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ACR–ARS PRACTICE PARAMETER FOR THE PERFORMANCE OF PROTON BEAM RADIATION THERAPY

PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care[1]. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the practitioner considering all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to the guidance in this document will not assure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The purpose of this document is to assist practitioners in achieving this objective.

[1] Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing 831 N.W.2d 826 (Iowa 2013) Iowa Supreme Court refuses to find that the *ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures* (Revised 2008) sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, Stanley v. McCarver, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do not establish the standard of care.

I. INTRODUCTION

This practice parameter was revised collaboratively by the American College of Radiology (ACR) and the American Radium Society (ARS).

In 1946, Robert Wilson proposed the clinical use of high-energy protons for the treatment of localized human tumors, recognizing the energy distribution of charged particles within tissue [1]. Unlike photon treatment, the charged proton releases most of its energy in the last few millimeters of its range, resulting in a sharp, localized region of high radiation dose known as Bragg peak. Proton beams of clinical use typically range from 60 MeV–300 MeV energy to treat superficial tumors like skin, eye, head and neck, and breast to deep seated tumors like lung, prostate, liver, and pancreas [2]. Higher energies can achieve deeper penetration within tissue with a quadratic relation with range and energy [3]. Spread out Bragg peak width and location can be tailored to deliver a high radiation dose within the target volume while avoiding irradiation to sensitive normal structures distal to the intended target [4]. Proton therapy systems traditionally use various synchrotron or cyclotron technologies. Technologies for proton generation include superconducting synchrocyclotrons and ultracompact synchrotrons. Proton radiotherapy may be combined with photon beam treatment [5]. Scanned beams capable of delivering intensity-modulated proton therapy (IMPT) are increasingly being used and have the potential to provide more conformal dose distribution compared with that of passive scattered proton therapy (PSPT), allowing for the potential for further reduced normal tissue toxicities [6-9].

The relative role of proton radiotherapy in the context of overall radiation oncology services will require further investigation, including studies of clinical outcome. On a societal level, the economic costs surrounding the widespread use of proton radiotherapy may also need to be considered [5]. Increasingly, there are now clinical data documenting the outcomes of proton radiotherapy across disease sites with many experiences supportive of a role for proton therapy [10-14].
Proton radiotherapy may permit improved therapeutic ratios with lower doses to sensitive normal structures and greater dose to target tumor tissues [15]. However, costs of proton treatments are higher than comparable photon treatments [16-18]. There are now clinical data documenting better outcomes across disease sites in support of proton therapy [19-24], and such data have provided early evidence for the cost-effectiveness of proton therapy in select clinical situations and improvement in long-term work productivity [25-28]. On a societal level, the economic cost-effectiveness surrounding the widespread adoption of proton radiotherapy should be further investigated [2,5,29,30].

As of 2022, there are 39 proton centers in the United States, a number rapidly growing with increased opening of single-gantry options [31]. Approximately half of these centers have opened since 2017. This practice parameter is developed to serve as a tool in the appropriate application of this evolving technology in the care of cancer patients or other patients with conditions in which radiation therapy is indicated. It addresses clinical implementation of proton radiation therapy, including personnel qualifications, quality assurance (QA) standards, indications, and suggested documentation. This practice parameter is not meant to assess the relative clinical indication of proton radiotherapy compared with other forms of radiotherapy but to focus on the best practices required to deliver proton therapy safely and effectively when clinically indicated. It also supplements the ACR–ASTRO Practice Parameter for Radiation Oncology, the ACR–AAPM Technical Standard for the Performance of Radiation Oncology Physics for External-Beam Therapy, the ACR–ASTRO Practice Parameter for Image-Guided Radiation Therapy (IGRT), and the ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy [32-35].

A literature search was performed to identify published articles regarding clinical outcomes, reviews, QA methodologies, and guidelines and standards for proton radiation therapy. Selected articles are referenced in the text. Many of the following recommendations are based on firsthand experiences of multiple clinical authorities who employ proton therapy and peer reviewed by experts at different practicing institutions.

II. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

See the ACR–ASTRO Practice Parameter for Radiation Oncology in which qualifications, credentialing, professional relationships, and development are outlined [32].

A. Chief Medical Officer or Medical Director

The Chief Medical Officer or Medical Director of Proton Therapy (or Radiation Oncology) is responsible for ensuring that there is an appropriate training and credentialing program for the radiation oncologists, physicists, dosimetrists, midlevel providers, nurses, and radiation therapists. A QA and performance improvement (PI) programs should be developed for continuing quality improvement (CQI) as described in the ACR–ASTRO Practice Parameter for Radiation Oncology [32]. It is the leadership's responsibility to respond to identified problems and coordinate with the Qualified Medical Physicist(s) in proton therapy to ensure that the corrective actions are performed, and a QA process evaluates the effectiveness of the corrective actions.

B. Radiation Oncologist

The training requirements of the radiation oncologist should conform to the qualifications and certification as outlined in the ACR–ASTRO Practice Parameter for Radiation Oncology [32]. Because this training does not currently specify proton therapy, specific training in proton therapy should be obtained before performing any such procedures.
The responsibilities of the radiation oncologist should be clearly defined and should include the following:

1. The radiation oncologist manages the overall disease-specific treatment regimen, including careful evaluation of disease stage, assessment of comorbidities and previous treatments, thorough exploration of various treatment options, ample and understandable discussion with patients regarding the impact of treatment, including benefits and potential harm, knowledgeable conduct of proton therapy as outlined below, and prudent follow-up after treatment.

2. The radiation oncologist determines and recommends a proper patient positioning method (with sedation as indicated) with attention to disease-specific targeting concerns, patient-specific capabilities (eg, arm position in arthritic patients, degree of recumbency in patients with severe chronic obstructive pulmonary disease), patient comfort, stability of setup, and accommodation of devices accounting for organ motion (eg, gating equipment) required for optimal targeting of the proton treatment.

3. The radiation oncologist determines and recommends a procedure to account for inherent organ motion (eg, breathing movement) for targets that are significantly influenced by such motion (eg, lung and liver tumors) as they relate to and integrate with the accurate delivery of proton therapy. This activity may include implementation of a variety of methods, such as respiratory gating, tumor tracking, organ motion dampening, additional imaging, dosimetric modification of target volumes, or patient- directed methods (such as active breath holding).

4. The radiation oncologist is responsible for the supervision of the patient's treatment simulation using appropriate imaging methods. The radiation oncologist must be aware of the spatial accuracy and precision of the simulation modality as well as of the proton therapy delivery mechanism. Steps must be taken to ensure that all aspects of simulation, including positioning and immobilization, are properly carried out.

5. After the planning images have been acquired, they will be transferred to the treatment-planning computer. Subsequently, the radiation oncologist contours the outline of the targets of interest. Normal organ structures can be contoured by the physicist, dosimetrist, anatomist, or physician and ultimately reviewed by the responsible radiation oncologist. Images from various platforms known to be useful for the specific disease treated should be registered with the planning data set in the image fusion process, which may serve to aid in defining target volumes. Incorporating information from all relevant imaging studies, the radiation oncologist coordinates the design of the target volumes and confirms that relevant normal tissues adjacent to and near the targets are identified and contoured. It should be noted that, because of the spatial dosimetry of the proton beam, particular consideration must be given to the distal and lateral edges, in as much as the sharp dose gradient of the beam risks underdosing of the target unless adequate margins are included within the treated volume. Radiobiological effects on normal tissues at the distal edge of the target must also be taken into careful consideration, especially when the distal edge is

near a critical structure.

6. The radiation oncologist conveys case-specific expectations for prescribing the radiation dose to the target volume and sets limits on dose to adjacent normal tissue. It may be required that certain normal tissues be tracked under image-guidance just as with the tumor target(s). Participating in the iterative process of plan development, the radiation oncologist approves the final treatment plan in collaboration with a medical physicist and dosimetrist.

7. After obtaining informed consent for the proton treatment, the radiation oncologist supervises the actual treatment process. The conduct of all members of the treatment team will be under the supervision of the radiation oncologist. The radiation oncologist will be responsible for deciding the acceptable or unacceptable day-to-day variations in the treatment setup.

8. The radiation oncologist participates in the QA processes, such as approval of proton therapy assessments, in order to ensure that the intended treatment is being delivered in the prescribed fashion.

C. Qualified Medical Physicist

The training requirements of the Qualified Medical Physicist should conform to the qualifications and certification as outlined in the ACR–ASTRO Practice Parameter for Radiation Oncology [32].

In addition, the Qualified Medical Physicist must meet any qualifications imposed by the state and/or local radiation control agency to practice radiation oncology physics and/or to provide oversight of the establishment and conduct of the physics quality management program.

The qualifications of a Qualified Medical Physicist and subsequent delineation of clinical privileges must be set forth in a job description and/or through the medical staff membership process in the appropriate category. Details regarding the qualifications and responsibilities of the Qualified Medical Physicist for proton therapy are enumerated in the ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy [33]. The proton therapy facility must have a process to review the credentials of the qualified medical physicist(s) who are providing proton clinical physics services especially in beam delivery technology such as scattered beam and scanning beam techniques. Additionally, the medical physicists should have knowledge of imaging, dose calculation (Hounsfield Unit (HU), electron density, stopping power), optimization techniques and treatment planning system (TPS) dose calculations engine. Physicists should also be trained in proton-specific imaging modalities for pretreatment and posttreatment imaging techniques. A strong understanding of the motion management system is critical as provided in the American Association of Physicists in Medicine (AAPM) TG-290 [36].

D. Medical Dosimetrist

The responsibilities of the medical dosimetrist or otherwise designated treatment planner should be clearly defined and should include the following:

1. Satisfactory understanding of anatomy, essential to contouring clearly discernible critical normal structures.

Ensuring proper orientation of volumetric patient image data on the radiation treatment planning (RTP) system.

2. Designing and generating the treatment plan under the direction of the radiation oncologist and medical physicist.
3. Generating all technical documentation required to implement the proton therapy treatment plan.

4. Being available for the first treatment and assisting with verification for subsequent treatments as necessary.

5. Knowledge of the motion management system to mitigate interplay effect

E. Radiation Therapist

The responsibilities of the radiation therapist should be clearly defined and should include the following:

1. Understanding the proper use of the patient immobilization/repositioning system and fabricating and understanding the proper use of devices for proton therapy.

2. Under the supervision of the radiation oncologist and medical physicist, performing initial (planning) simulation of the patient and generating the medical imaging data appropriate for the RTP system.

3. Implementing the proton therapy treatment plan under the supervision of the radiation oncologist and the medical physicist or of the medical dosimetrist under the direction of the medical physicist.

4. Acquiring periodic verification images for review by the radiation oncologist.

5. Performing periodic evaluation of the stability and ongoing reproducibility of the immobilization/repositioning system and reporting inconsistencies immediately to the radiation oncologist and the medical physicist.

6. Clear understanding of the motion management system operation

F. Continuing Medical Education

Continuing medical education programs should include radiation oncologists, medical physicists, medical dosimetrists, and radiation therapists.

The continuing education of the physician and Qualified Medical Physicist should be in accordance with the ACR Practice Parameter for Continuing Medical Education [37].

III. STANDARD CLINICAL INDICATIONS AND METHODOLOGIES OF TREATMENT MANAGEMENT

Proton therapy has been used to treat patients across a spectrum of malignancies and benign diseases for which radiation therapy is indicated. Proton radiotherapy may be seen as both a biologic and a technological option for the delivery of radiation treatment [38].

The practicing clinician should prescribe radiation therapy, whether photon- or proton-based, in accordance with the principles enumerated within the ACR–ASTRO Practice Parameter for Radiation Oncology, the ACR–ASTRO Practice Parameter for Communication: Radiation Oncology, the ACR Code of Ethics, and the AMA Code of Medical Ethics. These guidelines for professional conduct hold that the welfare of the patient is paramount because the radiation oncologist makes recommendations for cost-effective treatment [32,39-41].

In this context, the decision to include proton therapy as a component of the patient's radiation treatment plan should be discussed with the patient and that discussion should also include other treatment options along with their relative merits and potential risks. A summary of the consultation should be communicated to the referring physician and to other physicians involved in the care of the patient.

A. Central Nervous System Brain

1. Rationale:
   The application of proton therapy to treat sites within the brain is primarily to reduce radiation-associated potential adverse effects from reduction or avoidance of collateral radiation to structures such as uninvolved brain parenchyma [42], brainstem, eyes, lacrimal glands, pituitary, hippocampus [43], and cochleae [44]. Proton therapy may also enable safer radiation dose escalation compared to conventional photon-based

approaches.

Treatment of intracranial targets is particularly attractive for proton therapy for both clinical and dosimetric reasons. Clinically, there is a concern that additional surrounding normal tissue, primarily that of the brain, is radiation sensitive, and potential side effects may cause significant detriment to long-term cognition and quality of life [45]. In regard to treatment setup and planning, the cranium can be irradiated with greater accuracy because of both reproducible immobilization and greater precision in targeting small volumes. These factors reduce the amount of collateral normal tissue irradiation.

2. Immobilization and Simulation:
   The use of a thermoplastic masks with a customized occipital cushion is standard. Thicker plastic meshes that provide greater rigidity and less opportunity for patient movement may be preferred [46]; bite blocks should also be considered. Treatment of targets near or involving the base of skull should use a mask that encompasses the cranium, neck, and shoulders. Noninvasive cranial frames used for stereotactic treatments can be used to improve precision through reproducibility of setup and are particularly preferred for small intracranial targets of ≤2 cm in diameter [47].

3. Treatment Planning:
   Depending on location, volume, and dose, multiple fields are typically desired to optimally spare normal tissues and to spread out end-of-range uncertainty of the relative radiobiologic effectiveness (RBE) at the distal edge of the target. Avoidance of beams traversing the mastoid air cells and sphenoid/maxillary sinuses is generally preferred to reduce beam uncertainty from heterogeneous attenuation. Vertex fields that are often avoided in photon planning because of concerns of beam exiting into the body [48] are less of a concern with proton therapy and often create a more robust plan with less beam uncertainty by avoiding passage through mixed tissues with heterogeneous radiologic densities. Because of end-of-range uncertainties inherent with proton therapy today, it is preferred to avoid beams that end at an interface with a critical structure such as the optic pathway or brainstem, especially if prescription dose approaches normal tissue dose tolerance.

B. Spine or Paraspinal Site

1. Rationale:
   The anatomic location of spinal and paraspinal tumors that require radiation therapy makes them ideal candidates for proton therapy. The entrance dose, although less than that of X-rays, is often of little consequence when treating tumors in this location. The physics advantage of protons, compared to X-rays, is that they stop abruptly, which is particularly useful in superficial targets such as spinal and paraspinal targets. Depending on the exact location in the patient, using protons can significantly decrease dose to thyroid, heart, lungs, esophagus, spinal cord, kidneys, bowel, bone marrow, and/or reproductive organs.

2. Immobilization and Simulation:
   Immobilization and simulation are dependent primarily on two factors—patient comfort and the treatment table itself. Patients can be simulated supine or prone. A variety of immobilization devices can be used with the goal of patient comfort and reproducibility during daily treatments. These treatment devices should be "compatible" with proton therapy because the density of material traversed by the proton beam can impact range and robustness. This is much less of an issue in X-ray–based treatments. Decubitus positions are difficult to reproduce with high accuracy and should be used in only select circumstances. The treatment table may drive patient position in some situations. **Some** proton centers have treatment tables that have their base built into the treatment floor itself. As a result, there is an inferior limit to how low a patient can be treated with a posterior-anterior (PA) beam because the gantry may not be able to clear inferiorly. This lower limit, relative to the patient, is raised for taller patients. In centers with robotic patient positioning systems (PPS), this is less of an issue, although the treatment "knuckle" of the treatment couch may interfere with a PA beam angle. This can be mitigated if the couch is "dual elbowed," but some PPS are "single elbowed." Understanding the limitations of the treatment couch or PPS is critical for all members of the treatment team. For centers with such technical limitations alternative simulation approaches may include either simulating patients prone or in the "feet first" position. Prone positioning allows for a PA beam at the zero-degree gantry angle, avoiding the possibility of gantry-table

collisions. Simulating patients in the "feet first" position allows planning to move the treatment isocenter superior relative to the treatment couch.

3. Treatment Planning:
   PA-weighted beams are ideal for multiple reasons. As described in the rationale section, the physical properties of protons (measurable entrance dose but no significant exit dose) lend themselves well to spinal and paraspinal targets. Because skin dose can be higher for protons when a more limited number of beams are used for proton therapy relative to photon therapy, especially in scattering-based systems, slightly obliqued beams may be ideal, especially for high treatment doses, to reduce the risk of skin toxicity. Many patients with disease in the spine or paraspinal areas have prior surgical procedures. If hardware was placed, its specifications, namely, information such as material and density, must be obtained. This may require speaking directly with the surgical team and/or the manufacturer of the hardware. Ideally, this information is obtained before the patient is seen for consult because this may impact whether the patient is optimally treated with proton therapy from a physics perspective. The use of carbon fiber spinal hardware, which creates minimal artifacts and back scatter, is increasingly being employed and available in many medical centers [49]. If the use of proton therapy for a spinal or paraspinal tumor is anticipated, the treating radiation oncologist can communicate directly with the operating spine surgeon to consider using carbon fiber hardware, if available, before the operation.

C. Eye

1. Rationale:
   Proton therapy is used for ocular tumors for several reasons: (1) very high doses per fraction are used, which renders maximal avoidance of collateral normal tissue irradiation of great importance; (2) the eye is a small organ with multiple radiation-sensitive structures, such that unnecessary radiation spillage – should be minimized; (3) the tumors may be large relative to the size of the eye, maximizing importance of sparing of the remainder of the eye to maximally preserve vision; if feasible [50]; and (4) the superficial location of these tumors is ideal for protons to limit dose to deeper tissues.

2. Special Considerations:
   In general, a special beamline with low energy may be used for this treatment. The treatment of ocular tumors requires close collaboration between the ophthalmologist and radiation oncologist. In addition, specialized equipment may be required beyond the standard proton facility arrangement such that not every proton facility will be equipped to optimally deliver treatment for ocular tumors. Commonly, the ophthalmologist will guide patient selection with tumor/target definition through techniques such as funduscopic examination, fluorescein angiogram, ultrasound, and direct tumor measurements intraoperatively. Most commonly but not imperatively, radio-opaque fiducial markers are sutured to the sclera and used as references for tumor definition [51]. Other alternative approaches have been devised when special eye line is not available [52].

3. Immobilization and Simulation:
   Typically, a thermoplastic mask or similar device is used for positioning of the head; an additional device may be used for the maxillary teeth (eg, bite block) to help with positioning and stability. The thermoplastic mask is trimmed over one or both eyes to allow direct visualization of the eye by the treatment team.
   During simulation, patients' position must be reproducible and comfortable enough for the patient to remain in this position throughout the treatment. The patient will visually focus on a particular spot during simulation and treatment to help maintain eye position. The optimal gaze angle (direction in which the patient's gaze is focused) is vital and must be determined before treatment.

   Depending on the treatment technique and isodose planning system used, the images obtained during simulation may either be orthogonal kilovoltage radiographs or may be obtained with volumetric acquisition using CT imaging that are increasingly available on proton systems [53]. For the volumetric acquisition, typically very thin slice thickness images are obtained through the orbits. The fiducial markers and lid retraction devices make volumetric imaging more difficult because of the artifact from those devices.

4. Treatment Planning:
   Treatment planning for ocular tumors has been most frequently performed with a treatment planning algorithm and software system developed specifically for treatment of ocular tumors. This requires multiple measurements that are obtained by the ophthalmologist, both from clinical examination and from surgical evaluation at the time of fiducial clip placement. This technique primarily uses a single anterior beam in which the gaze angle is adjusted to maximally avoid treatment through the limbus, ciliary body, cornea, lens, macula, and optic disc. To a lesser extent, beam selection is selected to also avoid unnecessary lacrimal gland, eyelid, and eyelash irradiation. An option of volumetric technique can be used in which information from ophthalmologic examination, preclip imaging, and a treatment planning CT and/or MRI scan are used to create a true 3-D treatment plan. With this technique, typically two–three beams are used, potentially with lateral, superior, or inferior fields that also avoid the radiation sensitive anterior eye structures and eyelids.

5. Treatment:
   Similar to simulation, the eye position should be fixed or monitored and tracked during treatment, typically using a camera system mounted on or near the beamline. Depending on the treatment technique, lid retraction may be used to minimize collateral irradiation to the eyelids and eyelashes. If used, the eye should be anesthetized (eg, proparacaine eye drops), and a standard eyelid speculum can be used for retraction.

D. Head and Neck

1. Rationale:
   There are many radiation-sensitive critical normal structures in the head and neck region that impact quality of life during and after treatment when exposed to radiation or chemoradiation during curative cancer treatment [54]. Proton therapy is used to reduce the dose to those structures, including optic nerves, optic chiasm, pituitary gland, brain, brainstem, spinal cord, taste buds, salivary glands, pharyngeal constrictor muscles, oral cavity, larynx, and the emetogenic sites in the posterior fossa in order to reduce complications and improve patients' quality of life during and after treatment [22,55-57]. Proton therapy has enhanced biological effects that can improve the clinical outcomes on individual tumors [58-62]. The clinical development of multifield optimization associated with IMPT has rapidly established proton therapy as a standard treatment option for patients with head and neck malignancies in the primary, adjuvant, and reirradiation settings. A Phase II/III multi-institution randomized trial of IMPT versus IMRT for patients with advanced stage oropharyngeal tumors has recently completed accrual [8,22,58,60,63-66].

2. Immobilization and Simulation:
   Patients are typically treated in the supine position, which must be reproducible and comfortable enough for the patient to tolerate it throughout the treatment. Typically, a thermoplastic mask or similar device is use for positioning of the head; an additional device may be used for the maxillary teeth (eg, bite block or dental mold, ie, stent) [67,68] to help with overall positioning, stability, and tongue position. If posterior oblique beams are to be used, a frame should be used that encompasses the head, neck, and shoulders with a curving surface laterally (typically avoid thick edges, which may cause issues with dose calculation). An additional vacuum-lock bag or foam mold for the upper thorax and neck may be useful for reproducibility, especially for patients receiving treatment to cervical nodes. This is important because the head can be more easily immobilized in a reproducible fashion than the neck.

   Images should be obtained during simulation with volumetric acquisition using a CT scan. For the volumetric acquisition, typically thin-slice images are obtained through the head and neck. If there is significant metal in or near the treatment volume, additional imaging (eg, megavoltage CT scan) or CT scanner metal artifact reduction software may be useful to help define the normal anatomy.

3. Treatment Planning:
   Low energies are required for treatment of superficial structures in the head and neck. This may require the use of a range shift with water equivalent thickness (WET) [3] to achieve the appropriate range [69].

   There may be metallic objects within the treatment volume. These may include hardware for bone

stabilization placed at surgery (eg, mandibular plate) but more frequently are dental hardware. When possible, treatment beams should avoid traversing through the dense materials because of the added attenuation, scatter, and dosimetric uncertainty. If dental hardware cannot be avoided within treatment fields, in some cases it may be better to recommend replacement of amalgam fillings with composite resin or ceramic materials. If there is dental or surgical hardware, the relevant physics information (density) must be obtained. This may require speaking directly with the dentist, surgical team, and/or the manufacturer of the hardware. Ideally, this information is obtained before the patient is seen for consultation because this may impact whether the patient is optimally treated with proton therapy from a physics perspective.

Heterogeneity and abrupt changes in density of material along the beam path will create some beam attenuation and dose deposition uncertainty. Thus, avoidance of the mastoid air cells and paranasal sinuses is generally preferred. Additional imaging may be required during treatment to evaluate the air/fluid fill within the sinuses. Because of end-range uncertainties inherent with proton therapy, it is preferable to avoid beams that end at an interface with a critical structure such as the optic pathway or brainstem, especially if prescription dose approaches normal tissue dose tolerance [70]. For certain target volumes, such as those intended to treat bilateral cervical nodes, pencil beam scanning may offer the optimal balance of conformality and homogeneity.

E. Chest—Breast/Chest Wall

1. Rationale:
   There have been several recent reports highlighting the significant risk of major coronary events after even low-dose radiation exposure to the heart associated with prior photon-based radiotherapy to the breast and thorax [71-73]. Protons can allow for significant dose reduction to the heart while allowing for equivalent or superior coverage to the regions at risk, including internal mammary nodes. Protons are therefore an attractive option for these patients [74]. The dosimetric advantages of proton therapy may allow for fewer cardiac complications and lower rates of radiation pneumonitis and secondary malignancies relative to photon therapy [75]. Proton therapy may also have particular dosimetric advantages in the postmastectomy setting [76] and for patients with synchronous bilateral breast cancers [77]. Proton therapy may be the most optimal treatment modality for patients with recurrent or new primary breast cancer who received prior radiation, with a recent large institutional series demonstrating excellent locoregional control and few high-grade toxicities with proton reirradiation [78]. Prospective studies have demonstrated excellent local control and good cosmesis with proton therapy for partial breast irradiation [79]and high rates of disease control and low rates of toxicities with proton therapy for regional nodal irradiation[74].

2. Immobilization and Simulation:
   Reproducible neck, shoulder, and torso immobilization are of critical importance with proton therapy; immobilization devices such as a vacuum bag body mold are helpful to immobilize the patient from above the head to the lower scapular area, and neck immobilization can also be achieved with the vacuum bag or with a dedicated headrest. The most common patient treatment position is supine, with the patient's ipsilateral arm or bilateral arms up and their hand on top of their head or holding hand grips on an arm shuttle or breast board. Immobilization considerations that can maximize the avoidance of normal tissue irradiation may include turning the patient's head to the contralateral side with their chin extended. Common patient position comfort measures such as a large knee sponge can improve patient tolerance to setup.

3. Treatment Planning:
   Depending on the patient's anatomy, one or two enface fields are typically used for breast/chest wall treatment. Breast/chest wall tissues are defined as the target volume, often with the assistance of radio-opaque wires placed on the skin surface during simulation and generally exclude the ribs and intercostal muscle to avoid excessive dose to the lungs. Target volume can be trimmed off of the skin (usually by a few millimeters) in order to reduce skin dose and consequent reaction. Dosage to heart and esophagus should be kept as low as possible to minimize toxicities– to these organs at risk. Metals and artifacts from implants/tissue expanders must be contoured and overridden with density overrides and taken into account during planning. A randomized phase III clinical trial comparing protons and photons for locally advanced breast comprehensive nodal irradiation is currently nearing accrual completion [80].

F. Chest—Lung, Intrathoracic Sites

1. Rationale:
   Intrathoracic malignancies, including non–small-cell lung cancer, esophageal cancer, thymic tumors, and mesothelioma, present a significant clinical challenge from a radiotherapeutic standpoint because intrathoracic progression is a dominant pattern of failure. Because of the fact that these tumors are in close proximity to radiosensitive vital organs and other critical structures, such as the heart, lungs, esophagus, and spinal cord, protons offer a dosimetric advantage by allowing dose to be delivered to the target while minimizing collateral dose exposure to these neighboring critical structures. Additionally, in the case of non–small-cell lung cancer, in which dose escalation with photons was proven to be unsuccessful (–largely related to toxicity from dose to normal tissues) [81] despite suboptimal control rates with standard radiation dosing, protons may allow for safe escalation of tumor dose in a subset of patients [82]. A single-institution study has shown improved dosimetric conformality of IMPT associated with reduced adverse events from heart, lung, esophagus, and patient general fatigue when compared with PSPT [7]. Protons have also been used for reirradiation of recurrent lung cancer after prior concurrent chemoradiation, including in multicenter prospective studies [83,84], with encouraging outcomes [85-88]. In the setting of non–small-cell lung cancer, a meta-analysis suggested improved local control and reduced toxicity with proton versus photon hypofractionation for early stage disease [89], and a population-based study suggested improved survival with proton versus photon chemoradiation for locally advanced disease [19]. A phase III randomized trial comparing overall survival for proton versus photon chemoradiation conducted through NRG Oncology is approaching accrual completion [90].

   In the setting of esophageal cancer, a recent prospective randomized trial showed significant reduction of total toxicity burden, a decrease in hospital stays, and fewer cardiac adverse events with proton therapy [21]. In thymoma, the spare of the cardiac structures is optimized using proton beam therapy, which can lead to fewer toxicities and optimized treatment outcomes [91]. Additionally, in thymoma, in which life expectancy is near normal after complete surgical resection in the absence of local failure, protons represent an attractive option to deliver a radiation dose to the surgical bed while minimizing the risk of late radiation-induced cardiac injury [91].

   In the setting of mesothelioma, in which a complicated "rind-like" dose distribution must be delivered to a large volume of the hemithorax, often after surgical resection, protons allow for delivery of this dose without a significant dose being delivered to the contralateral lung, along with reduction in doses to the heart and upper gastrointestinal structures [92].

2. Immobilization and Simulation:
   The arms should generally be positioned above the patient's head, commonly with use of a wing board with hand grips and a plastic headrest. These are often the only devices routinely used for immobilization. Occasionally, padded sponges or equivalents can be used to support the elbows and knees.

3. Treatment Planning:
   In general, multiple fields should be used to optimize conformality and robustness. For the best accountability of internal organ and target motion, 4-D scanning during simulation should be used. Beams should be chosen to minimize collateral radiation dose to the lung, heart, esophagus, and spinal cord. IMPT can allow significant dosimetric benefits over passive scattering proton therapy, which can directly translate to fewer treatment-related toxicities and improved survival [7]. Motion management is more critical, however, for IMPT than passive scattering. Motion management such as respiratory gating, abdominal compression, and active breathing coordination may be considered during simulation if excessive tumor motion (>5-10 mm) is noted [93]. Volumetric or layer repainting might be used to mitigate tumor motion interplay effects if pencil beam scanning is to be used. Target volume can be defined in all phases from the breathing cycle, and the final dose calculation should be performed on the average scan. Proton beam is very sensitive to density change in the beam path when treating intrathoracic cancers. It is strongly recommended that repeat simulations during weeks 1 and 2 and weeks 4 and 5 in a six-week course of proton beam therapy are performed to evaluated any possible anatomic changes and need for adaptive planning, which could be indicated in as high as 29% of patients [94]. Scheduled replanning best optimizes

accounting for anatomical changes and may lead to reductions in toxicities and improvements in survival, with a recent preimmunotherapy prospective trial showing that regular replanning for locally advanced non-small cell lung cancer can achieve a five-year overall survival of 59%[95].

G. Abdomen—Stomach, Pancreas

1. Rationale:
   Radiation therapy for pancreatic cancers delivered in the postoperative or definitive setting, particularly when combined with concurrent chemotherapy, is often associated with severe fatigue and gastrointestinal (GI) toxicities, such as nausea, vomiting, diarrhea, abdominal discomfort, and anorexia. The application of proton therapy for pancreatic cancers is to reduce these GI toxicities that are primarily related to radiation dose to the stomach, duodenum (especially, in the setting of unresected tumors), and small bowel. A potential to concurrently combine radiation therapy with more aggressive regimens of chemotherapy (eg, gemcitabine, nab-paclitaxel, the FOLFIRINOX chemotherapy regimen) using proton therapy may also exist. In the setting of borderline resectable or locally advanced pancreatic cancers, proton therapy may also allow for safer dose escalation [96].

2. Immobilization and Simulation:
   4-D motion assessment during simulation is necessary to account for stomach, liver, small bowel, large bowel, and kidney motion. In the definitive treatment of pancreatic tumors, accounting for the tumor target motion is also important. To minimize the uncertainty of stomach content filling and to maximize the distance between the stomach and tumor target(s), simulation with an empty stomach is preferred –. For intact tumors, consideration of fiducial marker placement within the tumor should be made for optimal image-guided therapy, particularly in dose escalation and/or hypofractionated settings. Additionally, for these tumors, motion management strategies such as abdominal compression, breath-hold, or respiratory gating should be considered for tumors with >5–10 mm of movement, depending on proton therapy technique.

3. Treatment Planning:
   In the postoperative setting, two–three beams are typically used and arranged to minimize the dose to the aforementioned GI organs-at-risk (OAR) and minimize beam paths through areas of high uncertainty due to gas or filling content. A posterior beam delivered in between the kidneys is often the most robust beam and should always be considered as a beam angle unless the goal of treatment is to avoid the spinal cord in the setting of reirradiation. Additional beams through the right lateral, anterior oblique, or posterior oblique angles are often used because the target volumes often include right-sided (porta hepatic, portocaval) nodes and entrance through the stomach and descending colon; organs prone to interfractional uncertainty due to variable content filling or gas can be minimized. Similar beam arrangements may be used for patients with borderline resectable or unresectable tumors, but because the duodenum is also an important OAR that must be respected, consideration of additional beam angles anteriorly and left laterally may be made. However, caution must still be exercised when delivering dose to the duodenum for tumors in the pancreatic head given the close proximity/abutment of these tumors to the duodenum and the range uncertainty that must be taken into account. This issue is particularly important for dose escalation strategies.

H. Abdomen—Liver

1. Rationale:
   Normal liver tissue is highly radiosensitive to low doses of radiation, especially in cirrhotic livers that have inherent dysfunction from chronic liver damage. Radiation-related hepatotoxicity is a significant complication when irradiating liver tumors because no treatment other than supportive care currently exists to treat this complication that may be fatal. The use of proton therapy for liver cancers therefore is appealing to reduce dose to normal (uninvolved) liver tissue and to minimize the risk of radiation-related hepatotoxicity, particularly when treating patients with compromised liver function or with dose escalation [24]. In addition, reduced dose to surrounding GI organs such as the stomach, duodenum, kidney, and bowel may also result in reduced radiation-related GI toxicities. Proton therapy for liver cancers has

often been applied in the hypofractionated setting [97,98].

2. Immobilization and Simulation:
   To account for liver and tumor motion, simulation with 4-D assessment is critical to deliver the most accurate and robust treatment plan. Motion management strategies such as abdominal compression, breath-hold, or respiratory gating are essential to minimize uncertainty and the interplay effect when tumor motion is >5 to 10 mm, depending on the proton therapy technique being used. Fiducial marker placement is often important to evaluate the tumor motion on 4-D assessment as well as provide guidance for on-board imaging verification. To minimize the uncertainty of stomach content filling, simulation with an empty stomach is preferred. The use of intravenous (IV) iodinated contrast is important when simulating liver tumors because these tumors are often not well visualized on noncontrast CT images. It is highly encouraged to use multiphase (arterial, venous, delayed) contrast-enhanced images for primary liver tumors (hepatocellular carcinoma, intrahepatic cholangiocarcinoma) to allow for the most accurate delineation of tumors for treatment planning.

3. Treatment Planning:
   Various patient characteristics must be considered when treating liver tumors with proton therapy, including tumor location, size, and motion; prior treatment history; and baseline liver function. Design of beam angles and paths require careful consideration of multiple factors that must be individualized for each patient; no single set of beam arrangements are applicable for all patients. For example, angles that are optimal for beam robustness may compromise target dose conformality or increase dose to other OARs and vice versa. Generally, for patients with liver dysfunction, priority is given to selecting beam angles that are both robust and optimally spare normal liver tissue.

I. Abdomen—Retroperitoneum

1. Rationale:
   The median size of retroperitoneal sarcomas is 15 cm at diagnosis, making these among the largest tumors. Although the primary treatment of these tumors is surgery, local recurrence rate at five years has been reported to be as high as 50% even from experienced major referral centers. Often times, preoperative radiation therapy can improve local tumor control when the tumor itself displaces much normal tissue or perhaps the posterior tumor margin is difficult to resect. A randomized phase III study conducted by the European Organization for Research and Treatment of Cancer European Organization for Research and Treatment of Cancer (EORTC) (the STRASS study) that randomized patients with retroperitoneal sarcomas to either surgery alone or preoperative radiation therapy was a negative trial with preoperative radiotherapy at 50.4 Gy RBE generating a small effect on abdominal recurrence-free survival (RFS). However, a post hoc subgroup analysis suggested that preoperative radiotherapy might improve outcomes for patients with liposarcoma and low-grade retroperitoneal sarcoma, which comprised 75% of the subjects. In patients with liposarcomas, the abdominal RFS significantly favored preoperative radiotherapy over surgery alone [99]. Preoperative dose escalation to the high-risk posterior tumor margin, which is often very close or positive, has been associated with improved local tumor control. Protons are being evaluated in an ongoing clinical trial testing the safety and efficacy of further dose escalation to this margin, with separate scanned proton and photon IMRT cohorts to determine whether protons permit higher dose, less toxicity, or both, or alternatively whether proton therapy permits the use of an ultrahypofractionated approach with less toxicity and improved patient convenience and cost-effectiveness.

2. Immobilization and Simulation:
   CT simulation is performed in the supine position with the patient's arms positioned comfortably above their head and preferably with knee/ankle rests for leg support [71]. An immobilization device may be used (eg, vacuum fix bag). No specific bladder or bowel preparation is required except when the sarcoma is primarily located within the pelvis. In that situation, the degree of rectal and bladder filling should be assessed and documented at simulation with efforts to reproduce this during radiation. Oral and IV contrast may be used to aid in the delineation of targets and organs at risk if required, but a useful alternative is to co-register diagnostic MR or CT imaging with the simulation data set. The extent of the planning CT simulation scan is dependent on the overall size and position of the target but may need to

extend above the diaphragm (eg, tracheal bifurcation) and caudally to the level of the lesser trochanter. For smaller targets in the pelvis, the upper abdomen may be excluded, and, for upper abdominal targets, the pelvis may be excluded. Generally, the maximum slice thickness should be no more than 2 to 3 mm. The use of 4-D CT scans and respiratory gating apparatus are dependent on the position and motion of the target. For upper abdominal targets, the use of these to minimize or account for target motion is highly desirable, whereas, for lower abdominal or pelvic targets, respiration has a less significant effect on target motion and thus the use of these techniques may be omitted. Planning target volume (PTV) margins will range from 0.5 to 1.0 cm depending on image guidance.

3. Treatment Planning:
To help with gross tumor volume (GTV) delineation, registration of the diagnostic CT or T1-weighted postgadolinium MR scan with the free-breathing planning CT may be performed. However, this is not always necessary, because the GTV is often readily visible on the planning CT scan. The GTV should be contoured on the 4-D CT scan (to incorporate motion) and labeled internal GTV (iGTV). An international sarcoma expert radiation oncology consensus group developed guidelines for the clinical target volume (CTV) and internal target volume (ITV) delineation [100]. The ITV is the sum of the iGTV and CTV, the latter of which is defined as a 1.5-cm symmetric expansion of the iGTV. The ITV is then edited at interfaces of bone, retroperitoneal compartment, liver, and kidneys and cropped 3–5 mm below the skin surface. It is further edited such that the ITV expands 5 mm into bowel and air cavities; if the tumor extends to the inguinal canal, a 3-cm inferior expansion is added to the iGTV (as per extremity soft-tissue sarcoma.) The ITV should extend fully into retroperitoneal and abdominal wall musculature. If the ipsilateral kidney is planned to be resected, it is not necessary to edit the ITV to exclude this kidney. The recommended PTV is a 5-mm expansion to the ITV if frequent image guidance will be obtained; if this is not the case, a larger PTV expansion should be used. The recommended preoperative dose is 50–50.4 Gy in 1.8–2 Gy fractions. In addition to treating the entire retroperitoneal tumor to moderate dose (45–50 Gy), there has been interest in the concept first described by Tzeng et al of preoperative dose escalation to the part of the tumor considered to be at risk for positive margins following surgery. This is typically the region of tumor abutting the posterior abdominal wall, vertebral bodies, and great vessels; consensus guidelines have delineated the appropriate approach [101]. Early reports for this technique delivering 57 Gy in 25 fractions to the high-risk margin were encouraging, but further data for both safety and efficacy are warranted before this approach –should be considered –standard practice [102]. A Massachusetts General Hospital–led multicenter Phase I-II trial of proton and photon dose escalation is in progress. Until such data are available, preoperative dose escalation is best delivered only on protocol [103].

The selection of treatment beams should minimize the effect of bowel gas on the dosimetry. Often, combinations of PA, posterior oblique, and lateral beams are appropriate. Evolving proton arc techniques weighted posteriorly may also show benefit. Cone beam CT or replanning CT scans should be considered during treatment to validate the PTVs and allow for adaptive planning if any significant changes in the tumor occur over the course of treatment [104].

J. Pelvis—Genitourinary, Rectum, Anal, Gynecologic

1. Rationale:
The absence of exit dose with protons may permit improved sparing of bowel, rectum, bladder, uterus/ovaries or testes, and hip joints when irradiating tumors in the pelvis. This may be important in reducing acute and late toxicity of radiation therapy. Fertility preservation without ovarian pexation may be achieved in some patients with protons depending on the relationship of the target volumes to the ovaries. Other unique scenarios in which proton therapy may confer an advantage over photon therapy in the pelvis include patients with multiple synchronous pelvic malignancies requiring radiation; patients with inflammatory bowel diseases or other bowel disease that place them at increased risk of side effects and/or malignancy with radiation therapy; or patients with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the transplanted organ is critical.

2. Immobilization and Simulation:
Patients are generally treated supine, often in simple cushioned knee-foot lock**,** vacuum-lock, or other

similar immobilizing device with arms elevated. Some patients with posterior pelvic tumors, such as sarcomas arising in the sacrum, may benefit from prone positioning that may facilitate treatment with PA proton fields. A strategy for ensuring reproducibility with a constant amount of bladder filling, either by emptying the bladder or treating with a full or defined bladder volume (ie, instructing patient to empty bladder and drink 12 ounces of fluid 15 minutes before treatment), is advised and can be adjusted based on patient needs determined at simulation. Similarly, an endorectal balloon may be employed in certain scenarios to ensure some consistency ad reproducibility of the rectum while immobilizing the clinical target volume (eg, prostate or prostate bed) [38,105,106].

3. Treatment Planning:
   If oral or IV contrast is employed, the planners may need to manually correct the attenuation to water density for treatment planning. Treatment gantry angles should be chosen to minimize the impact of variable bowel and bladder filling. Concurrent MRI simulation is often used for genitourinary and gynecologic subsites to improve soft tissue delineation.

4. Special considerations:
   a. Pelvic nodes
      Protons with pencil beam scanning allow treatment of pelvic and para-aortic lymph nodes with a reduced dose to the bowel; this may have particular benefit for patients with increased radiation sensitivity, such as with inflammatory bowel disease. Beam angles should be chosen that minimize the possible effects of bowel gas and variable bladder distention on the intended dose distribution and thus may be favored posteriorly and laterally if needed [107,108]. Special attention should be given to proton penumbra for deep-seated tumors when penumbra could be as high as 15 mm [3].

   b. Prostate Cancer
      A randomized clinical trial and a large, multi-institutional, nonrandomized pragmatic trial of protons versus IMRT for treatment of prostate cancer have both recently completed accrual, with results pending [109]. Recent studies have similarly established the feasibility and efficacy in treating the prostatic fossa in the adjuvant setting [106,110,111] and is the subject of a randomized trial of proton versus photon therapy including hypofractionated regimens [112]. A clinical advantage for protons is related to the reduction in rectal, urinary, and erectile dysfunction toxicity [20] as measured through Common Terminology Criteria for Adverse Events (CTCAE) graded toxicity and/or patient reported outcomes, as well as a reduction in the risk of secondary malignancies [112,113]. Whether any RBE differences result in improved biochemical and local control as suggested by a recent National Cancer Database (NCDB) analysis [114] is the subject of secondary endpoints in the aforementioned clinical trials. As with treatment with IMRT, fiducial markers help with target localization, and rectal balloons or rectal spacers (used in appropriate indications) [115] may help limit the dose to the rectum.

   c. Gynecologic Cancers
      The dosimetric benefit of proton therapy in gynecologic cancers has been explored [116] in the setting of adjuvant therapy for posthysterectomy patients [117], extended pelvic field irradiation for endometrial cancer [118], cervical cancer [119], and recurrent vaginal cancer [120]. Protons may allow for delivery of high radiation doses to patients with pelvic sidewall and/ or local recurrences of gynecologic cancers, particularly in the reirradiation setting. An ongoing prospective phase II trial is examining the ability of adaptive proton therapy to reduce the impact on morbidity and the immune system in cervical cancer [121]. If protons are used for these or for locally advanced gynecologic malignancies, similar considerations as with prostate cancer with regard to bowel gas and bladder distention are important [117] in mitigating intra- and interfraction variability and dose delivery uncertainties.

   d. Sarcoma and Desmoid Tumors
      Protons have a long history of use for sarcomas and soft-tissue tumors in permitting dose escalation and retreatment of areas such as the pelvis that are difficult to manage with surgery and/or in medically inoperable patients [122-125]. Protons allow delivery of high radiation doses to pelvic sarcomas that are unresected or resected with positive margins, in which the necessary doses for tumor control exceed bowel and other OAR tolerances [126]. T4 colonic tumors may be adherent to the pelvic side wall,

where protons may permit delivery of dose escalated radiation to these areas with improved sparing of pelvic viscera.

e. Rectal Cancer or Colonic "T4"
Proton therapy can be used for initial irradiation or reirradiation of the pelvis in patients with locally recurrent rectal cancer, which often involves the pelvic sidewall or presacral tissues and in which radiation dose escalation, often in conjunction with chemotherapy, may be important for local disease control. These patients often require maximal sparing of surrounding OARs (bowel, bladder, ureters, pelvic bone, pelvic nerves) from additional radiation because of previously delivered radiation or prior or upcoming surgical interventions. Proton therapy used in initial treatment of rectal cancers preoperatively is currently under investigation. Special circumstances such as active inflammatory bowel disease or young age may warrant consideration of proton therapy in these patients [127-129]. Relatedly, T4 colonic tumors may be adherent to the pelvic side wall, where protons may permit delivery of dose escalated radiation to these areas with improved sparing of pelvic viscera [130].

f. Anal Cancer
Protons appear to reduce normal tissue radiation dose in the chemoradiation treatment of anal cancer, which often requires irradiation of a large target volume encompassing the primary site as well as perirectal, pelvic, and inguinal nodes. Protons may reduce the risk of acute and late radiation treatment-associated morbidity [131,132].

Definitive treatment of anal cancers with chemoradiation is frequently associated with severe skin, GI, genitourinary, and hematologic toxicities, largely owing to the irradiation of large target volumes encompassing the primary site as well as perirectal, pelvic, and inguinal nodes. Proton therapy may reduce radiation dose to small bowel, bladder, genitalia, and pelvic bone marrow with the potential to reduce the risk of acute and late radiation treatment-associated morbidity. The ability to achieve superior skin sparing in the inguinal and perianal regions compared to photons is uncertain and will depend on the specific planning technique being applied.

g. Fertility
Protons have provided the opportunity for both ovarian and testicular sparing from exit radiation dose with the need for ovarian pexation or secondary testicular shielding. This can be critical in young patients for maintaining fertility [133,134].

h. Testicular cancer (Seminoma)
Radiation therapy has evolved to play a limited but important role in the management of early-stage testicular seminoma (stage I and II). Because the clinical target generally involves the para-aortic nodes in patients with a relatively young median age, they may benefit from the reduction in integral dose and sparing of adjacent OARs [135-137]. Proton beam therapy for testicular seminoma resulted in excellent clinical outcomes and was associated with lower rates of acute diarrhea compared to photon therapy [138].

K. Pediatrics

Many of the principles surrounding adult disease sites apply to pediatric patients with cancer. For other aspects of proton therapy in children, these principles serve as a starting point that should be further modified to accommodate considerations of physical and mental development.

1. Anesthesia
Anesthesia is commonly required for the immobilization of young children [139]. As with photon therapy, this is an individualized decision that incorporates a child's stage of development, the physical discomfort of positioning, and the necessary radiation technique. For children undergoing proton therapy, three elements require additional consideration. First, proton therapy delivery may require a longer treatment session and therefore an extended period of immobilization. Second, the precision of proton therapy means it is very unforgiving to even slight movement associated with a young child's anxiety or agitation. Third, an average proton therapy gantry and/or treatment vault is often much larger in size

and scale compared to modern linear accelerators. This often translates into a more intimidating environment for young children. To address these unique considerations, centers may find a certified child life specialist valuable for patient preparation and subsequent delivery of proton therapy [140]. The use of virtual reality techniques to reduce or eliminate the need for daily sedation is being explored at multiple centers [141].

2. Growth Effects
   Although valuable in the avoidance of critical organs, the sharp dosimetric gradient of proton therapy may create asymmetry in developing bones and soft tissue, causing suboptimal functional or cosmetic outcomes [142]. Although this has been considered in some photon settings (such as Wilms tumor), the potential impact may be greater with proton therapy. In some situations a pediatric radiation oncologist may intentionally treat a larger volume to minimize the likelihood of developmental asymmetry. However, this approach is being challenged with current strategies that intentionally spare the anterior vertebral body in proton craniospinal irradiation (CSI) in children. The potential long-term musculoskeletal impact of vertebral body sparing CSI is being evaluated in ongoing trials [143].

3. Secondary Tumors
   Through the absence of exit dose, proton therapy consistently delivers a lower total body integral radiation dose compared to photon therapy delivered with the same number of beams. This is especially critical in children, who have a higher lifetime risk of radiation carcinogenesis. Initial modeling studies using older proton technology suggested out of field neutron scatter dose may lead an unexpected incidence of secondary tumors, but this is refuted by clinical outcomes [144]. Furthermore, newer techniques of pencil beam scanning, which reduces the hardware in the proton beam path, produce a neutron dose comparable to modern photon delivery. The use of any proton therapy has an approximate half reduction of integral radiation dose to nontarget tissues compared to photon therapy techniques [113,145].

L. Radiation Sensitivity

1. Reirradiation
   Reirradiation requires integration of prior radiation dose delivered in addition to current desired treatment [146,147]. Prior radiation plans should ideally be reconstructed to determine the extent of potential dose overlap. Beam arrangements should ideally seek to avoid overlap with the prior dose as much as possible. Generally, some dose discount can be made from prior irradiation, theoretically with approximately 50% dose discount for every five years removed from the present time and with more conservative discount when considering more highly radiation sensitive structures with more dire associated toxicity (eg, optic chiasm, brainstem). While proton therapy may be the most optimal way to deliver repeat external beam radiation therapy in many cases [148], with the potential for fewer toxicities relative to photon reirradiation, high-grade complications are still possible with proton reirradiation [149], especially when –the composite and time decay adjusted dose to the target significantly exceeds the tolerance of involved normal tissues.

2. Medical Comorbidity
   Patients with underlying disorders or conditions that increase ionizing radiation sensitivity will still carry such risks with treatment by proton therapy. It is possible, however, that the use of proton therapy to reduce or avoid collateral organ irradiation will achieve better tolerance to radiation therapy. For example, proton therapy of a brain tumor may reduce nontarget brain irradiation and thereby reduce the risk of a multiple sclerosis flare. Proton therapy to the spine will often avoid all radiation exposure to the GI track and thereby may prevent an inflammatory bowel disease flare.

3. Combined drug therapies
   Some chemotherapeutics known to sensitize radiation (eg, gemcitabine), some novel targeted agents (eg, vemurafenib), and many checkpoint inhibitors can accentuate combined modality treatment toxicity. Proton therapy may be helpful to reduce treatment toxicity by reduction of nontarget tissue radiation exposure. Although the incidence and severe of toxicities may be reduced [150], practitioners should not assume that the combination of systemic agents with proton therapy will be without risk, and caution should still be employed when providing proton therapy under high-risk or untested circumstances.

IV. DOCUMENTATION

Documentation should be in accordance with the ACR–ASTRO Practice Parameter for Communication: Radiation Oncology and the ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy [33,40].

V. PROCESS OF THERAPY AND EQUIPMENT SPECIFICATIONS

The ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy contains specifics regarding beam delivery and properties, dosimetry, geometry and dose-volume definition, treatment planning, motion management, imaging for treatment localization, and uncertainties [33]. Here, we present a short summary of these topics.

The diversity in existing and available technology to produce clinical proton beams necessitates highly specialized onsite technical knowledge of the delivery system based on vendor-specific training in order to set up appropriate technical policies and procedures (eg, radiation safety).

To ensure continuous accurate absolute dose calibration, clinics are encouraged to follow the International Atomic Energy Agency, Absorbed Dose Determination in External Beam Radiotherapy IAEA TRS 398 protocol and to participate in the Imaging and Radiation Oncology Core (IROC) annual independent dose verification program. In addition, initial IROC credentialing procedures are mandatory for participation in National Cancer Institute (NCI)-supported clinical trials.

For volume definition, it is recommended to follow International Commission on Radiation Units and Measurements (ICRU) reports 62 and 78, with a special emphasis on the consideration of various sources of uncertainty.

Dose computation for proton therapy is highly sensitive to tissue densities, as represented by CT Hounsfield units. Therefore, proper characterization of each CT scanner's Hounsfield unit to relative proton stopping power conversion is essential. In this regard, dual energy CT (DECT) may be advantageous [151]. Any devices used for patient immobilization must be proton-compatible, ie, minimally disturb the traversing particle beam, and avoid sharp density gradients. Immobilization and patient support must be considered for dose calculation. Motion management strategies are of great importance, particularly when treating with scanned particle beams. Clear guidelines for treatment of moving targets should be developed. When available, Monte Carlo simulation or TPS with Monte Carlo algorithms are recommended to be employed for dose computation.
Commissioning of the treatment planning system should follow general procedures also used in conventional therapy (eg, IAEA TRS 430). Furthermore, it is recommended to apply an RBE of 1.1 for the conversion between physical and biological dose (ICRU 78); however, the RBE may be variable depending on the cell line histology and fraction size as described in TG-256 [152].

Image guidance for patient setup is required in proton therapy. Various technologies are available with both 2-D and 3-D techniques. These should be validated and checked according to the existing ACR–ASTRO Practice Parameter for Image-Guided Radiation therapy (IGRT) [34].

During the treatment planning process, the impact of range uncertainties should be assessed. Robustness planning analysis and assessment may be performed on a site-specific basis, when first establishing a treatment protocol, or on a patient-specific basis when special concerns arise. Before moving on to treatment, phantom validation must be performed in each treatment modalities.

The ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy presents recommendations regarding all aspects of a proton QA program [33]. This section briefly summarizes its most important aspects.

It is recommended to develop QA procedures following the formalism suggested by AAPM TG100, which introduces the concept of Failure Mode and Effect Analysis in Radiotherapy. This approach improves both effectiveness and efficiency of QA efforts. The –AAPM TG224 [153] report –contains more prescriptive tests and acceptance criteria for proton beams that could be used, similar to TG142.

Some aspects of a proton beam QA program are set up very similarly to standard photon therapy procedures. These include mechanical QA (AAPM TG142), calibration of dosimetry equipment (IAEA, TRS 398), chart review and treatment planning system QA (ICRU 78, IAEA, TRS 430).

Dosimetric machine QA is not standardized and requires a specialized set of procedures and equipment because the physical quantities to be validated differ from conventional therapy. In addition, methods must be adjusted based on the vendor and beam delivery system; passively scattered and uniformly scanned beams require different types of tests than spot scanned beams. Proton centers are encouraged to develop a dosimetric QA program based on available literature, the nature of their equipment, and already gained institutional experience.

Patient specific QA should cover any field specific hardware and dosimetric checks. The latter can take the form of actual measurement (eg, single point or 2-D planes) or a computed secondary monitor unit (MU) check in the case of passive scattering and log file analysis combined with Monte Carlo simulations for spot scanned beams. With the introduction of new technologies, oftentimes guidelines of technical standards and procedures are produced in-house but proper validation and documentation of each step and implementation should be documented.

Before initiation of a clinical proton radiotherapy program, it is recommended to hold a treatment readiness review. Periodic external phantom dosimetric verification through IROC **is** highly encouraged.

VI. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education* on the ACR web site (https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement).

Specific proton therapy QA procedures require a thorough understanding of the system design under consideration. As detailed in the ACR–AAPM Technical Standard for the Performance of Proton Beam Radiation Therapy, QA policies and procedures should be developed according to detailed Failure Mode Effect Analysis (FMEA) principles [33,154,155]. These should include explicit detail of the FMEA-identified specific mitigations required to achieve a safe system along with the associated QA procedures and frequencies necessary to test that such specific mitigations are implemented correctly. These should include QA procedures for mechanical components, beam calibrations, treatment planning systems, and machine-specific considerations. Patient-specific QA procedures, medical physics chart review, implementation of new procedures, associated documentation of QA procedures, and peer review, including both on-site and remote monitoring, should all be addressed.

1. QA and Performance Improvement (QAPI) Program

Periodic review of the quality assessment and performance improvement (QAPI) program for Proton Therapy should be performed with selected personnel in Proton Therapy (radiation oncologists, Qualified Medical Physicists, dosimetrists, radiation therapists, nurses, and administrative staff). Participating in an incident reporting and learning system is necessary to facilitate continuous quality improvement and patient safety.

2. Credentialing and Training

The training requirements of the radiation oncologist should conform to the qualifications and certification as outlined in the ACR–ASTRO Practice Parameter for Radiation Oncology [32]. Because this training did not include proton therapy, specific training in proton therapy must be obtained before performing any such procedures. The American Board of Radiology has approved fellowship training programs in proton therapy within several academic medical centers across the United States.

3. Continuing Medical Education

Continuing medical education programs with an emphasis on proton therapy disease management, planning, and outcomes shall include radiation oncologists, medical physicists, medical dosimetrists, and radiation therapists.

The continuing education of the physician and Qualified Medical Physicist should be in accordance with the ACR Practice Parameter for Continuing Medical Education [37].

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REFERENCES

1. Wilson RR. Radiological use of fast protons. Radiology 1946;47:487-91.
2. Frank SJ, & In Zhu, X. R. *Proton Therapy: Indications, Techniques and Outcomes.* 1st ed; 2021.
3. Das IJ, and Harald Paganetti. *Principles and Practice of Proton Beam Therapy*. Madison, Wisconsin Published for the American Association of Physicists in Medicine by Medical Physics Publishing, Inc; 2015.
4. Durante M, Loeffler JS. Charged particles in radiation oncology. Nature reviews. Clinical oncology 2010;7:37-43.
5. DeLaney TF. Proton therapy in the clinic. Frontiers of radiation therapy and oncology 2011;43:465-85.
6. Mohan R, Das IJ, Ling CC. Empowering Intensity Modulated Proton Therapy Through Physics and Technology: An Overview. International journal of radiation oncology, biology, physics 2017;99:304-16.
7. Gjyshi O, Xu T, Elhammali A, et al. Toxicity and Survival After Intensity-Modulated Proton Therapy Versus Passive Scattering Proton Therapy for NSCLC. J Thorac Oncol 2021;16:269-77.
8. Frank SJ, Cox JD, Gillin M, et al. Multifield optimization intensity modulated proton therapy for head and neck tumors: a translation to practice. International journal of radiation oncology, biology, physics 2014;89:846-53.
9. Yepes P, Adair A, Frank SJ, et al. Fixed- versus Variable-RBE Computations for Intensity Modulated Proton Therapy. Advances in radiation oncology 2019;4:156-67.
10. Lin LL, Vennarini S, Dimofte A, et al. Proton beam versus photon beam dose to the heart and left anterior descending artery for left-sided breast cancer. Acta Oncol 2015;54:1032-9.
11. Mailhot Vega RB, Kim J, Bussiere M, et al. Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. Cancer 2013;119:4299-307.
12. Vogelius IR, Westerly DC, Aznar MC, et al. Estimated radiation pneumonitis risk after photon versus proton therapy alone or combined with chemotherapy for lung cancer. Acta Oncol 2011;50:772-6.
13. Yock TI, Bhat S, Szymonifka J, et al. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2014;113:89-94.
14. Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. The Lancet. Oncology 2016;17:287-98.
15. Suit H. The Gray Lecture 2001: coming technical advances in radiation oncology. International journal of radiation oncology, biology, physics 2002;53:798-809.
16. Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. Clin Oncol (R Coll Radiol) 2003;15:S37-50.
17. Steinberg ML, Konski A. Proton beam therapy and the convoluted pathway to incorporating emerging technology into routine medical care in the United States. Cancer J 2009;15:333-8.
18. Peeters A, Grutters JP, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2010;95:45-53.
19. Higgins KA, O'Connell K, Liu Y, et al. National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer. International journal of radiation oncology, biology, physics 2017;97:128-37.
20. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. Cancer 2014;120:1076-82.
21. Lin SH, Hobbs BP, Verma V, et al. Randomized Phase IIB Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for Locally Advanced Esophageal Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2020;38:1569-79.
22. Manzar GS, Lester SC, Routman DM, et al. Comparative analysis of acute toxicities and patient reported outcomes between intensity-modulated proton therapy (IMPT) and volumetric modulated arc therapy (VMAT) for the treatment of oropharyngeal cancer. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2020;147:64-74.
23. Patel SH, Wang Z, Wong WW, et al. Charged particle therapy versus photon therapy for paranasal sinus and nasal cavity malignant diseases: a systematic review and meta-analysis. The Lancet. Oncology 2014;15:1027-38.
24. Sanford NN, Pursley J, Noe B, et al. Protons versus Photons for Unresectable Hepatocellular Carcinoma: Liver

Decompensation and Overall Survival. International journal of radiation oncology, biology, physics 2019;105:64-72.
25. Verma V, Shah C, Rwigema JC, Solberg T, Zhu X, Simone CB, 2nd. Cost-comparativeness of proton versus photon therapy. Chin Clin Oncol 2016;5:56.
26. Huang D, Frank SJ, Verma V, et al. Cost-Effectiveness Models of Proton Therapy for Head and Neck: Evaluating Quality and Methods to Date. Int J Part Ther 2021;8:339-53.
27. Ning MS, Palmer MB, Shah AK, et al. Three-Year Results of a Prospective Statewide Insurance Coverage Pilot for Proton Therapy: Stakeholder Collaboration Improves Patient Access to Care. JCO Oncol Pract 2020;16:e966-e76.
28. Thaker NG, Boyce-Fappiano D, Ning MS, et al. Activity-Based Costing of Intensity-Modulated Proton versus Photon Therapy for Oropharyngeal Cancer. Int J Part Ther 2021;8:374-82.
29. Smith GL, Fu S, Ning MS, et al. Work Outcomes after Intensity-Modulated Proton Therapy (IMPT) versus Intensity-Modulated Photon Therapy (IMRT) for Oropharyngeal Cancer. Int J Part Ther 2021;8:319-27.
30. Thaker NG, Frank SJ, Feeley TW. Comparative costs of advanced proton and photon radiation therapies: lessons from time-driven activity-based costing in head and neck cancer. J Comp Eff Res 2015;4:297-301.
31. Particle Therapy Co-Operative Group. https://www.ptcog.ch/index.php/facilities-in-operation. Accessed July 16, 2022.
32. American College of Radiology. ACR–ASTRO practice parameter for radiation oncology Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/RadOnc.pdf. Accessed February 8, 2022.
33. American College of Radiology. ACR–AAPM technical standard for the performance of proton beam radiation therapy Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Proton-Therapy-TS.pdf. Accessed February 8, 2022.
34. American College of Radiology. ACR–ASTRO practice parameter for image-guided radiation therapy (IGRT) Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/IGRT-RO.pdf. Accessed February 8, 2022.
35. American College of Radiology. ACR–AAPM technical standard for the performance of radiation oncology physics for external beam therapy Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Ext-Beam-TS.pdf. Accessed February 8, 2022.
36. Li H, Dong L, Bert C, et al. AAPM Task Group Report 290: Respiratory motion management for particle therapy. Medical physics 2022;49:e50-e81.
37. American College of Radiology. ACR practice parameter for continuing medical education (CME). Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/CME.pdf. Accessed December 19, 2016.
38. Wang L, Yang L, Han S, et al. Patterns of protein expression in human head and neck cancer cell lines differ after proton vs photon radiotherapy. Head Neck 2020;42:289-301.
39. American College of Radiology. Code of Ethics - Article XIII. Available at: https://www.acr.org/-/media/ACR/Files/Governance/Code-of-Ethics.pdf. Accessed September 20, 2017.
40. American College of Radiology. ACR–ASTRO practice parameter for communication: radiation oncology Available at: https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Communication-RO.pdf. Accessed February 8, 2022.
41. American Medical Association. Code of Medical Ethics. Available at: https://www.ama-assn.org/about-us/code-medical-ethics. Accessed December 19, 2016.
42. Kahalley LS, Peterson R, Ris MD, et al. Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2020;38:454-61.
43. Sherman JC, Colvin MK, Mancuso SM, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. J Neurooncol 2016;126:157-64.
44. Dennis ER, Bussiere MR, Niemierko A, et al. A comparison of critical structure dose and toxicity risks in patients with low grade gliomas treated with IMRT versus proton radiation therapy. Technology in cancer research & treatment 2013;12:1-9.
45. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. The Lancet. Neurology 2009;8:810-8.
46. Barney CL, Brown AP, Grosshans DR, et al. Technique, outcomes, and acute toxicities in adults treated with proton beam craniospinal irradiation. Neuro-oncology 2014;16:303-9.
47. Wattson DA, Tanguturi SK, Spiegel DY, et al. Outcomes of proton therapy for patients with functional pituitary adenomas. International journal of radiation oncology, biology, physics 2014;90:532-9.
48. Das IJ, Cheng CW, Fein DA, Coia LR, Curran WJ, Jr., Fowble B. Dose estimation to critical organs from

vertex field treatment of brain tumors. International journal of radiation oncology, biology, physics 1997;37:1023-9.
49. Shi C, Lin H, Huang S, et al. Comprehensive Evaluation of Carbon-Fiber-Reinforced Polyetheretherketone (CFR-PEEK) Spinal Hardware for Proton and Photon Planning. Technology in cancer research & treatment 2022;21:15330338221091700.
50. Esmaeli B, Yin VT, Hanna EY, et al. Eye-sparing multidisciplinary approach for the management of lacrimal gland carcinoma. Head Neck 2016;38:1258-62.
51. Mishra KK, Daftari IK. Proton therapy for the management of uveal melanoma and other ocular tumors. Chin Clin Oncol 2016;5:50.
52. Hartsell WF, Kapur R, Hartsell SO, et al. Feasibility of Proton Beam Therapy for Ocular Melanoma Using a Novel 3D Treatment Planning Technique. International journal of radiation oncology, biology, physics 2016;95:353-59.
53. Veiga C, Janssens G, Teng CL, et al. First Clinical Investigation of Cone Beam Computed Tomography and Deformable Registration for Adaptive Proton Therapy for Lung Cancer. International journal of radiation oncology, biology, physics 2016;95:549-59.
54. Blanchard P, Gunn GB, Lin A, Foote RL, Lee NY, Frank SJ. Proton Therapy for Head and Neck Cancers. Semin Radiat Oncol 2018;28:53-63.
55. Holliday EB, Garden AS, Rosenthal DI, et al. Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy. International Journal of Particle Therapy 2015;2:19-28.
56. Holliday EB, Kocak-Uzel E, Feng L, et al. Dosimetric advantages of intensity-modulated proton therapy for oropharyngeal cancer compared with intensity-modulated radiation: A case-matched control analysis. Med Dosim 2016;41:189-94.
57. Sio TT, Lin HK, Shi Q, et al. Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes. International journal of radiation oncology, biology, physics 2016;95:1107-14.
58. Gunn GB, Garden AS, Ye R, et al. Proton Therapy for Head and Neck Cancer: A 12-Year, Single-Institution Experience. Int J Part Ther 2021;8:108-18.
59. Hanania AN, Zhang X, Gunn GB, et al. Proton Therapy for Major Salivary Gland Cancer: Clinical Outcomes. Int J Part Ther 2021;8:261-72.
60. Lin A, Chang JHC, Grover RS, et al. PTCOG Head and Neck Subcommittee Consensus Guidelines on Particle Therapy for the Management of Head and Neck Tumors. Int J Part Ther 2021;8:84-94.
61. Sherry AD, Pasalic D, Gunn GB, et al. Proton Beam Therapy for Head and Neck Carcinoma of Unknown Primary: Toxicity and Quality of Life. Int J Part Ther 2021;8:234-47.
62. Cao J, Zhang X, Jiang B, et al. Intensity-modulated proton therapy for oropharyngeal cancer reduces rates of late xerostomia. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2021;160:32-39.
63. Emma B. Holliday ASG, David I. Rosenthal, C. David Fuller, William H. Morrison, G. Brandon Gunn, Jack Phan, Beth M. Beadle, Xiarong R. Zhu, Xiaodong Zhang, Ehab Hanna, Bonnie S. Glisson, Katherine A. Hutcheson, Adel K. El-Naggar, Ji-Hong Hong, Tsung-Min Hung, Esengul K. Uzel, Gary Lewis, Steven J. Frank,. Proton Therapy Reduces Treatment-Related Toxicities for Patients with Nasopharyngeal Cancer: A Case-Match Control Study of Intensity-Modulated Proton Therapy and Intensity-Modulated Photon Therapy. International Journal of Particle Therapy 2015;2:19-28.
64. Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. The Lancet. Oncology 2017;18:e254-e65.
65. Frank SJ, Blanchard P, Lee JJ, et al. Comparing Intensity-Modulated Proton Therapy With Intensity-Modulated Photon Therapy for Oropharyngeal Cancer: The Journey From Clinical Trial Concept to Activation. Semin Radiat Oncol 2018;28:108-13.
66. Hernandez M, Lee JJ, Yeap BY, et al. The Reality of Randomized Controlled Trials for Assessing the Benefit of Proton Therapy: Critically Examining the Intent-to-Treat Principle in the Presence of Insurance Denial. Advances in radiation oncology 2021;6:100635.
67. Stieb S, Perez-Martinez I, Mohamed ASR, et al. The impact of tongue-deviating and tongue-depressing oral stents on long-term radiation-associated symptoms in oropharyngeal cancer survivors. Clin Transl Radiat Oncol 2020;24:71-78.
68. Zaid M, Koay EJ, Bajaj N, et al. A prospective parallel design study testing non-inferiority of customized oral stents made using 3D printing or manually fabricated methods. Oral Oncol 2020;106:104665.

69. Lin H, Shi C, Huang S, et al. Applications of various range shifters for proton pencil beam scanning radiotherapy. Radiat Oncol 2021;16:146.
70. Tilly N, Johansson J, Isacsson U, et al. The influence of RBE variations in a clinical proton treatment plan for a hypopharynx cancer. Physics in medicine and biology 2005;50:2765-77.
71. Baldini EH, Wang D, Haas RL, et al. Treatment Guidelines for Preoperative Radiation Therapy for Retroperitoneal Sarcoma: Preliminary Consensus of an International Expert Panel. International journal of radiation oncology, biology, physics 2015;92:602-12.
72. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. The New England journal of medicine 2013;368:987-98.
73. Dess RT, Sun Y, Matuszak MM, et al. Cardiac Events After Radiation Therapy: Combined Analysis of Prospective Multicenter Trials for Locally Advanced Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2017;35:1395-402.
74. Luo L, Cuaron J, Braunstein L, et al. Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2019;132:250-56.
75. Mutter RW, Choi JI, Jimenez RB, et al. Proton Therapy for Breast Cancer: A Consensus Statement From the Particle Therapy Cooperative Group Breast Cancer Subcommittee. International journal of radiation oncology, biology, physics 2021;111:337-59.
76. Oonsiri P, Nantavithya C, Lertbutsayanukul C, et al. Dosimetric evaluation of photons versus protons in postmastectomy planning for ultrahypofractionated breast radiotherapy. Radiat Oncol 2022;17:20.
77. Stick LB, Jensen MF, Bentzen SM, et al. Radiation-Induced Toxicity Risks in Photon Versus Proton Therapy for Synchronous Bilateral Breast Cancer. Int J Part Ther 2022;8:1-13.
78. Choi JI, Khan AJ, Powell SN, et al. Proton reirradiation for recurrent or new primary breast cancer in the setting of prior breast irradiation. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2021;165:142-51.
79. Pasalic D, Strom EA, Allen PK, et al. Proton Accelerated Partial Breast Irradiation: Clinical Outcomes at a Planned Interim Analysis of a Prospective Phase 2 Trial. International journal of radiation oncology, biology, physics 2021;109:441-48.
80. Bekelman JE, Lu H, Pugh S, et al. Pragmatic randomised clinical trial of proton versus photon therapy for patients with non-metastatic breast cancer: the Radiotherapy Comparative Effectiveness (RadComp) Consortium trial protocol. BMJ Open 2019;9:e025556.
81. Bradley JD, Hu C, Komaki RR, et al. Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non-Small-Cell Lung Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2020;38:706-14.
82. Lazarev S, Rosenzweig K, Samstein R, et al. Where are we with proton beam therapy for thoracic malignancies? Current status and future perspectives. Lung Cancer 2021;152:157-64.
83. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical Outcomes of Patients With Recurrent Lung Cancer Reirradiated With Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies. Pract Radiat Oncol 2019;9:280-88.
84. Chao HH, Berman AT, Simone CB, 2nd, et al. Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:281-92.
85. Hong JH, Kim YS, Lee SW, et al. High-Dose Thoracic Re-irradiation of Lung Cancer Using Highly Conformal Radiotherapy Is Effective with Acceptable Toxicity. Cancer Res Treat 2019;51:1156-66.
86. McAvoy S, Ciura K, Wei C, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. International journal of radiation oncology, biology, physics 2014;90:819-27.
87. T.P. Kegelman HHC, C.B. Simone, C. Aggarwal, J. Bauml, A. Singh, W.P. Levin, K.A. Cengel, S.J. Feigenberg, R. Rengan, C. Langer, C. Ciunci, J.P. Plastaras, A.T. Berman,. Long-term Update of Outcomes of Proton Beam Re-irradiation for Locoregionally Recurrent Non-Small Cell Lung Cancer. International Journal of Radiation Oncology*Biology*Physics 2020;108:e98.
88. Yang WC, Hsu FM, Chen YH, et al. Clinical outcomes and toxicity predictors of thoracic re-irradiation for locoregionally recurrent lung cancer. Clin Transl Radiat Oncol 2020;22:76-82.
89. Chi A, Chen H, Wen S, Yan H, Liao Z. Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-

analysis. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2017;123:346-54.
90. Giaddui T, Chen W, Yu J, et al. Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: phase III randomized trial comparing overall survival after photon versus proton radiochemotherapy for inoperable stage II-IIIB NSCLC. Radiat Oncol 2016;11:66.
91. Vogel J, Berman AT, Lin L, et al. Prospective study of proton beam radiation therapy for adjuvant and definitive treatment of thymoma and thymic carcinoma: Early response and toxicity assessment. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2016;118:504-9.
92. Zeng J, Badiyan SN, Garces YI, et al. Consensus Statement on Proton Therapy in Mesothelioma. Pract Radiat Oncol 2021;11:119-33.
93. Chang JY, Zhang X, Knopf A, et al. Consensus Guidelines for Implementing Pencil-Beam Scanning Proton Therapy for Thoracic Malignancies on Behalf of the PTCOG Thoracic and Lymphoma Subcommittee. International journal of radiation oncology, biology, physics 2017;99:41-50.
94. Yang P, Xu T, Gomez DR, et al. Patterns of Local-Regional Failure After Intensity Modulated Radiation Therapy or Passive Scattering Proton Therapy With Concurrent Chemotherapy for Non-Small Cell Lung Cancer. International journal of radiation oncology, biology, physics 2019;103:123-31.
95. Iwata H, Akita K, Yamaba Y, et al. Concurrent Chemo-Proton Therapy Using Adaptive Planning for Unresectable Stage 3 Non-Small Cell Lung Cancer: A Phase 2 Study. International journal of radiation oncology, biology, physics 2021;109:1359-67.
96. Raturi VP, Hojo H, Hotta K, et al. Radiobiological model-based approach to determine the potential of dose-escalated robust intensity-modulated proton radiotherapy in reducing gastrointestinal toxicity in the treatment of locally advanced unresectable pancreatic cancer of the head. Radiat Oncol 2020;15:157.
97. Nakayama H, Sugahara S, Fukuda K, et al. Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract. International journal of radiation oncology, biology, physics 2011;80:992-5.
98. Fukuda K, Okumura T, Abei M, et al. Long-term outcomes of proton beam therapy in patients with previously untreated hepatocellular carcinoma. Cancer Sci 2017;108:497-503.
99. Bonvalot S, Gronchi A, Le Pechoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology 2020;21:1366-77.
100. Baldini EH, Abrams RA, Bosch W, et al. Retroperitoneal Sarcoma Target Volume and Organ at Risk Contour Delineation Agreement Among NRG Sarcoma Radiation Oncologists. International journal of radiation oncology, biology, physics 2015;92:1053-59.
101. Baldini EH, Bosch W, Kane JM, 3rd, et al. Retroperitoneal sarcoma (RPS) high risk gross tumor volume boost (HR GTV boost) contour delineation agreement among NRG sarcoma radiation and surgical oncologists. Ann Surg Oncol 2015;22:2846-52.
102. Tzeng CW, Fiveash JB, Popple RA, et al. Preoperative radiation therapy with selective dose escalation to the margin at risk for retroperitoneal sarcoma. Cancer 2006;107:371-9.
103. DeLaney TF, Chen YL, Baldini EH, et al. Phase 1 trial of preoperative image guided intensity modulated proton radiation therapy with simultaneously integrated boost to the high risk margin for retroperitoneal sarcomas. Advances in radiation oncology 2017;2:85-93.
104. Wong P, Dickie C, Lee D, et al. Spatial and volumetric changes of retroperitoneal sarcomas during pre-operative radiotherapy. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2014;112:308-13.
105. Both S, Wang KK, Plastaras JP, et al. Real-time study of prostate intrafraction motion during external beam radiotherapy with daily endorectal balloon. International journal of radiation oncology, biology, physics 2011;81:1302-9.
106. Deville C, Jr., Jain A, Hwang WT, et al. Initial report of the genitourinary and gastrointestinal toxicity of post-prostatectomy proton therapy for prostate cancer patients undergoing adjuvant or salvage radiotherapy. Acta Oncol 2018;57:1506-14.
107. Butala AA, Ingram WS, O'Reilly SE, et al. Robust treatment planning in whole pelvis pencil beam scanning proton therapy for prostate cancer. Med Dosim 2020;45:334-38.
108. Whitaker TJ, Routman DM, Schultz H, et al. IMPT versus VMAT for Pelvic Nodal Irradiation in Prostate Cancer: A Dosimetric Comparison. Int J Part Ther 2019;5:11-23.
109. Medicine USNLo. Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer (PARTIQoL). https://clinicaltrials.gov/ct2/show/NCT01617161. Accessed July 16, 2022.
110. Deville C, Jr., Hwang WT, Barsky AR, et al. Initial clinical outcomes for prostate cancer patients undergoing

adjuvant or salvage proton therapy after radical prostatectomy. Acta Oncol 2020;59:1235-39.
111. Santos PMG, Barsky AR, Hwang WT, et al. Comparative toxicity outcomes of proton-beam therapy versus intensity-modulated radiotherapy for prostate cancer in the postoperative setting. Cancer 2019;125:4278-93.
112. Koerber SA, Katayama S, Sander A, et al. Prostate bed irradiation with alternative radio-oncological approaches (PAROS) - a prospective, multicenter and randomized phase III trial. Radiat Oncol 2019;14:122.
113. Xiang M, Chang DT, Pollom EL. Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy. Cancer 2020;126:3560-68.
114. Liu Y, Patel SA, Jani AB, et al. Overall Survival After Treatment of Localized Prostate Cancer With Proton Beam Therapy, External-Beam Photon Therapy, or Brachytherapy. Clin Genitourin Cancer 2021;19:255-66 e7.
115. Hamstra DA, Mariados N, Sylvester J, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. International journal of radiation oncology, biology, physics 2017;97:976-85.
116. Verma V, Simone CB, 2nd, Wahl AO, Beriwal S, Mehta MP. Proton radiotherapy for gynecologic neoplasms. Acta Oncol 2016;55:1257-65.
117. Lin LL, Kirk M, Scholey J, et al. Initial Report of Pencil Beam Scanning Proton Therapy for Posthysterectomy Patients With Gynecologic Cancer. International journal of radiation oncology, biology, physics 2016;95:181-89.
118. Xu MJ, Maity A, Vogel J, et al. Proton Therapy Reduces Normal Tissue Dose in Extended-Field Pelvic Radiation for Endometrial Cancer. Int J Part Ther 2018;4:1-11.
119. Shang H, Pu Y, Wang W, Dai Z, Jin F. Evaluation of plan quality and robustness of IMPT and helical IMRT for cervical cancer. Radiat Oncol 2020;15:34.
120. Li YR, Kirk M, Lin L. Proton Therapy for Vaginal Reirradiation. Int J Part Ther 2016;3:320-26.
121. Corbeau A, Nout RA, Mens JWM, et al. PROTECT: Prospective Phase-II-Trial Evaluating Adaptive Proton Therapy for Cervical Cancer to Reduce the Impact on Morbidity and the Immune System. Cancers (Basel) 2021;13.
122. Friedman Y, Fildes J, Mizock B, et al. Comparison of percutaneous and surgical tracheostomies. Chest 1996;110:480-5.
123. Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. International journal of radiation oncology, biology, physics 2005;63:852-9.
124. Seidensaal K, Harrabi SB, Weykamp F, et al. Radiotherapy in the treatment of aggressive fibromatosis: experience from a single institution. Radiat Oncol 2020;15:143.
125. Guttmann DM, Frick MA, Carmona R, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2017;124:271-76.
126. Weber DC, Rutz HP, Bolsi A, et al. Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: the Paul Scherrer institute experience. International journal of radiation oncology, biology, physics 2007;69:865-71.
127. Abigail T. Berman SB, Tiffany Sharkoski, Katie Goldrath, Zelig Tochner, Smith Apisarnthanarax, James M. Metz, John P. Plastaras. Proton Reirradiation of Recurrent Rectal Cancer: Dosimetric Comparison, Toxicities, and Preliminary Outcomes International Journal of Particle Therapy 2014;1:2-13.
128. Fok M, Toh S, Easow J, et al. Proton beam therapy in rectal cancer: A systematic review and meta-analysis. Surg Oncol 2021;38:101638.
129. Koroulakis A, Molitoris J, Kaiser A, et al. Reirradiation for Rectal Cancer Using Pencil Beam Scanning Proton Therapy: A Single Institutional Experience. Advances in radiation oncology 2021;6:100595.
130. Hawkins AT, Ford MM, Geiger TM, et al. Neoadjuvant radiation for clinical T4 colon cancer: A potential improvement to overall survival. Surgery 2019;165:469-75.
131. Mohiuddin JJ, Jethwa KR, Grandhi N, et al. Multi-institutional Comparison of Intensity Modulated Photon Versus Proton Radiation Therapy in the Management of Squamous Cell Carcinoma of the Anus. Advances in radiation oncology 2021;6:100744.
132. Vaios EJ, Wo JY. Proton beam radiotherapy for anal and rectal cancers. J Gastrointest Oncol 2020;11:176-86.
133. Gross JP, Kim SY, Gondi V, et al. Proton Radiotherapy to Preserve Fertility and Endocrine Function: A Translational Investigation. International journal of radiation oncology, biology, physics 2021;109:84-94.
134. Lester-Coll NH, Morse CB, Zhai HA, et al. Preserving Fertility in Adolescent Girls and Young Women Requiring Craniospinal Irradiation: A Case Report and Discussion of Options to Be Considered Prior to Treatment. J Adolesc Young Adult Oncol 2014;3:96-99.

135. Choo R, Kazemba B, Choo CS, Lester SC, Whitaker T. Proton Therapy for Stage IIA-B Seminoma: A New Standard of Care for Treating Retroperitoneal Nodes. Int J Part Ther 2018;5:50-57.
136. Haque W, Wages C, Zhu XR, et al. Proton therapy for seminoma: Case report describing the technique, efficacy, and advantages of proton-based therapy for seminoma. Pract Radiat Oncol 2015;5:135-40.
137. Simone CB, 2nd, Kramer K, O'Meara WP, et al. Predicted rates of secondary malignancies from proton versus photon radiation therapy for stage I seminoma. International journal of radiation oncology, biology, physics 2012;82:242-9.
138. Pasalic D, Prajapati S, Ludmir EB, et al. Outcomes and Toxicities of Proton and Photon Radiation Therapy for Testicular Seminoma. Int J Part Ther 2020;7:11-20.
139. Owusu-Agyemang P, Popovich SM, Zavala AM, et al. A multi-institutional pilot survey of anesthesia practices during proton radiation therapy. Pract Radiat Oncol 2016;6:155-59.
140. Scott MT, Todd KE, Oakley H, et al. Reducing Anesthesia and Health Care Cost Through Utilization of Child Life Specialists in Pediatric Radiation Oncology. International journal of radiation oncology, biology, physics 2016;96:401-05.
141. Holt DE, Hiniker SM, Kalapurakal JA, et al. Improving the Pediatric Patient Experience During Radiation Therapy-A Children's Oncology Group Study. International journal of radiation oncology, biology, physics 2021;109:505-14.
142. Hol MLF, Indelicato DJ, Rotondo RL, et al. Dose-Effect Analysis of Early Changes in Orbital Bone Morphology After Radiation Therapy for Rhabdomyosarcoma. Pract Radiat Oncol 2020;10:53-58.
143. Giantsoudi D, Seco J, Eaton BR, et al. Evaluating Intensity Modulated Proton Therapy Relative to Passive Scattering Proton Therapy for Increased Vertebral Column Sparing in Craniospinal Irradiation in Growing Pediatric Patients. International journal of radiation oncology, biology, physics 2017;98:37-46.
144. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. International journal of radiation oncology, biology, physics 2013;87:46-52.
145. Huynh M, Marcu LG, Giles E, Short M, Matthews D, Bezak E. Are further studies needed to justify the use of proton therapy for paediatric cancers of the central nervous system? A review of current evidence. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2019;133:140-48.
146. McDonald MW, Linton OR, Shah MV. Proton therapy for reirradiation of progressive or recurrent chordoma. International journal of radiation oncology, biology, physics 2013;87:1107-14.
147. Romesser PB, Cahlon O, Scher ED, et al. Proton Beam Reirradiation for Recurrent Head and Neck Cancer: Multi-institutional Report on Feasibility and Early Outcomes. International journal of radiation oncology, biology, physics 2016;95:386-95.
148. Simone CB, 2nd, Plastaras JP, Jabbour SK, et al. Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies. Semin Radiat Oncol 2020;30:253-61.
149. Verma V, Rwigema JM, Malyapa RS, Regine WF, Simone CB, 2nd. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2017;125:21-30.
150. Baumann BC, Mitra N, Harton JG, et al. Comparative Effectiveness of Proton vs Photon Therapy as Part of Concurrent Chemoradiotherapy for Locally Advanced Cancer. JAMA Oncol 2020;6:237-46.
151. Je E, Lee HH, Duan X, Li B, Jia X, Yang M. Optimal energy selection for proton stopping-power-ratio estimation using dual-energy CT-based monoenergetic imaging. Physics in medicine and biology 2019;64:195015.
152. Paganetti H, Blakely E, Carabe-Fernandez A, et al. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. Medical physics 2019;46:e53-e78.
153. Arjomandy B, Taylor P, Ainsley C, et al. AAPM task group 224: Comprehensive proton therapy machine quality assurance. Medical physics 2019;46:e678-e705.
154. Huq MS, Fraass BA, Dunscombe PB, et al. Task Group No. 100 method for evaluating QA needs in radiation therapy. Medical physics (Under Review).
155. Huq MS, Fraass BA, Dunscombe PB, et al. The report of Task Group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management. Medical physics 2016;43:4209.

*As of May 2010, all radiation oncology collaborative practice parameters are approved by the ACR Council Steering Committee and the ACR Board of Chancellors and will not go through the ACR Council (ACR Resolution

8, 2010). This collaborative radiation oncology practice parameter document becomes effective on the first day of the first month following 60 days after final adoption by the ACR BOC. This document is scheduled to begin revision with the other practice parameters and technical standards adopted at ACR Council during the same year.

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