events that are possibly, probably or definitely related to radiation therapy will be captured on the case report forms.

Late toxicity (Site specific):
Late toxicity is to be scored on a yearly follow-up basis for at least five years. Ten years is suggested but not required. Additional tests may be required as clinically indicated. Late toxicities will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

General studies at yearly follow-up visits:

1. History and Physical exam
2. Weight and height

Head and Neck:

- Neuro-psychiatric evaluation every other year (+/- 12 months) if >20% of the whole brain received 10% of the prescribed dose as determined by the radiation oncologist evaluating the treatment plan.
- Endocrine labs recommended to be drawn annually if the dose to the pituitary or hypothalamus received 20 Gy RBE or more, or if the whole thyroid was included in the radiation port. Labs include TSH, Free T4, Cortisol (AM value), IGF-1, IGF-BP3, LH, FSH, prolactin, estradiol (females) or testosterone (males).

Orbit:

- Annual ophthalmologic exam to be completed (+/- 6 months) if the orbit is in the involved field.

Ear or middle ear involvement

Annual audiometric exams with word recognition must be completed (+/- 6 months) if the mean radiation dose to the cochlea received 20 Gy RBE or more, or in patients in which the tumor involved one or both of the 8th cranial nerves. The word recognition portion of the exam will be administered to age and developmentally appropriate children, generally age 4 and over.

Comparison of Proton Plans and Photon Plans:
Normal structures will be contoured on treatment planning CT scan in the treatment planning systems. Dose volume histograms will be generated and compared for important normal structures as well as tumor targets that will receive dose and likely contribute to either acute or late morbidities. DVH levels at 90%, 50%, and 10% will be compared between the two plans. A mean average percent of total dose prescribed will be calculated based on the three DVH levels for each normal structure at risk for both proton and photon plans. The percent of normal tissue spared by using protons will be calculated by using the following equation.

$$\frac{\text{(mean X-ray dose - mean proton dose)}}{\text{mean X-Ray dose}}$$

The treatment volume will be contoured by the treating physician and the normal structures will be contoured by the treating physician, study physician, the dosimetrist, or the anatomist depending on the difficulty of the structure to be outlined.

V. RADIATION THERAPY

National protocols: For those patients who are treated on a national protocol such as a COG protocol, the COG radiation therapy guidelines will be used.

Treatment Volume Parameters:
For those patients who are not treated on a national protocol the ICRU 50 recommended terminology will be used to define the radiation treatment parameters. The definitions of clinical tumor volume (CTV) will vary according to the tumor location and disease characteristics and is delineated in detail by the IRS V protocols.

The GTV corresponds to the gross tumor visualized on MRI and CT scan images either after biopsy or resection. The CTV corresponds to the GTV plus the area that is likely to be microscopically involved with tumor.

The planning target volume (PTV) is defined as the clinical target volume plus a 2 to 20 mm margin for allowances in set-up uncertainties. A range is specified because the different parts of the body require more for set up uncertainty. For example, an intra-thoracic tumor can move as a result of breathing whereas a tumor in the orbit is less subject to normal physiologic motion once a patient has been appropriately immobilized.

Timing of the radiation therapy
1. The clinical situation dictates whether the tumor or tumor bed will be irradiated pre-operatively, post-operatively or definitively without a gross total resection. Each case will be decided on its own merits according to guidelines listed in the national protocols for rhabdomyosarcoma or by the recommendations of the treating physicians (i.e. radiation oncologist, pediatric oncologist and surgical oncologist primarily.)

2. If a patient is treated post-operatively, the radiation treatments should begin within 35 days of the final surgery but delays up to 45 days will be allowed. Sarcoma surgery often requires reconstructive surgery that requires additional wound healing time.

Patient Set-up and Immobilization:
Patient set-up and immobilization will be determined prior to obtaining the planning CT scan. The type of immobilization will be determined by the anatomic location of the site to be treated. For example, if the area to be treated is in the head and neck location, the head will be positioned such that the spinal cord will be as straight as possible, a head cup is often used in conjunction with a custom made aquaplast mask. If an extremity is to be treated, a custom immobilization device will be constructed to hold the area in the required position. An alpha cradle may be used to immobilize the trunk of the body as well. The immobilization device must be documented in writing in the patient care chart and by photograph.

Patient sedation:
Patient set-up reproducibility is critical for both conventional radiotherapy and proton radiotherapy and the use of sedation or anesthesia is strongly encouraged if necessary. An anesthesiologist will be supervising and administrating sedation. Sedated patients should be under constant surveillance during treatments with cameras, telemetry, and other devices. The need for anesthesia is not modality dependent. A child requiring sedation for photon therapy would require it for proton radiotherapy and vice versa.

CT simulation:
Patient undergoes a planning CT scan while in treatment position and properly immobilized. IV contrast is suggested but not required. In patients at risk for allergic reaction to contrast despite pre-medication, a planning CT scan may be obtained without contrast. Physicians are encouraged to use available MRI scans to aid in target and normal tissue delineation. Fusion of the MRI scans to the planning CT scans can help delineate structures. CT slices (generally 2 to 3.7 mm thick) are obtained through tumor bed and region and will include the full organs for which dose will be tracked.

Scans are sent to computer planning software. Adjustments in distance between slices can be made to accommodate the maximum number of slices at the discretion of the radiation oncologist and treatment planners.

Target delineation:
The following structures will be outlined on planning CT scans. It is recommended that the radiation oncologist outline the GTV. Cumulative dose volume histogram analysis will be completed for structures marked *:

* GTV and surgical bed
* CTV

At least 4 normal organs receiving any radiation will be drawn to delineate dose these receive. Organs will be site specific and left to the discretion of the treating physician

Suggestion of critical organs to track include:

- Head and neck organs: retinas, lens, bony orbit, pituitary gland, hypothalamus, whole brain, temporal lobe, Mandible, cochlea, larynx, orbit, thyroid gland, esophagus, spinal cord
- Thorax: Lung, Heart, left ventricle, bone, esophagus, spinal cord, nerves
- Abdomen: liver, kidney, stomach, spleen, bone spinal cord, small bowel
- Pelvis: testis, ovaries, small bowel, bladder, rectum
- Extremities: growth plate, nerve, vascular structures

Field Arrangements and Treatment Planning:
An optimized 3-D conformal proton plan will be designed in consultation with the treating physician. Whenever possible multiple fields will be designed to limit the dose to normal tissues and critical structures and promote symmetric bone growth/retardation where applicable.

An optimized IMRT comparison photon plan will also be generated for the first 79 patients. Appropriate measures such as cerrobend blocks or MLCs will be fabricated or programmed so that the patient can be treated with photons in the event of an equipment malfunction rendering proton therapy unavailable. A patient may receive up to 25% of the prescription dose with photons provided the normal tissue tolerance limits are respected. In addition, this photon plan will serve as a comparison of doses to normal surrounding organs in the form of Dose Volume Histograms. A comparison of normal tissue doses will be made between the two plans as a primary objective of this study.

Dose Specification and Schedule:
The dose given to a particular sarcoma depends on the setting and the histological subtype. Schema for radiation dose prescription and fractionation schedule is outlined in the current IRS protocols (D9803, D9602, D9802) available on the COG website or by contacting either Torunn Yock, MD (617-726-1836), Nancy Tarbell, MD (617-724-1836) or Shannon MacDonald, MD (617-724-1836). Patients typically will be treated once per day, 5 days per week unless otherwise specified by a co-existing protocol. For those patients not on a national protocol the current accepted standard of care doses will be used which are based on IRS IV and IRS V data. Standard fractionation will be used to minimize late toxicity and maximized efficacy, 1.8-2.0 Gy per fraction. Typical doses are 36 Gy, 41.4 Gy, 45 Gy and 50.4 Gy depending on the circumstances.

Each proton field is normalized individually to usually the 97 to 100% isodose line. Doses will be prescribed to the appropriate isodose line encompassing the CTV such that the gradient within a volume is +7% to –5%. Dose will be reported in CGE, Cobalt Gray Equivalent (where 1 CGE = proton dose Gy x RBE [radiobiological effective dose], RBE = 1.1). An RBE of 1.1 has been selected for protons and is based on RBE determinations in animal and cell culture systems[21,22]. Patients will not receive doxorubicin or actinomycin-D concurrent with radiotherapy unless explicitly required by a national protocol.

Proton beam physical factors:
The FHBPTC cyclotron at MGH produces a 230 MeV proton beam. The synchrotron at MDACC produces a 250 MeV proton beam. The energy can be degraded to an appropriate energy to treat the desired depth. The SAD (Source to Axis Distance) at MGH is 2.27 meters; the SAD at MDACC is 2.7 meters.

Proton Beam modification / Blocking:
Beam shaping will be accomplished using primary collimation by the gantry jaws. The penumbra is large and field shaping by secondary collimation will be necessary using a downstream custom cut brass aperture. Tertiary collimation can be applied by installing a cone to hold a second brass aperture downstream from the 1st aperture. Apertures will be constructed on brass alloy of sufficient thickness to attenuate 100% of protons. 3-D lucite compensators are fabricated to conform dose to the target at the distal aspect.

Quality Assurance:

Beam verification:
Pre-treatment port films should be compared with a digitally reconstructed radiography (DRR) constructed from the treatment planning system. Film or digital images will be taken in accordance with the proton center's standard practice for all patients. These images are used to verify the position of the patient and the aperture.

Dose Uniformity:
Dose gradient in CTV should remain within +7% to –5% of prescribed dose.

Dose verification:
A physicist will be responsible for dose verification.

Rapid Review of Treatment Plans:
To ensure protocol compliance, the treatment plans for the first three patients treated at each site will be reviewed by the Principal Investigator and Participating Site's PI.

Concurrent Protocols and Which Radiation Therapy Guidelines to Follow:
For patients who are enrolled on co-existing protocols such as COG, physicians will adhere to the radiation therapy guidelines of the companion protocol which specify their own guidelines for the following parameters: total dose, dose per fraction, fractionation schedule and sequencing with other therapy (e.g. chemotherapy). If any questions or discrepancies arise, then contact. Torunn Yock, MD at (617) 724-1836 (tyock@partners.org), Nancy Tarbell, MD (617) 724-1836 (ntarbell@partners.org) or Shannon MacDonald, MD (617-724-1836 or smacdonald@partners.org) before beginning radiation treatments.

Treatment Delay:
To avoid treatment delays resulting from the machine being down, photon beam radiation can be administered. The maximum dose delivered by photons will be 25% of the prescribed dose. Treatment delays will be allowed if a serious adverse event occurs due to protocol therapy. Treatment delays will also be allowed for patients who experience a serious adverse event not related to protocol therapy (e.g. concurrent chemotherapy requiring hospitalization for neutropenia).

VI. BIOSTATISTICAL ANALYSIS

Primary outcomes are acute and late complications following proton beam irradiation to the tumor or tumor bed. Late complications are defined as the delayed effects attributable to radiation which occur > 90 days following completion of radiation, while acute side effects are those occurring during radiotherapy or up to 90 days after the last dose. Allowing for 5% inflation for unevaluable patients due to ineligibility or early dropout, the revised accrual goal is a total of 115 patients with a minimum follow-up of another 2

years following the patient enrollment for observing the late complications of proton beam irradiation.

The goal of utilizing protons is an improvement in the historical complication rate, which varies by site and type of complication. The literature for parameningeal or other head and neck rhabdomyosarcomas has reported endocrine effects occurring in 50-100% and impaired orbital function in 70-100% of patients (23-27). For children treated for pelvic tumors, late effects were significantly higher among patients treated, ranging from 54% to 77% (28). Across all anatomic sites, the likelihood of one or more reported late effects has been approximately 70% or more among those who received conventional radiation. Among a total of 110 patients, the probability is 81% that 70 or fewer of them will develop any late effect if the overall complication rate is truly decreased to 60% with the use of protons. The decision rule is associated with only 9% probability if the underlying rate were truly similar to the 70% historical rate observed with conventional radiation.

Due to a difference in the radiation doses used for treating patients with different tumor characteristics (typical doses are 36 Gy, 41.4 Gy, 45 Gy and 50.4 Gy), the outcomes will be analyzed according to dose group, $\leq$ 45 Gy and $\geq$45 Gy. Data on the enrolled patients shows a 1:4 ratio in the distribution of patients receiving low versus intermediate radiation doses. Constitutional symptoms, namely fatigue and malaise, as well as skin reactions in the radiation port will be analyzed according to dose group.

As rhabdomyosarcoma may occur at almost any site, many of the side effects will be determined by the range of tumor location. Thus analysis of tissue-specific toxicities has depended typically on relatively small patient numbers and was limited generally to descriptive statistics. Moreover, subgroup analysis of acute symptoms may be confounded by the type of concurrent chemotherapy. Accrual has been increased to obtain reasonable precision for the estimation of tissue-specific toxicities associated with the most common tumor sites, especially late effects arising during long-term follow-up. Patients will not be evaluable for late effects following treatment failure in local, regional and/or metastatic sites, development of a secondary malignancy or death due to any cause. In particular, projection of the current patient distribution indicates the increased accrual will comprise 56 patients with parameningeal tumors and 24 patients with orbital sarcomas. These expected numbers are associated with 95% exact confidence intervals of maximal width +/-14% and +/-22%, respectively. The corresponding numbers evaluable for late effects are projected to be 42 and 18 patients based on the five-year event-free survival of 69% observed among the first 57 protocol patients. The maximal interval widths are +/-17% and +/-25%, respectively, at five years following proton radiotherapy. We also expect to enroll 3-6 patients with each of the rare tumor sites (non-parameningeal head and neck, trunk, prostate/bladder, extremity, perineal/anal and liver/biliary tract regions).

All toxicity grading will be coded according to the COG/RTOG scales provided in the appendices. Toxicities and events not listed in these scales will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. Many patients are expected to be co-enrolled on COG protocols comparing chemotherapy

regimens. Since interim analysis will be performed on the parent COG protocols and any action taken will impact directly on the proton protocol, no formal sequential monitoring of efficacy is planned within this protocol.

VII. RISKS AND DISCOMFORTS

It is not known whether the treatment with proton beam in this study will result in less effective anti-cancer therapy compared to conventional photon beam radiation therapy. However, based on our previous experience treating thousands of patients with other types of tumors with proton radiation therapy, there has been no decreased effectiveness in anti-cancer therapy compared to photon beam radiation therapy. While on the study, a patient is at risk for the side effects described below. There may also be other side effects that we cannot predict. Medications may be given to make side effects less serious and uncomfortable. These side effects generally go away days or weeks after radiation therapy is stopped, but in some cases side effects can be permanent.

The risks and discomforts of proton radiation are likely to be less than that of photon radiation. The side effects of radiation treatment can be broken down into two groups, acute and generally self-limited and late effects (often chronic). Acute side effects include skin reaction, fatigue, and possible decrease of blood counts. Additionally the acute side effects are related to the tissues being irradiated. If mucosal surfaces are irradiated, it can result in mucositis. This manifests itself as pain and denuding of the superficial surfaces of mucous membranes.

Side effects (all reversible) during radiation therapy or shortly after: (those that apply will be checked for you by the doctor on the consent form)

PHYSICAL RISKS:	FREQUENCY
☐ Temporary hair loss in area being treated	common
☐ Skin reaction in radiation port	common
☐ Nausea and/or vomiting	occasional
☐ Diarrhea or change in bowel habits	occasional
☐ Loss of appetite and weight loss	common
☐ Fatigue	common
☐ Decrease in bone marrow cells	common
☐ Difficulty swallowing: can be painful enough to lead to hospitalization	occasional
☐ Irritation of the eye	common
☐ Sore mouth or throat	common
☐ Alterations of taste	occasional
☐ Inflammation of lung, liver or kidney	occasional
☐ Thrush	occasional
☐ Headache	common
☐ Dehydration	occasional

NON PHYSICAL RISKS:	FREQUENCY
☐ Inability to perform at school, job	common
☐ Need for Treatment break or delay in finishing treatments	uncommon

Side Effects Occurring Months or Years After Radiation Therapy (can be irreversible): The doctor will check those boxes that apply on the consent form and circle the expected frequency

PHYSICAL RISKS:	FREQUENCY
☐ Permanent hair loss	occasional
☐ New cancer or tumor due to radiation	uncommon, but serious
☐ Cataract or other eye dysfunction	uncommon to common
☐ Hearing loss	uncommon to common
☐ Diminished hormone production	common
☐ Bone or soft tissue growth abnormality	common
☐ Abnormal curvature of spinal column	uncommon
☐ Hypothyroidism	unknown
☐ Scarring/damage to esophagus	occasional
☐ Peptic ulcer formation in stomach	rare
☐ Scarring of bowel	rare
☐ Premature failure of ovaries	occasional
☐ Abnormal development of uterus	occasional
☐ Damage to spinal cord or brain tissue	rare, but serious
☐ Limb length discrepancy	uncommon to common

NON PHYSICAL RISKS:	FREQUENCY
☐ Deterioration in memory function	occasional
☐ Inability to have children	unknown
☐ Difficulty in school, job performance	uncommon

Standard diagnostic radiological tests (MRI) and plain films of the region and CT scans of the region may be used to follow this treatment and at subsequent follow-up visits.

Reproductive risks: Because radiation therapy can affect an unborn baby, you should not become pregnant or father a baby before or during radiation treatments. You should also not nurse your baby. You may be asked to do a pregnancy test before you begin your radiation treatments if there is a concern about being pregnant.

For more information about the risks and side effects, ask the investigator or your doctor.

VIII. POTENTIAL BENEFITS

If a patient agrees to take part in this study, there may or may not be direct medical benefit to them. There is the potential benefit that protons will decrease some long-term

side effects. It is hoped that the information learned from this study will benefit other patients receiving radiation for rhabdomyosarcoma in the future.

IX. MONITORING AND QUALITY ASSURANCE

Monitoring of data:
Since proton beam radiation is a novel approach to treating pediatric rhabdomyosarcoma, and since toxicities are site specific, a monitoring rule is provided in the event of serious unexpected complications. Accrual will be suspended for a comprehensive review in the case of a non-cancer death or grade 4 (life-threatening) toxicity within 12 months following completion of radiation if it may be possibly related to radiation or another cause cannot be determined. The probability of one or more such event occurring among a total of 80 patients is more than 98% assuming the true rate were 5% or higher. If the underlying event rate were only 0.5%, the probability of suspension at any time throughout the accrual period is 33%.

Reporting Adverse Events:
Adverse events will be reported per institutional guidelines.

In addition, the following severe toxicities should be reported to the principal investigator within 24 hours of the caring physician becoming aware of the problem:

- transverse myelitis
- neuropathy
- any other grade 4 acute toxicity except myelosupression
- death

Additional adverse event reporting guidelines are included in the attached Data and Safety Monitoring Plan, Appendix III.

X. REGULATORY REQUIREMENTS

Declaration of Helsinki:
The PI will ensure that this study will be conducted in full conformity with the current revision of the Declaration of Helsinki and with U.S. FDA requirements.

Patient Confidentiality:
The investigators will ensure that patient anonymity is maintained.

XI. REFERENCES

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