



NCCN GUIDELINES ON PROTON THERAPY (AS OF 4/23/18)

BONE (Version 2.2018, 03/28/18)

- Radiation Therapy
 - Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with protons, carbon ions, or other heavy ions; stereotactic radiosurgery (SRS); or fractionated SRS (FSRT) should be considered as clinically indicated in order to deliver high radiation doses while maximizing normal tissue sparing.
 - The RT doses listed below for Chondrosarcoma and Chordoma are recommended total doses for external beam radiation therapy using conventional daily fractionation of 1.8 to 2 Gy. Alternative dosing schemes are necessary for other specialized techniques such as stereotactic radiosurgery, or fractionated stereotactic RT and particle therapy such as protons or carbon ions.
- Chondrosarcoma
 - Proton beam RT alone or in combination with photon beam RT has been associated with an excellent local tumor control and long-term survival in the treatment of patients with low-grade skull base and cervical spine chondrosarcomas. In two separate studies, proton beam RT resulted in local control rates of 92% and 94% in patients with skull base chondrosarcoma.
 - Post-operative treatment with proton and/or photon beam RT may be useful for patient with tumors in an unfavorable location not amenable to resection, especially in chondrosarcomas of the skull base and axial skeleton.
- Chordoma
 - Particle Beam RT with high-energy protons or carbon ions has resulted in local control rates ranging from 62% to 81% in patients with skull base as well as extracranial chordomas involving the spine and sacrum.
- Osteosarcoma
 - Combined photon/proton or proton beam RT has been shown to be effective for local control in some patients with unresectable or incompletely resected osteosarcoma.

CENTRAL SERVICE SYSTEM (Version 1.2018, 03/20/18)

- Adult Medulloblastoma
 - To reduce toxicity from craniospinal irradiation in adults, consider the use of intensity-modulated radiotherapy or protons if available."
- Intracranial and Spinal Ependymoma
 - Proton beam craniospinal irradiation may be considered when toxicity is a concern.
- Medulloblastoma & Supratentorial PNET
 - It is reasonable to consider proton beam for craniospinal irradiation where available as it is associated with less toxicity.

ESOPHAGUS AND ESOPHAGOGASTRIC JUNCTION (Version 1.2018, 03/16/18)

- Simulation and Treatment Planning Section
 - CT simulation and conformal treatment planning should be used. Intensity-modulated radiation therapy (IMRT) or proton beam therapy* is appropriate in clinical settings



where reduction in dose to organs at risk (eg, heart, lungs) is required that cannot be achieved by 3-D techniques. **Data regarding proton beam therapy are early and evolving. Ideally, patients should be treated with proton beam therapy within a clinical trial.*

HEAD & NECK (Version 1.2018, 02/15/18)

- Ethmoid Sinus Tumors – “Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.”
- Maxillary Sinus Tumors – “Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.”
- Radiation Techniques Section
 - “IMRT or other conformal techniques (3-D conformal, helical tomotherapy, VMAT, and proton beam therapy [PBT]) may be used as appropriate depending on the stage, tumor location, physician training/expertise, and available physics support.”
 - “Advanced radiation therapy technologies such as IMRT, IGRT and PBT may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs) such as the brain, brain stem, cochlea, semicircular canals, optic chiasm and nerves, other cranial nerves, retina, lacrimal glands, cornea, spinal cord, brachial plexus, mucosa, salivary glands, bone (skull base and mandible), pharyngeal constrictors, larynx and esophagus; and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control. The demonstration of significant dose-sparing of these OARs reflects best clinical practice.”
 - “Randomized studies to test these concepts are unlikely to be done since the above specific clinical scenarios are relatively rare. In light of that, the modalities and techniques that are found best to reduce the doses to the OARs in a clinically meaningful way without compromising target coverage should be considered.”
 - “Proton Beam Therapy - Achieving highly conformal dose distributions is especially important for patients whose primary tumors are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus; extend intracranially or exhibit extensive perineural invasion; and who are being treated with curative intent and/or who have long life expectancies following treatment. Nonrandomized single institution clinical reports and systematic comparisons demonstrate safety and efficacy of proton beam therapy in the above mentioned specific clinical scenarios. Proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy.”
- **Proton Beam Therapy**
 - At present, proton therapy is the predominant particle therapy under active clinical investigation in the United States. Proton therapy has been used to treat oropharyngeal cancers, sinonasal malignancies, adenoid cystic carcinomas, and MMs. A systematic review and meta-analysis of non-comparative observation studies concluded that patients with malignant diseases of the nasal cavity and paranasal sinuses who received proton therapy appeared to have better outcomes than those receiving photon therapy. A review of proton therapy in patients with H&N cancers included 14 retrospective reviews and 4 prospective nonrandomized studies. The 2- to 5-year local control rates were as low as 17.5% for T4 or recurrent paranasal sinus cancers and as high as 95% in other types of tumors.



In institutional reports, outcomes for proton therapy have been reported. Recent reports show that proton beam therapy (PBT) for treatment of sinonasal cancer is associated with good locoregional control, freedom from distant metastasis, and acceptable toxicity. Another recent institutional report ($N = 41$) showed that PBT may be associated with greater normal tissue sparing without sacrificing target coverage, which may be associated with reduced toxicity compared to IMRT.

Results from a retrospective study comparing 40 patients with cancer of the nasopharynx, nasal cavity, or paranasal sinuses who received either PBT or IMRT to the H&N (with or without chemotherapy) showed that PBT was associated with lower mean doses to the oral cavity, esophagus, larynx, and parotid glands, regardless of nodal status and compared to IMRT.²³⁰ PBT was also associated with less dependence on opioid pain medication and gastrostomy tube placement, compared to IMRT.

Occasional fatal outcomes have been reported with proton therapy, including 3 deaths secondary to brainstem injury.²³¹⁻²³³ A report from Japan described long-term toxicities after proton therapy in 90 patients with nasal cavity, paranasal sinus, or skull base malignancies.²³⁴ Late toxicities reached grade 3 in 17 patients (19%) and grade 4 in 6 patients (7%) (encephalomyelitis infection in 2 patients, optic nerve disorder in 4 patients). This rate of grade 3 to 4 late toxicity with protons (19%) was similar to the rate reported for conventional RT with photons (16%).²³⁵ Other clinicians have reported low rates of serious toxicities when using strict dose limits for proton therapy.

Proton therapy has typically been used to treat patients with the most challenging disease, for which other RT options were not felt to be safe or of any benefit. As described above, nonrandomized institutional reports and a small number of systemic reviews have shown that PBT may be safe to use in some settings. In patients with tumors that are periocular in location and/or invade the orbit, skull base, and/or cavernous sinus, and tumors that extend intracranially or exhibit extensive perineural invasion, as well as in patients being treated with curative intent and/or have long life expectancies, achieving highly conformal dose distributions is crucial. An accurate comparison of benefits to other RT options should ideally take place in the controlled setting of randomized clinical trials. An alternative approach may be to develop prospectively maintained databases to raise the quality of institutional reports of clinical experiences.

HEPATOBIILIARY CANCERS (Version 1.2018, 02/14/18)

- Hepatocellular Carcinoma (HCC)
 - Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended
 - Proton Beam therapy (PBT) may be appropriate in specific situations.
- Hepatocellular Carcinoma
 - The panel advises that PBT may be considered and appropriate in select settings for HCC.
- Gallbladder Cancer
 - Hypofractionation with photons or protons is an acceptable option for intrahepatic tumors, though treatment at centers with experience is recommended.
- Hepatocellular Carcinoma
 - In 2014, ASTRO (American Society for Radiation Oncology) released a model policy supporting the use of proton beam therapy (PBT) in some oncology populations. In a



recent phase II study, 94.8% of patients with unresectable HCC who received high-dose hypo fractionated PUT demonstrated >80% local control after two years, as defined by RECIST criteria. In a recent meta-analysis including 70 studies, charged particle therapy (mostly including PBT) was compared to SORT and conventional radiotherapy. OS (RR, 25.9; 95% CI, 1.64–408.5; $P = .02$), PFS (RR, 1.86; 95% CI, 1.08–3.22; $P = .013$), and locoregional control (RR, 4.30; 95% CI, 2.09–8.84; $P < .001$) through five years were greater for charged particle therapy than for conventional radiotherapy. There were no significant differences between charged particle therapy and SBRT for these outcomes.

HODGKIN'S LYMPHOMA (Version 3.2018, 04/16/18)

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced radiation therapy (RT) technologies such as IMRT, breath hold, or respiratory gating, image-guided RT, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk (OAR) such as the heart (including coronary arteries, valves, and left ventricle), lungs, kidneys, spinal cord, esophagus, carotid artery, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.

NON-HODGKIN'S LYMPHOMA – B-CELL LYMPHOMAS (Version 3.2018, 04/13/18)

- Treatment with photons, electrons, or protons may all be appropriate, depending on clinical circumstances.
- Advanced radiation therapy technologies such as IMRT, breath hold or respiratory gating, image-guided therapy, or proton therapy may offer significant and clinically relevant advantages in specific instances to spare important organs at risk such as the heart (including coronary arteries and valves), lungs, kidneys, spinal cord, esophagus, bone marrow, breasts, stomach, muscle/soft tissue, and salivary glands and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.

NON-SMALL CELL LUNG CANCER (Version 3.2018, 02/21/18)

- Principles of Radiation Therapy Section
 - “More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy.”
- “Advanced Stage/Palliative RT Section
 - “When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3D-CRT and including IMRT or proton therapy as appropriate) ~~should~~ may be used.”

PROSTATE (Version 2.2018, 03/18/18)



- Photon and proton beam radiation are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles.
- The NCCN panel believes no clear evidence supports a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise.

SOFT TISSUE SARCOMA (Version 2.2018, 3/27/18)

- Extremity/Superficial Trunk, Head/Neck and Retroperitoneal/Intra-abdominal
 - When EBRT is used, sophisticated treatment planning with IMRT, tomotherapy, and/or proton therapy can be used to improve therapeutic effect.
 - Newer RT techniques such as IMRT and 3D conformal RT using protons or photons may allow tumor target coverage and acceptable clinical outcomes within normal tissue dose constraints to adjacent organs at risk.