# ASTRO

## **Model Policies**

### PROTON BEAM THERAPY (PBT)

This Model Policy\* addresses coverage for Proton Beam Therapy.

#### DESCRIPTION

Proton Beam Therapy (PBT) is a technology for delivering conformal external beam radiation with positively charged subatomic particles to a well-defined treatment volume. PBT is approved by the U.S. Food and Drug Administration.

PBT has unique dose deposition characteristics and can deliver radiation to specified anatomic targets while giving less collateral dose to surrounding normal tissues in comparison to photon/X-ray-based forms of external beam radiotherapy.

Photon/X-ray beams deliver most of their energy in tissues just beneath the patient's surface, with the remainder deposited along the beams' path as photons/X-ray pass through the target and exit the body. In contrast, the physical profile of proton beams allows delivery of dose over a narrow range of depth in the body with no exit dose. Compared to photon beams, proton beams deposit less dose upon entering the body, with subsequent dose deposition then rapidly increasing over a narrow range of tissue at a desired depth to produce an intense dose distribution pattern called the Bragg peak. Beyond the Bragg peak, energy and dose deposition rapidly decrease, resulting in small, insignificant amounts of dose to normal tissues that lay beyond the target. A single proton beam can offer uniform dose to target volume. Multiple beams can be combined and optimized to achieve highly conformal dose distributions.

#### TREATMENT

#### **PBT Treatment Planning**

PBT can allow for radiation treatment plans that are highly conformal to anatomic targets and minimize dose to normal tissues. Specifics of PBT planning include appropriate determination of device configuration (e.g., necessary field sizes, number of beams, gantry angles, beam energy selection, robust optimization) needed to achieve the desired radiation dose distribution.

An assessment of patient suitability for PBT is an important step in the process of care. Anatomical changes, such as patient weight, or alterations in the density and composition of tissues in the path of the beam can have a much greater impact on the delivered dose and plan integrity for protons than photons/X-ray.

PBT treatment planning is a multi-step process like other forms of external beam radiation therapy planning:

1. Simulation and Imaging: Three-dimensional capture of relevant anatomy employing CT, CT/ PET and/or MR imaging is an essential prerequisite to PBT treatment planning. If respiratory or other normal organ motion is expected to produce significant movement of the target region during radiation therapy delivery, the radiation oncologist may request multiphasic treatment planning image sets to account for target and/or normal tissue motion. Supportive motion management strategies such as abdominal compression and/or breath hold can also be employed, like their routine use in photon radiation therapy. As in other forms of external beam radiation, immobilization is critical. Patient immobilization devices must be carefully designed to minimize impacting the dose distribution.

\*ASTRO Model Policies were developed as a means to efficiently communicate what ASTRO believes to be correct coverage policies for radiation oncology services. The ASTRO Model Policies do not serve as clinical guidelines and they are subject to periodic review and revision without notice. The ASTRO Model Policies may be reproduced and distributed, without modification, for noncommercial purposes.

- 2. Contouring: Defining the target and avoidance structures is a multi-step process:
  - a. The radiation oncologist reviews the three-dimensional images and delineates the treatment target on each slice of the image set. The summation of these contours defines the Gross Tumor Volume (GTV). The physician may outline separate GTVs on multiple image sets to account for the effect of respiratory motion upon target location and shape, commonly termed the Internal Target Volume (ITV). Some patients may not have GTVs if they have had previous treatment with surgery or chemotherapy, in which case treatment planning is based on CTVs as described below.
  - b. The radiation oncologist creates a margin around the GTV or delineates other key anatomic areas to generate Clinical Target Volumes (CTV) which defines region areas at risk for harboring microscopic disease (i.e., not visible on imaging studies).
  - c. In photon therapy, an additional margin is added to create a Planning Target Volume (PTV), a volume expanded to account for set up uncertainties. In PBT planning, the geometric PTV approach is insufficient to generate robust plans due to more complex sources of uncertainty along each beam direction. Instead of a uniform expansion, separate margins are adopted perpendicular to and along the beam direction. Rather, planning must be specifically optimized to ensure robustness of CTV coverage while incorporating sources of uncertainty such as set up and proton range uncertainty.
  - d. Nearby normal structures that could potentially be harmed by radiation (i.e., "organs at risk," or OARs) are also contoured.
- 3. Radiation Dose Prescription: As is done with photon planning, the radiation oncologist assigns specific dose objectives for the target, which for proton planning is the CTV, and directs that these goals be met even in the presence of set up and range uncertainties. Target coverage with proton planning is evaluated by assessing a "band of DVH's," each of which corresponds to a pre-specified positional shift or assumed range perturbation or both. Additionally, proton planning must routinely account for respecting dose constraints for OARs on both the nominal plan and in the presence of setup and range uncertainties. A treatment plan that satisfies such requirements should maximize the potential for disease control and minimize the risk of radiation injury to normal tissue. The degree to which the dose deviation to the target and OARs are weighed in plan evaluation is at the discretion of the treating physician.
- 4. Dosimetric Planning and Calculations: The qualified clinical medical physicist or dosimetrist calculates a treatment plan to deliver the prescribed radiation dose to the CTV and simultaneously satisfy the normal tissue dose constraints by delivering significantly lower doses to nearby organs. Delivery mechanisms vary but using scanning magnets or scattering devices PBT plans spread protons laterally over the extent of a target volume. In some cases, the lateral spread of the protons is shaped and conformed using an aperture. Additionally, multiple proton energies are combined, through the use of mechanical absorbers or accelerator (i.e., synchrotron) energy changes, to deliver the planned dose distribution over the longitudinal extent of the target, called spread-out Bragg peak (SOBP). For passive scattering PBT delivery, beam-specific range compensation devices are often used to shape the range of the proton beam to the distal edge of the target. Regardless of the delivery technique, all delivery parameters and/or field specific hardware are developed by a medical physicist or dosimetrist during the treatment planning stage. An expected dose distribution is calculated based on these parameters and devices. For PBT plans, nominal treatment plans should be evaluated for robustness considering both positional and range uncertainties to ensure that the planned CTV coverage and normal tissue sparing meet prespecified metrics in the presence of uncertainties.
- 5. **Patient Specific Dose Verification:** An independent dose calculation and/or measurement should confirm that the intended dose distribution for the patient is physically verified and feasible for delivery.

Documentation of all aspects of the treatment planning process is essential.

#### PBT Treatment Delivery

Proton delivery methods can be described in one of two forms: scattering or scanning.

In scattered deliveries, the beam is broadened laterally by scattering devices, beam energies are combined by mechanical absorbers, and the beam is shaped by placing devices such as collimators and compensators into the proton beam path.

In scanning deliveries, the beam is swept laterally over the target with scanning magnets instead of scatter devices. Collimators are still sometimes used for lateral beam shaping, but field shaping hardware is not generally required for spot scanning beam delivery because the scanning magnets allow the lateral extent of the beam to be varied with each energy level, a technique sometimes called intensity-modulated proton therapy (IMPT).

The basic requirement for all forms of PBT treatment delivery is that the technology must accurately produce the calculated dose distribution described by the PBT plan.

Precise delivery is vital for high-quality treatment. Therefore, imaging techniques such as stereoscopic X-ray, Cone Beam CT scan, or CT-on-rails scan (collectively referred to as Image Guided Radiation Therapy or IGRT) should be utilized to verify accurate and consistent patient and target setup for every treatment fraction. Especially, volumetric images should be considered to confirm the consistent beam path and anatomic positions.

#### **Documentation Requirements**

Documentation in the patient medical record must:

- 1. Support one or more medical necessity requirement(s) as provided under the "Indications and Limitations of Coverage and/ or Medical Necessity" section of this policy, if not enrolled on a clinical protocol or registry.
- 2. Include a treatment prescription that defines the goals of the treatment plan including specific dose-volume parameters for the target and nearby critical structures as well as pertinent details of beam delivery, such as the method of beam modulation, field arrangement, and expected positional and range uncertainties.
- 3. Include a treatment plan, signed by a physician, which meets the prescribed dose-volume parameters for the clinical target volume (CTV) and surrounding organs at risk (OARs) in the presence of expected uncertainties.
- 4. Describe the target setup verification methodology, including patient positioning, immobilization, image guidance and frequencies.
- 5. Include verification of planned dose distribution via independent dose calculation or physical measurement.

#### INDICATIONS AND LIMITATIONS OF COVERAGE AND/OR MEDICAL NECESSITY Indications for Coverage

PBT is considered reasonable in instances where sparing the surrounding normal tissue is of added clinical benefit to the patient and cannot be adequately achieved with photon-based radiation therapy. Examples of such an advantage include, but are not limited to:

- 1. The target volume is near one or more critical structures and a steep dose gradient outside the target must be achieved to avoid exceeding the tolerance dose to the critical structure(s), which would portend a higher risk of toxicity.
- 2. A proton-based technique would decrease the probability of clinically meaningful normal tissue toxicity by lowering an integral dose-based metric and/or organ at risk dose volume constraint associated with toxicity.
- 3. The same or an immediately adjacent area has been previously irradiated, and the dose distribution within the patient must be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

In addition to satisfying at least one of the three selection criteria noted above, the radiation oncologist's decision to employ PBT requires an informed assessment of the benefits and risks including:

- Determination of patient suitability for PBT allowing for reproducible treatment delivery.
- Adequate definition of the target volumes and OARs.
- Equipment capability, including ability to account for organ motion when relevant.
- Physician, physicist and staff training.
- Adequate quality assurance and safety procedures.

Coverage decisions may extend beyond ICD-10 codes to incorporate additional considerations of clinical scenario and medical necessity with appropriate documentation, which in certain circumstances may include comparative dose volume histograms.

#### Group 1

Based on the medical necessity requirements and published clinical data that meets the selection criteria above, disease sites that frequently support the use of PBT include the following:

#### GENERAL

Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria noted above under "indications for coverage" apply

Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria noted above under "indications for coverage" apply

Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1/2, Lynch syndrome, etc.

Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery

Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)

Primary malignant or benign bone tumors

#### **CENTRAL NERVOUS SYSTEM**

Ocular tumors, including intraocular melanomas

Tumors that approach or are located at the base of skull, including but not limited to:

- Chordoma
- Chondrosarcomas
- Other histologies arising in this site

Malignant and benign primary CNS tumors excluding IDH wild-type GBM, that are treated with curative intent and with potential for long term prognosis

Primary spine or spinal cord tumors or metastatic tumors to the spine or spinal cord where organ at risk tolerance may be exceeded with photon treatments

Primary and metastatic tumors requiring craniospinal irradiation

#### HEAD AND NECK

Cancers of the nasopharynx, nasal cavity, paranasal sinuses and other accessory sinuses

Advanced stage and unresectable head and neck cancers

#### THORACIC

Primary cancers of the esophagus

Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas Malignant pleural mesothelioma

#### Hepatocellular cancer and intra-hepatic biliary cancers

Non-metastatic retroperitoneal sarcomas

#### PELVIC

Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease

Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical

PBT is one of the acceptable forms of external beam radiation therapy that may be used to administer Stereotactic Body Radiation Therapy (SBRT) or Stereotactic Radiosurgery (SRS). Separate ASTRO Model Policies for SBRT and SRS include technology descriptions and a list of indications for which SBRT or SRS should be covered. When PBT is used to administer SBRT or SRS, the delivery and management codes relevant for SBRT or SRS apply, and the same clinical indications apply as for those treatment strategies.

#### Group 2

While PBT is not a new technology, there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT for various disease sites. All other indications not listed in Group 1 are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under the CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED2. At this time, no indications are deemed inappropriate for CED and therefore Group 2 includes various systems such as, but not limited to, the following:

#### HEAD AND NECK

All other head and neck cancers not included in Group 1 i.e., Periorbital tumors, primary tumors of the salivary glands, Head and neck cancers with indications for concurrent systemic therapy

Cutaneous tumors with cranial nerve invasion to the base of skull, cavernous sinus and/or brainstem

Head and neck cancers requiring ipsilateral radiation treatment (e.g., oral cavity, salivary gland)

Mucosal melanoma

Occult primary of head and neck

#### BREAST

Bilateral breast cancers requiring nodal treatment on at least one side

Locally advanced breast cancer requiring comprehensive nodal irradiation inclusive of the internal mammary lymph node chain

Breast cancer patients being treated with definitive intent and who have unfavorable anatomy (e.g., pectus excavatum) that would deliver unacceptably high doses to organs-at-risk

Breast cancer patients who have limited ipsilateral arm range of motion and require treatment in the arms down position

Early stage left sided breast cancer in which dose to the heart is unacceptably high with conventional photon or photon/electron using cardiac sparing techniques

Patients with clinically involved or suspicious internal mammary lymph nodes in whom dose escalation to the internal mammary chain is clinically indicated

#### THORACIC

Early-stage lung cancer in which a photon-based plan cannot meet the prespecified constraints or is associated with higher risk of toxicity

Locally advanced lung cancer

#### ABDOMINAL

Abdominal malignancies, including non-metastatic primary pancreatic, kidney and adrenal cancers

Oligometastatic liver lesions being treated with curative intent in which a photon based plan cannot meet constraints

#### GENITOURINARY

Prostate cancer, not fitting pelvic and/or para-aortic lymph node coverage as per Group 1

#### PELVIC

Pelvic malignancies, including non-metastatic rectal, bladder and cervical cancers

Tumors of the pelvis, such as anal cancer, or proximal thigh where use of protons results in significant dose reduction to genitalia or reproductive organs

Coverage under CED requirements will help expedite more permanent coverage decisions for all indications. Due to the numerous studies under way, proton coverage policies need to be reviewed on a frequent basis. As additional clinical data is published, this policy will be revised to reflect appropriate coverage.

#### ICD-10-CM Codes that may be Associated with Medical Necessity

Note: Diagnosis codes are based on the current ICD-10-CM codes that are effective at the time of the Model Policy publication. Any updates to ICD-10-CM codes will be reviewed by ASTRO, and coverage should not be presumed until the results of such review have been published/posted. These ICD diagnosis codes support medical necessity under this Model Policy.

#### Group 1: Medically Necessary

SITE	ICD-10	DESCRIPTION		
Central Nervous System				
Ocular tumors, including intraocular melanomas	C69.00 - C69.82	Malignant neoplasm of ocular structures		
Tumors that approach or are located at the base of skull, including but not limited to: • Chordoma • Chondrosarcomas • Other histologies arising in this site	C41.0 - C41.2 C75.1, C75.2, C75.4, C75.5 D16.4, D16.6 D35.3	Malignant neoplasm of bones of skull and face, mandible, vertebral column; Malignant neoplasm of other endocrine glands and related structures; Benign neoplasm of bone; Benign neoplasm of craniopharyngeal duct		
Malignant and benign primary CNS tumors excluding GBM, that are treated with curative intent and with potential for long term prognosis	C70.0 - C72.59, C75.3 D32.0 - D33.7	Malignant neoplasm of meninges, brain, cranial nerves, spinal cord, pineal gland; Benign neoplasm of meninges, brain, cranial nerves, spinal cord		
Primary spine or spinal cord tumors or metastatic tumors to the spine or spinal cord where organ at risk tolerance may be exceeded with conventional photon treatments	C41.2, C41.4 C70.1 C72.0, C72.1 D16.6, D16.8, D32.1, D33.4	Malignant neoplasm of bones of vertebral column, sacrum, and coccyx; Malignant neoplasm of spinal meninges; Malignant neoplasm of spinal cord and cauda equina; Benign neoplasm of vertebral column, sacrum, coccyx, spinal meninges, spinal cord		
Primary and metastatic tumors requiring craniospinal irradiation	C70.0 - C72.59, C75.3	Malignant neoplasm of meninges, brain, cranial nerves, spinal cord, pineal gland		

	Head and Neck	
Cancers of the nasopharynx, nasal cavity, paranasal sinuses, and other accessory sinuses Advanced stage and unresectable head and neck	C11.0 - C11.8 C30.0, C30.1 C31.0 - C31.8 C00.0 - C14.8	Malignant neoplasm of nasopharynx; Malignant neoplasm of nasal cavity and middle ear; Malignant neoplasm of accessory sinuses Malignant neoplasm of head and neck sites
cancers		
	Thoracic	
Primary cancers of the esophagus	C15.3 - C15.8	Malignant neoplasm of esophagus
Primary tumors of the mediastinum, including thymic tumors, mediastinal tumors, mediastinal lymphomas and thoracic sarcomas	C33 C38.0 - C38.8 C81.02 C81.12 C81.22 C81.32 C81.42 C81.72 C82.32 C82.42 C83.02 C83.12 C83.52 C83.72 C83.82	Malignant neoplasm of trachea; Malignant neoplasm of heart, mediastinum, and pleura; Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes; Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes; Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes; Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes; Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes; Other Hodgkin lymphoma, intrathoracic lymph nodes; Follicular lymphoma grade IIIa, intrathoracic lymph nodes; Small cell B-cell lymphoma, intrathoracic lymph nodes; Mantle cell lymphoma, intrathoracic lymph nodes; Diffuse large B-cell lymphoma, intrathoracic lymph nodes; Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes; Burkitt lymphoma, intrathoracic lymph nodes; Other non-follicular lymphoma, intrathoracic lymph nodes;
Malignant pleural mesothelioma	C45.0	Mesothelioma of pleura
	Abdominal	
Hepatocellular cancer and intra-hepatic biliary cancers	C22.0 - C22.7	Malignant neoplasm of liver and intrahepatic bile ducts
Non-metastatic retroperitoneal sarcomas	C48.0 - C48.8	Malignant neoplasm of retroperitoneum and peritoneum
	Pelvic	
Advanced and unresectable pelvic tumors with significant pelvic and/or peri-aortic nodal disease	various	
Patient with a single kidney or transplanted pelvic kidney with treatment of an adjacent target volume and in whom maximal avoidance of the organ is critical	various	

Skeletal		
Primary malignant or benign bone tumors	C40.0 - C40.8; C41.0 - C41.8 D16.0 - D16.8	Malignant neoplasm of bone and articular cartilage; Benign neoplasm of bone and articular cartilage
Reirradiation		
Various regions	Z92.3 T66.XXXA*	Personal history of irradiation

\*ICD-10-CM T66.XXXA (Effects of Radiation, Unspecified) may only be used where prior radiation therapy to the site is the governing factor necessitating PBT in lieu of other radiotherapy. An ICD diagnosis code for the anatomic diagnosis must also be used with appropriate documentation.

**Group 2:** The remaining ICD-10-CM (C00-D49) Neoplasm codes should be considered suitable for CED, so long as at least one of the criteria listed in the "Indications of Coverage" section of this policy is present.

#### PHYSICIANS' CURRENT PROCEDURAL TERMINOLOGY (CPT®)/HCPCS

Note: CPT is a trademark of the American Medical Association (AMA)

#### **Preparing for Treatment**

Due to the complexity of this treatment technology and the cases commonly appropriate for it, all PBT cases satisfy the criteria for complex clinical treatment planning. The clinical treatment plan is the initial process in preparing the patient for treatment.

#### **CPT<sup>®</sup>** Code for Clinical Treatment Planning

**77263** Therapeutic Radiology Treatment Planning; complex *This code is typically reported only once per course of PBT.* 

Following clinical treatment planning and a decision to proceed with PBT, treatment simulation is performed. By definition, the simulation process is complex for protons since it involves particle therapy. CT guidance is now packaged into 77290 and is no longer separately billable.

#### **CPT Code for Simulation**

77290	Therapeutic radiology simulation-aided field setting; complex This code is typically reported only once per course of PBT.
+77293	Respiratory motion management simulation (List separately in addition to code for primary procedure) This is an add-on code and cannot be billed on its own. It should be billed with either CPT code 77295 or 77301.

The add-on code +77293 would be used in situations where respiratory motion may cause significant changes in target definition and localization for proton treatment delivery, most commonly in patients with lung or upper gastrointestinal malignancies.

#### Medical Radiation Physics, Dosimetry and Treatment Devices

In addition, when planning for any special beam such as particles (i.e., protons), a special teletherapy port plan may be necessary. The special teletherapy port plan must be reviewed, signed and dated by the radiation oncologist and physicist. The radiation oncologist must document involvement in the planning and selection of special beam parameters used for treatment.

#### **CPT<sup>®</sup>** Code for Special Teletherapy Port Plan

Special teletherapy port plan, particles, hemibody, total body
Use for particle beam isodose planning. Use for electrons, protons and neutron therapy; half body or total body therapy.

Isodose planning typically involves 3-dimensional dosimetry. For cases in which there is a need to optimize the dose distribution by modulating the beam energy and/or fluence across the field, an intensity modulated treatment plan may be indicated and should be reported using CPT 77301.

#### **CPT Codes for Isodose Planning**

77295	Therapeutic radiology simulation-aided field setting; 3-dimensional Use for particle beam isodose planning. Use for electrons, protons and neutron therapy; half body or total body therapy. This code has been moved to the medical physics and dosimetry section, since it represents the work of physics and dosimetry planning rather than the work performed in simulation.
77301	Intensity Modulated Radiation Therapy (IMRT) plan, including dose-volume histograms for target and critical structure partial tolerance specifications. This code may be reported for isodose plans in which beam intensity is modulated using pencil beam scanning. This code is typically reported only once per course of IMRT.
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan. Some proton beam systems use an MLC device to modulate beam intensity, and 77338 may be reported. Report once per IMRT plan.

Compensation of the beams may be performed with specific physical compensating devices (custom fabricated lucite or wax compensators) or with compensation using electromagnetic alterations of the beam (pencil-beam scanning or spot scanning).

#### Image-Guided Radiation Therapy

Image-Guided Radiation Therapy (IGRT) allows for modification of treatment delivery to increase precision. The following codes may be billed with PBT.

#### **CPT<sup>®</sup> Codes for IGRT**

77014	Computed tomography guidance for placement of radiation fields Used with CT-based systems (i.e., integrated cone beam CT, CT/linear accelerator on rails).
77387	Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed
G6001	Ultrasonic guidance for placement of radiation therapy fields
G6002	KV imaging- Stereoscopic X-ray guidance for localization of target volume for the delivery of radiation therapy
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3-D positional tracking, gating, 3-D surface tracking), each fraction of treatment

#### **ADDITIONAL INFORMATION**

#### **Coding Guidelines**

As a reminder, for Medicare claims, the HCPC/CPT<sup>®</sup> code(s) may be subject to Correct Coding Initiatives (CCI) edits. This policy does not take precedence over CCI edits. Please refer to the CCI for correct coding guidelines and specific applicable code combinations prior to billing Medicare.

#### REFERENCES

The following is only a sample of the available literature that meets certain criteria and should not be utilized as an exhaustive list. Included articles were published within the last 10 years and report patient outcome data. For disease sites recommended for CED, dosimetry and technical feasibility publications were accepted.

#### General

- 1. Chung CS, Tock TI, Nelson K, et al. Incidence of second malignancies among patients treated with proton versus photo radiation. *Int J Radiat Oncol Biol Phys.* 2013; 87(1): 46-52.
- Coverage with Evidence Development Requirements Position Statement. American Society for Radiation Oncology Web site. <u>https://www.astro.org/ Practice-Management/Reimbursement/Coverage-Position-Statement.aspx</u>. Published November 15, 2013. Accessed December 13, 2013.
- 3. Foote RL, Stafford SL, Petersen IA, et al. The clinical case for proton beam therapy. *Radiat Oncol.* 2012; 7:174.
- Proton Beam Therapy for Prostate Cancer Position Statement. American Society for Radiation Oncology Web site. <u>https://www.astro.org/ Practice- Management/</u><u>Reimbursement/Proton-Beam-Therapy.aspx</u>. Published November 15, 2013. Accessed April 9, 2014.
- Stereotactic Body Radiation Therapy (SBRT) Model Policy. American Society for Radiation Oncology Web site. <u>https://www.astro.org/</u> <u>uploadedFiles/Main\_Site/Practice\_Management/</u> <u>Reimbursement/2013HPcoding%20 guidelines\_SBRT\_</u> <u>Final.pdf</u>. Published April 17, 2013. Accessed April 9, 2014.
- Stereotactic Radiosurgery (SRS) Model Coverage Policy. American Society for Radiation Oncology Web site. <u>https://www.astro.org/uploadedFiles/ Main\_Site/</u> <u>Practice\_Management/Reimbursement/SRSMPJuly2011.</u> pdf. Published July 25, 2011. Accessed April 9, 2014.
- 7. 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.* Feb 1 2020;6(2):237-246.
- Stoker J, Keole SR, Grosshans DR, et al. An Investigation of Hippocampal-Sparing Capabilities of Intensity Modulated Proton Therapy During Whole-Brain Irradiation. *Int J Radiat Oncol Biol Phys.* 2016 Oct1;96(2S):E129.
- 9. Vernimmen FJ, Harris JK, Wilson JA, et al. Stereotactic proton beam therapy of skull base meningiomas. *Int J Radiat Oncol Biol Phys.* 2011;49(1):99-105.
- 10. Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015; 33: 2345- 2352.
- 11. Morioka T, Miyoshi-Imamura T, Blyth BJ, et al. Ionizing radiation, inflammation, and their interactions in colon carcinogenesis in Mlh1-deficient mice. *Cancer Sci* 2015;106(3):217-226.

#### Anus/Rectum

- 12. Radu C, Norrlid O, Braendengen M, et al. Integrated peripheral boost in preoperative radiotherapy for the locally most advanced non-resectable rectal cancer patients. *Acta Oncol.* 2013; 52(3): 528-37.
- 13. Wolff HA, Wagner DM, Conradi L, et al. Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: A planning study with clinical implications. *Radiother Oncol.* 2012; 102(1): 30-7.
- Wo JY, Plastaras JP, Metz JM, et al. Pencil Beam Scanning Proton Beam Chemoradiation Therapy With 5-Fluorouracil and Mitomycin-C for Definitive Treatment of Carcinoma of the Anal Canal: A Multiinstitutional Pilot Feasibility Study. *Int J Radiat Oncol Biol Phys* 2019;105(1):90-95.
- 15. Chuong MD, Kozarek J, Rubens M, et al. Reduced Acute Toxicity after Proton Versus Photon Chemoradiation for Anal Cancer: Outcomes from the Proton Collaborative Group REG001-09 Trial. *Int J Radiat Oncol Biol Phys* 2019;105(1):S158.
- Mohiuddin JJ, Jethwa KR, Grandhi N, et al. Multiinstitutional Comparison of Intensity Modulated Photon Versus Proton Radiation Therapy in the Management of Squamous Cell Carcinoma of the Anus. *Adv Radiat Oncol* 2021;6(5):100744.

#### Breast

- Bush, David A. et al. Partial Breast Radiation Therapy With Proton Beam: 5-Year Results With Cosmetic Outcomes. *Int J Radiat Oncol Biol Phys.* 2014;90(3): 501-505.
- Bush DA, Slater JD, Garberoglio C, et al. Partial breast irradiation delivered with proton beam: results of a phase II trial. *Clin Breast Cancer.* 2011; 11(4):241-245.
- 19. Chang JH, Lee NK, Kim JY, et al. Phase II trial of proton beam accelerated partial breast irradiation in breast cancer. *Radiother Oncol.* 2013; 108(2):209-214.
- 20. MacDonald SM, Patel SA, Hickey S, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys.* 2013; 86(3): 484-90.
- 21. Garda AE, Hunzeker AE, Michel AK, et al. Intensity modulated proton therapy (IMPT) for bilateral breast/ chest wall and comprehensive nodal irradiation for synchronous bilateral breast cancer: initial clinical experience and dosimetric comparison. *Adv Radiat Oncol.* 2022.

#### **PROTON BEAM THERAPY (PBT)**

- 22. Bernstein MB, Walker K, Gillespie E, et al. Bilateral Regional Nodal Irradiation Using Voumetric Modulated Arc Therapy: Dosimetric Analysis and Feasibility. *Prat Radiat Oncol.* 2022.
- 23. Vyfhuis MAL, Zhu M, Agyepong B, Nichols EM. Techniques for treating bilateral breast cancer patients using pencil beam scanning technology. *Int J Part Ther* 2019;6:1–11.
- 24. Sun T, Lin X, Tong Y, et al. Heart and cardiac substructure dose sparing in synchronous bilateral breast radiotherapy: A dosimetric study of proton and photon radiation therapy. *Front Oncol* 2019;9:1456.
- 25. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–998.
- 26. Taylor C, McGale P, Bronnum D, et al. Cardiac structure injury after radiotherapy for breast cancer: Cross-sectional study with individual patient data. *J Clin Oncol* 2018;36:2288–2296.
- 27. MacDonald SM, Jimenez R, Paetzold P, et al. Proton radiotherapy for chest wall and regional lymphatic radiation; dose comparisons and treatment delivery. *Radiation Oncol* 2013;8:71.
- 28. Jimenez RB, Hickey S, DePauw N, et al. Phase II study of proton beam radiation therapy for patients with breast cancer requiring regional nodal irradiation. *Journal of Clinical Oncology.* 2019.
- 29. Luo L, Cuaron J, Braunstein L, et al. Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. *Radiother Oncol.* 2018.
- McGee LA, Iftekaruddin Z, Chang JHC, et al. Postmastectomy Chest Wall Reirradiation With Proton Therapy for Breast Cancer. *Int J Radiat Oncol Biol Phys.* 2017;99(2S):E34.
- 31. Santos AM, Kotsanis A, Cunningham L, et al. Estimated the second primary cancer risk due to proton therapy compared to hybrid IMRT for left sided breast cancer. *Acta Oncologica*. 2020.
- 32. Stick LB, Yu J, Maraldo MV, et al. Joint estimation of cardiac toxicity and recurrence risks after comprehensive nodal photon vs. proton therapy for breast cancer. *Int J Radiat Oncol Biol Phys.* 2016;97(4):754-761.
- Verma V, Shah C, Mehta MP. Clinical outcomes and toxicity of proton radiotherapy for breast cancer. *Clin Breast Cancer*. 2016 Jun;16(3):145-154.
- Depauw N, Batin E, Johnson A, MacDonald S, Jimenez R. Arms positioning in post-mastectomy proton radiation: Feasibility and development of a new arms down contouring atlas. *Phys Imaging Radiat Oncol* 2020;14:6– 11.

- 35. Andring LM, Diao K, Sun S, et al. Locoregional Management and Prognostic Factors in Breast Cancer Patients with Ipsilateral Internal Mammary and Axillary Lymph Node Involvement. *Int J Radiat Oncol Biol Phys* 2022.
- 36. van den Bogaard VA, Ta BD, van der Schaaf A, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three dimensional dose distributions to cardiac substructures. J Clin Oncol 2017;35:1171–1178.
- 37. Lorenzen EL, Rehammar JC, Jensen M, et al. Radiationinduced risk of ischemic heart disease following breast cancer radiotherapy in Denmark, 1977-2005. *Radiother Oncol* 2020;152:103-110.
- 38. Teichman SL, Do S, Lum S, et al. Improved long-term patient-reported health and well-being outcomes of early-stage breast cancer treated with partial breast proton therapy. *Cancer Medicine*. 2018;7:6064-6076.

#### **Central Nervous System**

- Brown AP, Barney CL, Grosshans DR, et al. Proton Beam Craniospinal Irradiation Reduces Acute Toxicity for Adults With Medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2013; 86(2): 277-84.
- 40. Dinh J, Stoker J, Georges RH, et al. Comparison of proton therapy techniques for treatment of the whole brain as a component of craniospinal radiation. *Radiation Oncology* (*London, England*). 2013;8:289.
- 41. Giantsoudi, Drosoula et al. Incidence of CNS Injury for a Cohort of 111 Patients Treated With Proton Therapy for Medulloblastoma: LET and RBE Associations for Areas of Injury. *Int J Radiat Oncol Biol Phys.* 2016;95(1):287-296.
- 42. Hattangadi JA, Chapman PH, Bussiere MR, et al. Planned Two-Fraction Proton Beam Stereotactic Radiosurgery for High-Risk Inoperable Cerebral Arteriovenous Malformations. *Int J Radiat Oncol Biol Phys.* 2012; 83(2): 533-41.
- 43. Hauswald H, Rieken S, Ecker S, et al. First experiences in treatment of low-grade glioma grade I and II with proton therapy. *Radiat Oncol.* 2012; 7:189.
- 44. Mizumoto M, Tsubio K, Igaki H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2010; 77(1): 98-105.
- Moignier, Alexandra et al. Theoretical Benefits of Dynamic Collimation in Pencil Beam Scanning Proton Therapy for Brain Tumors: Dosimetric and Radiobiological Metrics. *Int J Radiat Oncol Biol Phys.* 2016;95(1):171-180.

- 46. Weber DC, Schneider R, Goitein G, et al. Spot scanningbased proton therapy for intracranial meningioma: longterm results from the Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys.* 2012;83(3):865-871.
- 47. Yang TJ, Wijetunga NA, Yamada J, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. *Neuro Oncol.* Jan 30 2021;23(1):134-143.
- Lim PS, Tran S, Kroeze SGC, et al. Outcomes of adolescents and young adults treated for brain and skull base tumors with pencil beam scanning proton therapy. *Pediatr Blood Cancer.* Dec 2020;67(12):e28664.
- Florijn MA, Sharfo AWM, Wiggenraad RGJ, et al. Lower doses to hippocampi and other brain structures for skull-base meningiomas with intensity modulated proton therapy compared to photon therapy. *Radiother Oncol.* Jan 2020;142:147-153.
- 50. Tabrizi S, Yeap BY, Sherman JC, et al. Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma. *Radiother Oncol.* Aug 2019;137:95-101.
- 51. Mohan R, Liu AY, Brown PD, et al. Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: phase II randomized study of protons vs photons. *Neuro Oncol.* Feb 25 2021;23(2):284-294.
- 52. Atkins KM, Pashtan IM, Bussiere MR, et al. Proton stereotactic radiosurgery for brain metastases: a single institution analysis of 370 patients. *Int J Radiat Oncol Biol Phys.* 2018.
- 53. Beer J, Kountouri M, Kole AJ, et al. Outcomes, prognostic factors and salvage treatment for recurrent chordoma after pencil beam scanning proton therapy at the Paul Scherrer Institute. *Clin Oncol (R Coll Radiol).* 2020 Aug;32(8):537-544.
- 54. Gunther JR, Rahman AR, Dong W, et al. Craniospinal irradiation prior to stem cell transplant for hematologic malignancies with CNS involvement: Effectiveness and toxicity after photon or proton treatment. *Prac Radiat Oncol.* 2017 Nov;7(6):e401-e408.
- 55. Grosshans DR, Zhu XR, Melancon A, et al. Spot scanning proton therapy for malignancies of the base of skull: treatment planning, acute toxicities, and preliminary clinical outcomes. *Int J Radiat Oncol Biol Phys.* 2014 Nov 1;90(3):540-546.
- 56. Leeman JE, Lee NY, Zhou Y, et al. Endoscopic resection followed by proton therapy with pencil beam scanning for skull base tumors. *The Laryngoscope*. 2018.
- 57. Amsbaugh MJ, Grosshans DR, McAleer MF, et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1419-1424.

- Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol.* 2016 Jun;18(6):881-887.
- 59. Murray FR, Snider JW, Schneider RA, et al. Prognostic factors for spinal chordomas and chondrosarcomas treated with postoperative pencil-beam scanning proton therapy: a large, single-institution experience. *Journal of Neurosurgery*. 2020.

#### Chordoma

- 60. Chen YL, Liebsch N, Kobayashi W, et al. Definitive highdose photon/proton radiotherapy for unresected mobile spine and sacral chordomas. *Spine*. 2013; 38(15):E930-6.
- 61. Deraniyagala RL, Yeung D, Mendenhall WM, et al. Proton therapy for skull base chordoma: an outcomes study from the University of Florida Proton Therapy Institute. *J Neurol Burg B Skull Base*. 2014; 75(1): 53-7.
- 62. McDonald MW, Linton OR, Shah MV. Proton Therapy for Reirradiation of Progressive or Recurrent Chordoma. *Int J Radiat Oncol Biol Phys.* 2013; 87(5): 1107-14.
- 63. Mima M, Demizu Y, Jin D, et al. Particle Therapy Using Carbon Ions or Protons as a Definitive Therapy for Patients with Primary Sacral Chordoma. *Br J Radiol.* 2013 Nov 28 [Epub Ahead of Print].
- 64. Staab A, Rutz HP,Ares C, et al. Spot-scanning-based proton therapy for extracranial chordoma. *Int J Radiat Oncol Biol Phys.* 2011. 81(4):e489-96.

#### Esophagus

- 65. Doyen, Jérôme, Falk AT, Floquet V, Hérault J, Hannoun-Lévi JM. Proton beams in cancer treatments: Clinical outcomes and dosimetric comparisons with photon therapy. *J Gastro Hepat.* 2016;30(5)957-963.
- 66. Echeverria A, McCurdy M, Castillo R, et al. Proton therapy radiation pneumonitis local dose–response in esophagus cancer patients. *Radiother Oncol.* 2013; 106: 124-9.
- 67. Hong TS, Wo JY, Yeap BY, et al. Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. *Journal of Clinical Oncology*. 2016;34(5):460-468.
- 68. Lin SH, Komaki R, Liao Z, et al. Proton Beam Therapy and Concurrent Chemotherapy for Esophageal Cancer. *IntJRadiat OncolBiolPhys*.2012. 83(3):e345-51.
- 69. Mizumoto M, Sugahara S, Okumura T, et al. Hyperfractionated concomitant boost proton beam therapy for esophageal carcinoma. *Int J Radiat Oncol Biol Phys.* 2011; 81(4): e601-6.

- 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. J Clin Oncol. 2020;38(14):1569-1579.
- Xi M, Xu C, Liao Z, et al. Comparative Outcomes After Definitive Chemoradiotherapy Using Proton Beam Therapy Versus Intensity Modulated Radiation Therapy for Esophageal Cancer: A Retrospective, Single-Institutional Analysis. *Int J Radiat Oncol Biol Phys.* 2017;99(3):667-676.
- 72. Lin SH, Merrell KW, Shen J, et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer. *Radiother Oncol.* 2017;123(3):376-381.
- Wang J, Wei C, Tucker SL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. *Int J Radiat Oncol Biol Phys.* 2013;86(5):885-91.
- 74. Lin SH, Hobbs B, Thall P, et al. Results of a Phase II Randomized Trial of Proton Beam Therapy vs Intensity Modulated Radiation Therapy in Esophageal Cancer. *Int J Radiat Oncol Biol Phys.* 2019;105(3):680-681.

#### Gynecologic

- 75. Clivio A, Kluge A, Cozzi L, et al. Intensity Modulated Proton Beam Radiation for Brachytherapy in Patients with Cervical Carcinoma. *Int J Radiat Oncol Biol Phys.* 2013; 87(5): 897-903.
- Verma V, Simone CB 2nd, Wahl AO, Beriwal S, Mehta MP. Proton radiotherapy for gynecologic neoplasms. *Acta Oncol* 2016;55(11):1257-1265.

#### Head and Neck

- 77. A Jakobi, et. al., NTCP reduction for advanced head and neck cancer patients using proton therapy for complete or sequential boost treatment versus photon therapy. *Acta Oncologica* 2015;54:1658-1664.
- Dagan, Roi et al. Outcomes of Sinonasal Cancer Treated With Proton Therapy. *Int J Radiat Oncol Biol Phys.* 2016;95(1):377-385.
- 79. El-Sawy T, et. al., Multidisciplinary Management of Lacrimal Sac/nasolacrimal Duct Carcinomas. *Ophthal Plast Reconstr Surg.* 2013;29:454-457.
- Fukumitsu N, Okumura T, Mizumoto M, et al. Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or recurrent nasal cavity and paranasal sinus carcinoma treated with proton beam. *Int J Radiat Oncol Biol Phys.* 2012; 83(2):704-11.
- 81. Hojo H, Zenda S, Akimoto T, et al. Impact of early radiological response evaluation on radiotherapeutic outcomes in the patients with nasal cavity and paranasal sinus malignancies. *J Radiat Res.* 2012; 53(5):704-9.

- Holliday, Emma B. et al. Proton Radiation Therapy for Head and Neck Cancer: A Review of the Clinical Experience to Date. *Int J Radiat Oncol Biol Phys.* 2014;89(2):292-302.
- Ramaekers BL, Grutters JP, Pijls-Johannesma M, et al. Protons in Head-and-Neck Cancer: Bridging the Gap of Evidence. *Int J Radiat Oncol Biol Phys.* 2013; 85(5): 1282-8.
- 84. Romesser PB, Cahlon O, Scher ED, Hug EB, Sine K, DeSelm C, Fox JL, Mah D, Garg MK, Chang JH, Lee NY. Proton beam reirradiation for recurrent head and neck cancer: multi-institutional report on feasibility and early outcomes. *Int J Radiat Oncol Biol Phys.* 2016;95(1): 386-395.
- Sio, Terence T. et al. Intensity Modulated Proton Therapy Versus Intensity Modulated Photon Radiation Therapy for Oropharyngeal Cancer: First Comparative Results of Patient-Reported Outcomes. *Int J Radiat Oncol Biol Phys.* 2016;95(4): 1107-1114.
- 86. Zenda S, Kawashima M, Nishio T, et al. Proton Beam Therapy as a nonsurgical approach to mucosal melanoma of the head and neck: a pilot study.*Int J Radiat Oncol Biol Phys.*2011;81(1):135-9.
- 87. Zenda S, Kohno R, Kawashima M, et al. Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses. *Int J Radiat Oncol Biol Phys.* 2011; 81(5): 1473-8.
- Damico NJ, Wu AK, Kharouta MZ, et al. Proton Beam Therapy in the Treatment of Periorbital Malignancies. *Int J Part Ther.* 2021;7(4):42-51.
- Zakeri K, Wang H, Kang JJ, et al. Outcomes and prognostic factors of major salivary gland tumors treated with proton beam radiation therapy. *Head Neck*. 2021;43(4):1056-1062.
- 90. 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. *Lancet Oncol.* 2014 Aug;15(9):1028-1038.
- 91. Jeans EB, Shiraishi S, Manzar G, Morris LK, Amundson A, McGee LA, Rwigema JC, Neben-Wittich M, Routman DM, Ma DJ, Patel SH, Foote RL, Lester SC. An comparison of acute toxicities and patient-reported outcomes between intensity-modulated proton therapy and volumetric-modulated arc therapy after ipsilateral radiation for head and neck cancers. *Head Neck.* 2022 Feb;44(2):359-371.
- 92. Bahig H, Gunn BG, Garden AS, Ye R, Hutcheson K, Rosenthal DI, Phan J, Fuller CD, Morrison WH, Reddy JP, Ng SP, Gross ND, Sturgis EM, Ferrarotto R, Gillison M, Frank SJ. Patient-Reported Outcomes after Intensity-Modulated Proton Therapy for Oropharynx Cancer. Int J Part Ther. 2021 Jun 25;8(1):213-222.

- 93. Yoon HG, Ahn YC, Oh D, Noh JM, Park SG, Nam H, Ju SG, Kwon D, Park S. Early Clinical Outcomes of Intensity Modulated Radiation Therapy/Intensity Modulated Proton Therapy Combination in Comparison with Intensity Modulated Radiation Therapy Alone in Oropharynx Cancer Patients. *Cancers (Basel)*. 2021 Mar 27;13(7):1549.
- 94. Meijer TWH, Scandurra D, Langendijk JA. Reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. *Br J Radiol.* 2020 Mar;93(1107):20190955.
- 95. Sharma S, Zhou O, Thompson R, Gabriel P, Chalian A, Rassekh C, Weinstein GS, O'Malley BW Jr, Aggarwal C, Bauml J, Cohen RB, Lukens JN, Swisher-McClure S, Ghiam AF, Ahn PH, Lin A. Quality of Life of Postoperative Photon versus Proton Radiation Therapy for Oropharynx Cancer. *Int J Part Ther.* 2018 Fall;5(2):11-17.
- 96. Blanchard P, Garden AS, Gunn GB, Rosenthal DI, Morrison WH, Hernandez M, Crutison J, Lee JJ, Ye R, Fuller CD, Mohamed AS, Hutcheson KA, Holliday EB, Thaker NG, Sturgis EM, Kies MS, Zhu XR, Mohan R, Frank SJ. Intensity-modulated proton beam therapy (IMPT) versus intensity-modulated photon therapy (IMRT) for patients with oropharynx cancer - A case matched analysis. *Radiother Oncol.* 2016 Jul;120(1):48-55.
- 97. Grant SR, Hutcheson KA, Ye R, Garden AS, Morrison WH, Rosenthal DI, Brandon Gunn G, Fuller CD, Phan J, Reddy JP, Moreno AC, Lewin JS, Sturgis EM, Ferrarotto R, Frank SJ. Prospective longitudinal patient-reported outcomes of swallowing following intensity modulated proton therapy for oropharyngeal cancer. *Radiother Oncol.* 2020 Jul;148:133-139.
- 98. Rwigema JM, Langendijk JA, Paul van der Laan H, Lukens JN, Swisher-McClure SD, Lin A. A Model-Based Approach to Predict Short-Term Toxicity Benefits With Proton Therapy for Oropharyngeal Cancer. Int J Radiat Oncol Biol Phys. 2019 Jul 1;104(3):553-562.
- 99. Aggarwal P, Hutcheson KA, Garden AS, Mott FE, Lu C, Goepfert RP, Fuller CD, Lai SY, Gunn GB, Chambers MS, Sturgis EM, Hanna EY, Shete S. Determinants of patientreported xerostomia among long-term oropharyngeal cancer survivors. *Cancer*. 2021 Dec 1;127(23):4470-4480.
- 100. Meijer TWH, Scandurra D, Langendijk JA. Reduced radiation-induced toxicity by using proton therapy for the treatment of oropharyngeal cancer. *Br J Radiol.* 2020 Mar;93(1107):20190955.

Liver

- Bush DA, Kayali R, Slater JH. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. *Cancer* 2011;117:3053-3059.
- Fukumitsu N, Hashimoto T, Okumura T, et al. Investigation of the geometric accuracy of proton beam irradiation in the liver. *Int J Radiat Oncol Biol Phys.* 2012; 82(2): 826-33.
- 103. Fukumitsu N, Sugahara S, Nakayama H, et al. A prospective study of hypofractionated proton beam therapy for patients with hepatocellular carcinoma. *Int J Radiat Oncol Phys.* 2009; 74(3): 831-6.
- 104. Hashimoto T, Tokuuye K, Fukumitsu N, et al. Repeated proton beam therapy for hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2006; 65(1):196-202.
- 105. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for aged patients with hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys.* 2007; 69(3):805-12.
- 106. Hata M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma with limited treatment options. *Cancer.* 2006; 107: 591-8.
- 107. Hong TS, DeLaney TF, Mamon HJ et al. A prospective feasibility study of respiratory gated proton beam therapy. *Pract Radiat Oncol* 2014;4(5):316-322.
- 108. Ja Young Kim, et al. Normal liver sparing by proton beam therapy for hepatocellular carcinoma: Comparison with helical intensity modulated radiotherapy and volumetric modulated arc therapy. *Acta Oncologica*. 2015;54(10): 1827-1832.
- 109. Kawashima M, Furuse J, Nishio T, et al. Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma. *J Clin Oncol.* 2005; 23: 1839-46.
- 110. Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. *Int J Radiat Oncol Biol Phys.* 2011; 81(4): 1039-45.
- 111. Mizumoto M, Tokuuye K, Sugahara S, et al. Proton beam therapy for hepatocellular carcinoma adjacent to the porta hepatis. *Int J Radiat Oncol BiolPhys.* 2008; 71(2): 462-67.
- 112. Nakayama H, Sugahara S, Fukuda K, et al. Proton beam therapy for hepatocellular carcinoma located adjacent to the alimentary tract. *Int J Radiat Oncol Biol Phys.* 2011; 80(4): 992-5.
- 113. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. *Cancer.* 2009; 115(23):5499-506.
- 114. Sugahara S, Oshiro Y, Nakayama H, et al. Proton Beam Therapy for Large Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys.* 2010; 76(2): 460-6.

- 115. Takayuki Hashimoto T, Tokuuye K, Fukumitsu N, et al. Repeated Proton Beam Therapy for Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys.* 2006; 65(1): 196-202.
- 116. Hong TS, Wo JY, Yeap BY, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *J Clin Oncol.* 2016;34(5): 460-468.
- 117. Hong TS, Wo JY, Borger DR, et al. Phase II Study of Proton-Based Stereotactic Body Radiation Therapy for Liver Metastases: Importance of Tumor Genotype. J Natl Cancer Inst.2017;109(9):djx031.
- 118. Kang JI, Sufficool DC, Hsueh CT, et al. A phase I trial of proton stereotactic body radiation therapy for liver metastases. Journal of Gastrointestinal Oncology. 2018.
- 119. Parzen JS, Hartsell W, Chang J, et al. Hypofractionated proton beam radiotherapy in patients with unresectable liver tumors: multi-institutional prospective results from the Proton Collaborative Group. *Research Square*. 2020.

#### Lung/Thoracic

- 120. Bush DA, Cheek G, Zaheer S, et al. High-Dose Hypofractionated Proton Beam Radiation Therapy Is Safe and Effective for Central and Peripheral Early-Stage Non-Small Cell Lung Cancer: Results of a 12-Year Experience at Loma Linda University Medical Center. Int J Radiat Oncol Biol Phys.2013; 86(5):964-98.
- 121. Chang JY, Komaki R, Lu C, et al. Phase 2 Study of High-Dose Proton Therapy With Concurrent Chemotherapy for Unresectable Stage III Nonsmall Cell Lung Cancer. *Cancer.* 2011; 117(20): 4707-13.
- 122. Chang JY, Komaki R, Wen HY, et al. Toxicity and Patterns of Failure of Adaptive/AblativeProtonTherapyFor Earlystage, Medically Inoperable Non-small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2011; 80(5): 1350-1357.
- 123. Colaco, Rovel J. et al. Dosimetric rationale and early experience at UFPTI of thoracic proton therapy and chemotherapy in limited-stage small cell lung cancer. *Acta Oncologica*. 2013;52(3): 506-513.
- 124. Gomez DR, Gillin M, Liao Z, et al. Phase 1 Study of Dose Escalation in Hypofractionated Proton Beam Therapy for Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2013;86(4):665-70.
- 125. Hoppe BS. Phase II trial of concurrent chemotherapy and proton therapy for stage 3 NSCLC. *Int J Particle Ther* 2014;2:58.
- 126. Hoope BS, Flampouri S, Henderson RH, et al. Proton Therapy With Concurrent Chemotherapy for Non– Small-Cell Lung Cancer: Technique and Early Results. *Clin Lung Cancer.* 2012; 13(5): 352-8.

- 127. Hoppe, Bradford S. et al. A Phase 2 Trial of Concurrent Chemotherapy and Proton Therapy for Stage III Non-Small Cell Lung Cancer: Results and Reflections Following Early Closure of a Single-Institution Study. *Int J Radiat Oncol Biol Phys.* 2016;95(1): 517-522.
- 128. Iwata H, Demizu Y, Fujii O, et al. Long-term outcome of proton therapy and carbon-therapy for large (T2a-T2bN0M0) non-small-cell lung cancer. *J Thorac Oncol.* 2013; 8(6): 726-35.
- 129. Koay EJ, Lege D, Mohan R, et al. Adaptive/Nonadaptive Proton Radiation Planning and Outcomes in a Phase II Trial for Locally Advanced Non-small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2012; 84(5): 1093-100.
- Nakayama H, Satoh H, Sugahara S, et al. Proton Beam Therapy Of Stage II and III Non-Small-Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2011; 81(4): 979-84.
- 131. Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. *Radiother Oncol* 2015; 115:367-372.
- Oshiro Y, Mizumoto M, Okumura T, et al. Results of Proton Beam Therapy without Concurrent Chemotherapy for Patients with Unresectable Stage III Non-small Cell Lung Cancer. J Thorac Oncol. 2012; 7(2): 370-5.
- 133. Oshiro Y, Okumura T, Kurishima K, et al. High-dose concurrent chemo-proton therapy for stage III NSCLC: Preliminary results of a phase II study. *J Radiat Res* 2014;55:959-965.
- Schild S, et al. Proton beam therapy for locally advanced lung cancer: A review. World *J Clin Oncol* 2014; 5(4): 568-575.
- 135. Sejpal S, Komaki R, Tsao A, et al. Early Findings on Toxicity of Proton Beam Therapy With Concurrent Chemotherapy for Nonsmall Cell Lung Cancer. *Cancer*. 2011; 117(13): 3004-13.
- 136. Vogel J, Berman AT, Lin L, Pechet TT, Levin WP, Gabriel P, Khella SL, Singhal S, Kucharczuk JK, Simone CB 2nd. Prospective study of proton beam radiation therapy for adjuvant and definitive treatment of thymoma and thymic carcinoma: Early response and toxicity assessment. *Radiother Oncol.* 2016 Mar;118(3):504-9.
- 137. Rice SR, Li YR, Busch TM, Kim MM, McNulty S, Dimofte A, Zhu TC, Cengel KA, Simone CB 2nd. A Novel Prospective Study Assessing the Combination of Photodynamic Therapy and Proton Radiation Therapy: Safety and Outcomes When Treating Malignant Pleural Mesothelioma. *Photochem Photobiol.* 2019 Jan;95(1):411-418.

- 138. Higgins KA, O'Connell K, Liu Y, Gillespie TW, McDonald MW, Pillai RN, Patel KR, Patel PR, Robinson CG, Simone CB 2nd, Owonikoko TK, Belani CP, Khuri FR, Curran WJ, Ramalingam SS, Behera M. National Cancer Database Analysis of Proton Versus Photon Radiation Therapy in Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys.* 2017 Jan 1;97(1):128-137.
- 139. Boyce-Fappiano D, Nguyen QN, Chapman BV, Allen PK, Gjyshi O, Pezzi TA, De B, Gomez D, Lin SH, Chang JY, Liao Z, Lee P, Gandhi SJ. Single Institution Experience of Proton and Photon-based Postoperative Radiation Therapy for Non-small-cell Lung Cancer. *Clin Lung Cancer.* 2021 Sep;22(5):e745-e755.
- 140. Iwata H, Akita K, Yamaba Y, Kunii E, Takakuwa O, Yoshihara M, Hattori Y, Nakajima K, Hayashi K, Toshito T, Ogino H, Shibamoto Y. Concurrent Chemo-Proton Therapy Using Adaptive Planning for Unresectable Stage 3 Non-Small Cell Lung Cancer: A Phase 2 Study. *Int J Radiat Oncol Biol Phys.* 2021 Apr 1;109(5):1359-1367.
- 141. Rwigema JM, Verma V, Lin L, Berman AT, Levin WP, Evans TL, Aggarwal C, Rengan R, Langer C, Cohen RB, Simone CB 2nd. Prospective study of proton-beam radiation therapy for limited-stage small cell lung cancer. *Cancer.* 2017 Nov 1;123(21):4244-4251.
- 142. Kharod SM, Nichols RC, Henderson RH, et al. Imageguided hypofractionated double-scattering proton therapy in the management of centrally-located early-stage non-small cell lung cancer. *Acta Oncol.* 2020;59(10):1164-1170

#### Lymphoma

- 143. Andolino DL, Hoene T, Xiao L, et al. Dosimetric Comparison of Involved Field Three Dimensional Conformal Photon Radiotherapy and Breast Sparing Proton Therapy for Treatment of Hodgkin's Lymphoma in Female Pediatric Patients. *Int J Radiat Oncol Biol Phys.* 2011; 81(4): e667-71.
- 144. Bhakta N, Liu Q, Yeo F, et al. Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. *Lancet Oncol* 2016;17:1325-1334.
- 145. Bhatti P, Veiga LH, Ronckers CM, et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. *Radiat Res* 2010;174:741-752.
- 146. Boukheris H, Stovall M, Gilbert ES, et al. Risk of salivary gland cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys* 2013;85:776-783.

- 147. Castellino SM, Geiger AM, Mertens AC, et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. *Blood* 2011;117:1806-1816.
- 148. Cella L, Conson M, Pressello MC, et al. Hodgkin's lymphoma emerging radiation treatment techniques: trade-offs between late radio-induced toxicities and secondary malignant neoplasms. *Radiat Oncol* 2013;8:22.
- 149. Cutter DJ, Schaapveld M, Darby SC, et al. Risk of valvular heart disease after treatment for Hodgkin lymphoma. J Natl Cancer Inst 2015;107.
- 150. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987-998.
- 151. Dietz AC, Chen Y, Yasui Y, et al. Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 2016;122:3687-3696.
- 152. Dores GM, Curtis RE, van Leeuwen FE, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. *Ann Oncol* 2014;25:2073-2079.
- 153. Fox AM, Dosoretz AP, Mauch PM, et al. Predictive factors for radiation pneumonitis in Hodgkin lymphoma patients receiving combined-modality therapy. *Int J Radiat Oncol Biol Phys* 2012;83:277-283.
- 154. Hoppe BS, Flampouri S, Lynch J, et al. Improving the Therapeutic Ratio in Hodgkin Lymphoma Through the Use of Proton Therapy. Oncology (Williston Park). 2012; 26(5): 456-9, 462-5.
- 155. Hoppe BS, Flampouri S, Su Z, et al. Consolidated Involved-Node Proton Therapy for Stage IA-IIIB Mediastinal Hodgkin Lymphoma: Preliminary Dosimetric Outcomes From a Phase II Study. Int J Radiat Oncol Biol Phys. 2012; 83(1): 260-7.
- 156. Hoppe BS, Flampouri S, Su Z, et al. Effective Dose Reduction to Cardiac Structures Using Protons Compared With 3DCRT and IMRT in Mediastinal Hodgkin Lymphoma. *Int J Radiat Oncol Biol Phys.* 2012; 84(2): 449-55.
- 157. Hoppe BS, Flampouri S, Zaiden R, et al. Involvednode proton therapy in combined modality therapy for Hodgkin lymphoma: results of a phase 2 study. *Int J Radiat Oncol Biol Phys* 2014;89:1053-1059.
- 158. Hoppe BS, Hill-Kayser CE, Tseng YD, et al. The Use of Consolidative Proton Therapy After First-Line Therapy Among Patients With Hodgkin Lymphoma at Academic and Community Proton Centers. Int J Radiat Oncol Biol Phys 2016;96:S39.
- 159. Hoppe BS, Tsai H, Larson G, et al. Proton therapy patterns-of-care and early outcomes for Hodgkin lymphoma: results from the Proton Collaborative Group Registry. *Acta Oncol* 2016;55:1378-1380.

- 160. Horn S, Fournier-Bidoz N, Pernin V, et al. Comparison of passive-beam proton therapy, helical tomotherapy and 3D conformal radiation therapy in Hodgkin's lymphoma female patients receiving involved-field or involved site radiation therapy. *Cancer Radiother* 2016;20:98-103.
- 161. Inskip PD, Sigurdson AJ, Veiga L, et al. Radiation-Related New Primary Solid Cancers in the Childhood Cancer Survivor Study: Comparative Radiation Dose Response and Modification of Treatment Effects. *Int J Radiat Oncol Biol Phys* 2016;94:800-807.
- 162. Jorgensen AY, Maraldo MV, Brodin NP, et al. The effect on esophagus after different radiotherapy techniques for early stage Hodgkin's lymphoma. *Acta Oncol* 2013;52:1559-1565.
- 163. Knausl B, Lutgendorf-Caucig C, Hopfgartner J, et al. Can treatment of pediatric Hodgkin's lymphoma be improved by PET imaging and proton therapy? *Strahlenther Onkol* 2013;189:54-61.
- Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys.* 2011; 81(1):167-74.
- 165. Maraldo MV, Brodin NP, Aznar MC, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for earlystage mediastinal Hodgkin lymphoma. *Ann Oncol* 2013;24:2113-2118.
- 166. Milano MT, Li H, Constine LS, et al. Survival after second primary lung cancer: a population-based study of 187 Hodgkin lymphoma patients. *Cancer* 2011;117:5538-5547.
- Morton LM, Dores GM, Curtis RE, et al. Stomach cancer risk after treatment for hodgkin lymphoma. *J Clin Oncol* 2013;31:3369-3377.
- 168. Morton LM, Gilbert ES, Stovall M, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. *Haematologica* 2014;99:e193-196.
- 169. Moskowitz CS, Chou JF, Wolden SL, et al. Breast cancer after chest radiation therapy for childhood cancer. *J Clin Oncol* 2014;32:2217-2223.
- 170. Ng AK. Review of the cardiac long-term effects of therapy for Hodgkin lymphoma. *Br J Haematol* 2011;154:23-31.
- 171. Pinnix CC, Smith GL, Milgrom S, et al. Predictors of radiation pneumonitis in patients receiving intensity modulated radiation therapy for Hodgkin and non-Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys* 2015;92:175-182.
- 172. Plastaras JP, Vogel J, Elmongy H, et al. First Clinical Report of Pencil Beam Scanned Proton Therapy for Mediastinal Lymphoma. *Int J Radiat Oncol Biol Phys* 2016;96:E497.

- 173. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med* 2015;373:2499-2511.
- 174. Swerdlow AJ, Cooke R, Bates A, et al. Breast cancer risk after supradiaphragmatic radiotherapy for Hodgkin's lymphoma in England and Wales: a National Cohort Study. J Clin Oncol 2012;30:2745-2752.
- 175. Toltz A, Shin N, Mitrou E, et al. Late radiation toxicity in Hodgkin lymphoma patients: proton therapy's potential. *J Appl Clin Med Phys* 2015;16:5386.
- 176. Tukenova M, Diallo I, Anderson H, et al. Second malignant neoplasms in digestive organs after childhood cancer: a cohort-nested case-control study. *Int J Radiat Oncol Biol Phys* 2012;82:e383-390.
- 177. Tukenova M, Guibout C, Hawkins M, et al. Radiation therapy and late mortality from second sarcoma, carcinoma, and hematological malignancies after a solid cancer in childhood. *Int J Radiat Oncol Biol Phys* 2011;80:339-346.
- 178. van Nimwegen FA, Schaapveld M, Cutter DJ, et al. Radiation Dose-Response Relationship for Risk of Coronary Heart Disease in Survivors of Hodgkin Lymphoma. *J Clin Oncol* 2016;34:235-243.
- 179. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. *JAMA Intern Med* 2015;175:1007-1017.
- Veiga LH, Holmberg E, Anderson H, et al. Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies. *Radiat Res* 2016;185:473-484.
- 181. Voong KR, McSpadden K, Pinnix CC, et al. Dosimetric advantages of a "butterfly" technique for intensitymodulated radiation therapy for young female patients with mediastinal Hodgkin's lymphoma. *Radiat Oncol* 2014;9:94.
- 182. Winkfield KM, Gallotto S, Adams JA, et al. Proton Therapy for Mediastinal Lymphomas: An 8-year Single-institution Report. *Int J Radiat Oncol Biol Phys* 2015;93:E461.
- Wray J, Flampouri S, Slayton W, et al. Proton Therapy for Pediatric Hodgkin Lymphoma. *Pediatr Blood Cancer* 2016;63:1522-1526.
- Zeng C, Plastaras JP, James P, et al. Proton pencil beam scanning for mediastinal lymphoma: treatment planning and robustness assessment. *Acta Oncol* 2016;55:1132-1138.
- 185. Hoppe BS, Hill-Kayser CE, Tseng YD, Flampouri S, Elmongy HM, Cahlon O, Mendenhall NP, Maity A, McGee LA, Plastaras JP. Consolidative proton therapy after chemotherapy for patients with Hodgkin lymphoma. Ann Oncol. 2017 Sep 1;28(9):2179-2184.

- 186. Vega RBM, Patel S, Bates JE, et al. Cost-effectiveness of proton therapy for young adults with mediastinal lymphoma: analysis of an institutional cohort. *Klin Padiatr.* 2020;232(02):103.
- 187. Li J, Dabaja B, Reed V, et al. Rationale for and preliminary results of proton beam therapy for mediastinal lymphoma. *Int J Radiat Oncol Biol Phys.* 2011;81(1):167-174.
- 188. Hoppe BS, Flampouri S, Su Z, et al. Effective dose reduction to cardiac structures using protons compared with 3DCRT and IMRT in mediastinal Hodgkin lymphoma. *Int J Radiat Oncol Biol Phys.* 2012 Oct 1;84(2):449-455.

#### Ocular Melanoma

- 189. Caujolle J, Mammar H, Chamorey E, et al. Proton beam radiotherapy for uveal melanomas at Nice Teaching Hospital: 16 years' experience. *Int J Radiat Oncol Biol Phys.* 2010; 78(1): 98-103.
- 190. Caujolle J-P, Paoli V, Chamorey E, et al. Local recurrence after uveal melanoma proton beam therapy: recurrence types and prognostic consequences. *Int J Radiat Oncol Biol Phys.* 2013;85(5):1218-24.
- Damato B, Kacperek A, Chopra M, et al. Proton bean radiotherapy of chorodial melanoma: the Liverpool-Clatterbridge experience. *Int J Radiat Oncol Biol Phys.* 2005; 62(5): 1405-11.
- 192. Damato B, Kacperek A, Chopra M, et al. Proton beam radiotherapy of iris melanoma. *Int J Radiat Oncol Biol Phys.* 2005; 63(1):109-115.
- 193. Dendale R, Lumbroso-Le Rouic L, Noel G, et al. Proton beam radiotherapy for uveal melanoma: results of Curie Institut-Orsay proton therapy center (ICPO). *Int J Radiat Oncol Biol Phys.* 2006; 65(3):780-787.
- 194. Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res.* 2006; 38(5):255-260.
- 195. Egger E, Zografos L, Schalenbourg A, et al. Eye retention after proton beam radiotherapy for uveal melanoma. *Int J Radiat Oncol Biol Phys.* 2003; 55(4): 867-80.
- 196. Lumbroso-Le Rouic L, Delacroix S, Dendale R, et al. Proton beam therapy for iris melanomas. *Eye (Lond)*. 2006; 20(11): 1300-5.
- 197. Macdonald EC, Cauchi P, and Kemp EG. Proton beam therapy for the treatment of uveal melanoma in Scotland. *Br J Ophthalmol.* 2011; 95(12): 1691-5.
- 198. Marucci L, Ancukiewicz M, Lane AM, et al. Uveal Melanoma Recurrence after Fractionated Proton Beam Therapy: Comparison of Survival in Patients Treated With Reirradiation or with Enucleation. *Int J Radiat Oncol Biol Phys.* 2011; 79(3): 842-6.

- 199. Mosci C, Lanza FB, Barla A, et al. Comparison of clinical outcomes for patients with large choroidal melanoma after primary treatment with enucleation or proton beam radiotherapy. *Ophthalmologica*. 2012; 227(4): 190-6.
- 200. Sethi RV, Shih HA, Yeap BY, et al. Second Nonocular Tumors Among Survivors of Retinoblastoma Treated With Contemporary Photon and Proton Radiotherapy. *Cancer.* 2014; 120(1): 126-33.

#### Pancreas

- 201. Hong TS, Ryan DP, Blaszkowsky LS, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. *Int J Radiat Oncol Biol Phys.* 2011; 79(1): 151-7.
- 202. Nichols RC Jr, George TJ, Zaidden RA Jr, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. *Acta Oncologica*. 2013; 52: 498-505.
- 203. Nichols RC Jr, Huh SN, Prado KL, et al. Protons Offer Reduced Normal Tissue Exposure for Patients Receiving Postoperative Radiotherapy for Resected Pancreatic Head Cancer. *Int J Radiat Oncol Biol Phys.* 2012; 83(1): 158-63.
- 204. Terashima K, Demizu Y, Hashimoto N, et al. A phase I/ II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiother Oncol.* 2012; 103(1): 25-31.

#### Pediatrics

- 205. Amsbaugh MJ, Grosshans DR, McAleer MF, et al. Proton therapy for spinal ependymomas: planning, acute toxicities, and preliminary outcomes. *Int J Radiat Oncol Biol Phys.* 2012;83(5):1419-24.
- 206. Childs SK, Kozak KR, Friedmann AM, et al. Proton radiotherapy for parameningeal rhabdomyosarcoma: clinical outcomes and late effects. *Int J Radiat Oncol Biol Phys.* 2012;82(2):635-642.
- 207. Cotter SE, Herrup DA, Friedmann A, et al. Proton Radiotherapy for Pediatric Bladder/ Prostate Rhabdomyosarcoma: clinical Outcomes and Dosimetry Compared to Intensity Modulated Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2011; 81(5): 1367-73.
- 208. De Amorim Bernstein K, Sethi R, Trofimov, et al. Early clinical outcomes using proton radiation for children with central nervous system atypical teratoid rhabdoid tumors. *Int J Radiat Oncol Biol Phys.* 2013; 86(1):114-20.
- 209. Hattangadi JA, Rombi B, Yock TI, et al. Proton radiotherapy for high-risk pediatric neuroblastoma: early outcomes and dose comparison. *Int J Radiat Oncol Biol Phys.* 2012; 83(3):1015-22.

#### PROTON BEAM THERAPY (PBT)

- 210. Hill-Kayser C, Tochner Z, Both S, et al. Proton versus photon radiation therapy for patients with high-risk neuroblastoma: the need for a customized approach. *Pediatr Blood Cancer.* 2013; 60(10):1606-11.
- 211. Jimenez RB, Sethi R, Depauw N, et al. Proton radiation therapy for pediatric medulloblastoma and supratentorial primitive neuroectodermal tumors: outcomes for very young children treated with upfront chemotherapy. *Int J Radiat Oncol Biol Phys.* 2013; 87(1):120-06.
- 212. Kuhlthau KA, Pulsifer MB, Yeap BY, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radio- therapy. *J Clin Oncol.* 2012; 30(17): 2079-86.
- 213. MacDonald SM, Sethi R, Lavally B, et al. Proton radiotherapy for pediatric central nervous system ependymoma: clinical outcomes for 70 patients. *Neuro Oncol.* 2013; 15(11): 1552-9.
- 214. Oshiro Y, Mizumoto M, Okumura T, et al. Clinical results of proton beam therapy for advanced neuroblastoma. *Radiat Oncol.* 2013;8(1):142.
- 215. Rombi B, Ares C, Hug EB, et al. Spot-scanning proton radiation therapy for pediatric chordoma and chondrosarcoma: clinical outcome of 26 patients treated at Paul Scherrer Institute. *Int J Radiat Oncol Biol Phys.* 2013; 86(3):578-84
- 216. Indelicato, D.J., et al., Second tumor risk in children treated with proton therapy. *Pediatr Blood Cancer*, 2021. 68(7): p. e28941.
- 217. Indelicato, D.J., et al., Proton Therapy for Pediatric Ependymoma: Mature Results From a Bicentric Study. *Int J Radiat Oncol Biol Phys*, 2021. 110(3): p. 815-820.
- 218. Indelicato, D.J., et al., Outcomes Following Proton Therapy for Group III Pelvic Rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*, 2020. 106(5): p. 968-976.
- 219. Kharod, S.M., et al., Outcomes following proton therapy for Ewing sarcoma of the cranium and skull base. *Pediatr Blood Cancer*, 2020. 67(2): p. e28080.
- 220. Uezono, H., et al., Proton therapy following induction chemotherapy for pediatric and adolescent nasopharyngeal carcinoma. *Pediatr Blood Cancer*, 2019. 66(12): p. e27990.
- 221. Baliga, S., et al., Decade Long Disease, Secondary Malignancy, and Brainstem Injury Outcomes in Pediatric and Young Adult Medulloblastoma Patients Treated with Proton Radiotherapy. *Neuro Oncol*, 2021.
- 222. Jimenez, R.B., et al., Proton Radiation Therapy for Pediatric Craniopharyngioma. *Int J Radiat Oncol Biol Phys*, 2021. 110(5): p. 1480-1487.
- 223. Liu, K.X., et al., A Multi-institutional Comparative Analysis of Proton and Photon Therapy-Induced Hematologic Toxicity in Patients With Medulloblastoma. *Int J Radiat Oncol Biol Phys*, 2021. 109(3): p. 726-735.

- 224. Aldrich, K.D., et al., Comparison of hypothyroidism, growth hormone deficiency, and adrenal insufficiency following proton and photon radiotherapy in children with medulloblastoma. *J Neurooncol*, 2021. 155(1): p. 93-100.
- 225. Bagley, A.F., et al., Efficacy of proton therapy in children with high-risk and locally recurrent neuroblastoma. *Pediatr Blood Cancer*, 2019. 66(8): p. e27786.
- 226. Kahalley LS, Peterson R, Ris MD, et al. Superior Intellectual Outcomes After Proton Radiotherapy Compared With Photon Radiotherapy for Pediatric Medulloblastoma. *J Clin Oncol.* Feb 10 2020;38(5):454-461.
- Hardin AP, Hackell JM, Committee on Practice and Ambulatory Medicine. Age Limit of Pediatrics. *Pediatrics*. 2017;140(3):e20172151.
- 228. Cheng E, Blackburn HN, Ng K, et al. Analysis of Survival Among Adults With Early-Onset Colorectal Cancer. *JAMA Network Open* 2021;4(6):e2112539.
- Curtis RE, Freedman DM, Ron E et al: New malignancies among cancer survivors. SEER Cancer Registries, 1973 -2000. National Cancer Institute, NIH, Publ. No. 05-5302.
- 230. Bleyer A, Barr A: A Bleyer M O'Leary R Barr Highlights and challenges Cancer Epidemiology in Older Adolescents and Young Adults 15 to 29 Years of Age, Including SEER Incidence and Survival 1975–2000,2006 Bethesda, MD National Cancer Institute NIH publication 06-5767.
- 231. Bhandari A,Woodhouse M, Gupta S. Colorectal cancer is a leading cause of cancer incidence and mortality among adults younger than 50 years in the USA: a SEER-based analysis with comparison to other young-onset cancers. *J Investig Med 2017*;65(2):311-315
- 232. Lim PS, Tran S, Kroeze SGC, et al. Outcomes of adolescents and young adults treated for brain and skull base tumors with pencil beam scanning proton therapy. *Pediatric Blood & Cancer.* 2020.

#### Pelvic

- 233. Thomas J Whitaker, David M Routman, Heather Schultz, et al. IMPT versus VMAT for Pelvic Nodal Irradiation in Prostate Cancer: A Dosimetric Comparison. *Int J Part Ther* Winter 2019;5(3):11-23.
- 234. Vedang Murthy, Priyamvada Maitre, Sadhana Kannan , et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. J Clin Oncol. 2021 Apr 10;39(11):1234-1242.
- 235. Pollack A, Karrison TG, Balogh Jr. AG, et al. LBA5 -Short term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/ RTOG 0534 SPPORT Trial. ASTRO 2019.

- 236. Liu Y, Patel SA, Jani AB, et al. Overall Survival After Treatment of Localized Proton Cancer With Proton Beam Therapy, External-Beam Photon Therapy, or Brachytherapy. *Clin Genitourin Cancer*. 2021;19(2):255-266.
- 237. Chuong MD, Hartsell WH, Larson GL, Tsai HK, Laramore GE, Rossi CJ, Wilkinson B, Kaiser A, Vargas CE. Minimal Toxicity After Proton Beam Therapy for Prostate and Pelvic Nodal Irradiation: Results From the Proton Collaborative Group REG001-09 trial. *Int J Radiat Oncol Biol Phys.* 2017;99(2S): E223.
- 238. Choi S, Blanchard P, Ye R, et al. Outcomes Following Proton Therapy for the Treatment of Prostate Cancer: Efficacy and Toxicity Results from 2 Prospective Single Institution Cohorts. *Int J Radiat Oncol Biol Phys.* 2017;99(2S):E221.
- 239. Bryant C, Smith TL, Henderson RH, et al. Five-year biochemical results, toxicity, and patient-reported quality of life following delivery of dose-escalated image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2016;95(1):422-434.
- 240. Buchberger D, Kreinbrink P, Kharofa J, et al. Proton Therapy in the Treatment of Anal Cancer in Pelvic Kidney Transplant Recipients: A Case Series. *Int J Part Ther.* 2019, 6(1):28-34
- 241. Engels EA, Pfeiffer RM, Fraumeni JF, Jr, et al. Spectrum of cancer risk among US solid organ transplant recipients. *J Am Med Assoc.* 2011;306:1891–901
- 242. Kasiske BL, Snyder JJ, Gilbertson DT, et al. Cancer after kidney transplantation in the United States. *Am J Transplant.* 2004;4:905–13
- 243. Ogilvie JW, Park IU, Downs LS, et al. Anal dysplasia in kidney transplant recipients. *J Am Coll Surg.* 2008;207:914–21
- 244. Meeuwis KA, Melchers WJ, Bouten H, et al. Anogenital malignancies in women after renal transplantation over 40 years in a single center. *Transplantation*. 2012;93:914–22
- 245. Meeuwis KA, Hilbrands LB, IntHout J, et al. Cervicovaginal HPV infection in female renal transplant recipients: an observational, self-sampling based, cohort study. *Am J Transplant*. 2015, 15(3):723-33
- 246. Vaidic CM, McDonald SP, McCredie MR, et al. Cancer incidence before and after kidney transplantation. *JAMA*. 2006;296:2823–31

#### Prostate

- 247. Bryant, Curtis et al. Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys.* 2016;95(1);422-434.
- 248. Coen JJ, Bae K, Zietman AL, et al. Acute and late toxicity after dose escalation to 82 GyE using conformal proton radiation for localized prostate cancer: initial report of American College of Radiology phase II study 03-12. *Int J Radiat Oncol Biol Phys.* 2011; 81(4):1005-9.
- 249. Coen JJ, Paly JJ, Niemierko A, et al. Long-term quality of life outcome after proton beam monotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2012; 82(2):e201-9.
- 250. Henderson RH, Hoppe BS, Marcus RB Jr, et al. Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate- risk prostate cancer: results of two prospective trials. *Acta Oncol.* 2013; 52(3):463-9.
- 251. 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*. 2013. [Epub ahead of print].
- 252. Hoppe BS, Nichols RC, Henderson RH, et al. Erectile function, incontinence, and other quality of life outcomes following proton therapy for prostate cancer in men 60 years old and younger. *Cancer*. 2012; 118(18):4619-26.
- 253. Johansson S, Astrom L, Sandin F, Isacsson U, Montelius A, Turesson I. Hypofractionated proton boost combined with external beam radiotherapy for treatment of localized prostate cancer. *Prostate Cancer*. 2012; 654861.
- 254. Mendenhall NP, Hoppe BS, Nichols RC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2014; 88(3): 596-602.
- 255. Yu JB, Soulos PR, Herrin J, et al. Proton Versus Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity. *J Natl Cancer Inst.* 2013; 105(1): 25-32.
- 256. Thomas J Whitaker, David M Routman , Heather Schultz, et al. IMPT versus VMAT for Pelvic Nodal Irradiation in Prostate Cancer: A Dosimetric Comparison. *Int J Part Ther* Winter 2019;5(3):11-23.
- 257. Vedang Murthy, Priyamvada Maitre, Sadhana Kannan , et al. Prostate-Only Versus Whole-Pelvic Radiation Therapy in High-Risk and Very High-Risk Prostate Cancer (POP-RT): Outcomes From Phase III Randomized Controlled Trial. *J Clin Oncol.* 2021 Apr 10;39(11):1234-1242.

- 258. Pollack A, Karrison TG, Balogh Jr. AG, et al. LBA5 -Short term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/ RTOG 0534 SPPORT Trial. ASTRO 2019.
- 259. Liu Y, Patel SA, Jani AB, Gillespie TW, Patel PR, Godette KD, Hershatter BW, Shelton JW, McDonald MW. Overall Survival After Treatment of Localized Prostate Cancer With Proton Beam Therapy, External-Beam Photon Therapy, or Brachytherapy. *Clin Genitourin Cancer.* 2021 Jun;19(3):255-266.e7.

#### Sarcomas

- 260. Ciernik IF, Niemierko A, Harmon DC, et al. Proton based radiotherapy for unresectable or incompletely resected osteosarcoma. *Cancer*. 2011; 117(19): 4522-30.
- 261. Delaney TF, Liebsch NJ, Pedlow FX, et al. Phase II Study of High Dose photon/Proton Radiotherapy in the management of Spine Sarcomas. *Int J Radiat Oncol Biol Phys.* 2009; 74(3): 732-9.
- 262. 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. *Int J Radiat Oncol Biol Phys.* 2007; 69(3):865-871.
- 263. Brady S. Laughlin, Michael A. Golafshar, Safia Ahmed, Matthew Prince, Justin D. Anderson, Tamara Vern-Gross, Mahesh Seetharam, Krista Goulding, Ivy Petersen, Todd DeWees, Jonathan B. Ashman; Early Experience Using Proton Beam Therapy for Extremity Soft Tissue Sarcoma: A Multicenter Study. *Int J Part Ther* 1 June 2022; 9 (1): 1–11.

#### **Skull Base**

- 264. Combs SE, Kessel K, Habermehl, et al. Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base. *Acta Oncol*.2013; 52(7):1504-1509.
- 265. Iannalfi A, D'Ippolito E, Riva G, et al. Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy. *Neuro Oncol.* Sep 29 2020;22(9):1348-1358.
- 266. Fung V, Calugaru V, Bolle S, et al. Proton beam therapy for skull base chordomas in 106 patients: A dose adaptive radiation protocol. *Radiother Oncol.* Aug 2018;128(2):198-202.
- 267. Weber DC, Badiyan S, Malyapa R, et al. Longterm outcomes and prognostic factors of skull-base chondrosarcoma patients treated with pencil-beam scanning proton therapy at the Paul Scherrer Institute. *Neuro Oncol.* Feb 2016;18(2):236-43.