

Proton Beam Radiation Therapy

Policy Number: RADIOLOGY 045.1 T2
Effective Date: November 1, 2021

[Instructions for Use](#)

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Related Policies

- [Intensity-Modulated Radiation Therapy](#)
- [Radiation Therapy: Fractionation, Image-Guidance, and Special Services](#)
- [Stereotactic Body Radiation Therapy and Stereotactic Radiosurgery](#)

Coverage Rationale

Note: This policy applies to persons 19 years of age and older. Proton beam radiation therapy (PBRT, PBT) is covered without further review for persons younger than 19 years of age.

The following are proven and medically necessary:

- PBT for [Definitive Therapy](#) of the following indications:
 - Hepatocellular carcinoma (HCC) (localized, unresectable) in the curative setting when documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques, including intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT), and selective internal radiation spheres, and transarterial therapy (for example, chemoembolization) is contraindicated or not technically feasible
 - Intracranial arteriovenous malformations (AVMs)
 - Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body and choroid)
 - Skull-based tumors (e.g., chordomas, chondrosarcomas, paranasal sinus or nasopharyngeal tumors)
- PBT may be covered for a diagnosis that is not listed above as proven, including recurrences or metastases in selected cases. Requests for exceptions will be evaluated on a case-by-case basis when both of the following criteria are met:
 - Documentation is provided that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques; and
 - Evaluation includes a comparison of treatment plans for PBT, IMRT and SBRT

PBT and IMRT are proven and considered clinically equivalent for treating prostate cancer. Medical necessity will be determined based on the terms of the member’s benefit plan.

PBT is unproven and not medically necessary due to insufficient evidence of efficacy for treating all other indications not listed above as proven, including but not limited to:

- Age related macular degeneration (AMD)
- Bladder cancer

- Brain and spinal cord tumors
- Breast cancer
- Choroidal hemangioma
- Esophageal cancer
- Gynecologic cancers
- Head and neck tumors not noted above as proven
- Lung cancer
- Lymphomas
- Pancreatic cancer
- Vestibular tumors (e.g., acoustic neuroma or vestibular schwannoma)
- PBT used in conjunction with IMRT

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

Required Clinical Information

Proton Beam Radiation Therapy (PBT)

Medical notes documenting the following, when applicable:

- History of medical condition requiring treatment
- Documentation that sparing of the surrounding normal tissue cannot be achieved with standard radiation therapy techniques
- Evaluation includes a comparison of treatment plans for PBT, IMRT, and stereotactic body radiation therapy (SBRT)
- For hypofractionated radiation, provide the prescribed total dose and dose per fraction
- For delivery of radiation therapy course with standard fractionation, provide the dose prescription along with documentation in the form of a clearly labeled, color comparative proton, and IMRT dose volume histogram and dose table, in absolute doses noting that sparing of the surrounding normal tissue cannot be achieved with IMRT techniques
Note: If citing an RTOG dose constraint, provide the RTOG protocol number
- Physician's treatment plan

Note: The color comparative proton and IMRT dose volume histogram and dose table images can be submitted via the external portal at <http://www.uhcprovider.com/paan>; faxes of images will not be accepted.

Definitions

Definitive Therapy: Definitive Therapy is treatment with curative intent. Treatment of a local recurrence of the primary tumor may be considered "Definitive" if there has been a long disease free interval (generally ≥ 2 years) and treatment is with curative intent.

Prior Authorization Requirements

CPT Codes 77301 and 77338

Referral is required in the Office and Outpatient settings. Prior Authorization is required in the Inpatient and Home settings.

All Other CPT/HCPCS Codes

Prior authorization is required in all sites of service.

Providers can log into the [Prior Authorization and Notification](#) website to submit a prior authorization request.

Notes:

- Participating providers in the office setting: Prior authorization is required for services performed in the office of a participating provider.
- Non-participating/out-of-network providers in the office setting: Prior authorization is not required but is encouraged for out-of-network services. If prior authorization is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
77301	Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

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HCPCS Code	Description
G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session
G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Diagnosis Code	Description
C11.0	Malignant neoplasm of superior wall of nasopharynx
C11.1	Malignant neoplasm of posterior wall of nasopharynx
C11.2	Malignant neoplasm of lateral wall of nasopharynx
C11.3	Malignant neoplasm of anterior wall of nasopharynx
C11.8	Malignant neoplasm of overlapping sites of nasopharynx
C11.9	Malignant neoplasm of nasopharynx, unspecified
C22.0	Liver cell carcinoma
C30.0	Malignant neoplasm of nasal cavity

Diagnosis Code	Description
C31.0	Malignant neoplasm of maxillary sinus
C31.1	Malignant neoplasm of ethmoidal sinus
C31.2	Malignant neoplasm of frontal sinus
C31.3	Malignant neoplasm of sphenoid sinus
C31.8	Malignant neoplasm of overlapping sites of accessory sinuses
C31.9	Malignant neoplasm of accessory sinus, unspecified
C41.0	Malignant neoplasm of bones of skull and face
C61.0	Malignant neoplasm of prostate
C69.30	Malignant neoplasm of unspecified choroid
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
D09.20	Carcinoma in situ of unspecified eye
D09.21	Carcinoma in situ of right eye
D09.22	Carcinoma in situ of left eye
D14.0	Benign neoplasm of middle ear, nasal cavity and accessory sinuses
D16.4	Benign neoplasm of bones of skull and face
D31.30	Benign neoplasm of unspecified choroid
D31.31	Benign neoplasm of right choroid
D31.32	Benign neoplasm of left choroid
D31.40	Benign neoplasm of unspecified ciliary body
D31.41	Benign neoplasm of right ciliary body
D31.42	Benign neoplasm of left ciliary body
Q28.2	Arteriovenous malformation of cerebral vessels
Q28.3	Other malformations of cerebral vessels

Description of Services

Unlike other types of radiation therapy (RT) that use x-rays or photons to destroy cancer cells, proton beam therapy (PBT) uses a beam of special particles (protons) that carry a positive charge. There is no significant difference in the biological effects of protons versus photons; however, protons can deliver a dose of radiation in a more confined way to the tumor tissue than photons. After they enter the body, protons release most of their energy within the tumor region and, unlike photons, deliver only a minimal dose beyond the tumor boundaries. (American College of Radiology (ACR) website, updated 2019)

Proton beam radiation therapy (PBRT) is intended to deliver higher, more targeted radiation with less damage to collateral healthy tissue than external beam radiation therapy (EBRT) using photons (x-rays) when used to treat solid tumors. While PBRT has been used for several solid cancer tumor types (e.g., breast, lung, prostate, head and neck, central nervous system (CNS)) in adults and in certain pediatric cancers, evidence is lacking regarding clear benefits over EBRT. (ECRI, 2017)

Proven Indications

Hepatocellular Carcinoma (HCC)

Fukuda et al. (2017) performed an observational study to assess the long-term efficacy of PBT in patients with previously untreated HCC. Between January 2002 and December 2009, 129 patients at a single institution received PBT via one of 3 protocols based on tumor location with dose volumes of 77.0 GyE in 35 fractions, 72.6 GyE in 22 fractions and 66.0 GyE in 10 fractions for the gastrointestinal (GI), hilar and standard protocols, respectively. Primary outcome measures were local tumor control (LTC), OS, and PFS. All 129 patients completed PBT without experiencing severe complications, and no treatment-related deaths were observed. The median patient observation period was 55 months. The 5-year LTC, PFS, and OS rates were 94%, 28%, and 69% for patients with 0/A stage disease (n=9/21), 87%, 23%, and 66% for patients with B stage disease (n=34), and 75%, 9%, and 25% for patients with C stage disease (n=65), respectively. The 5-year LTC and OS rates of 15 patients with tumor thrombi in major vessels were 90% and 34%, respectively. The major study limitation cited was the heterogeneous patient population, with most subjects selecting receiving PBT because they refused surgery or conventional interventional RT. The authors concluded that PBT achieved long term tumor control with less toxicity and is a viable treatment option for localized HCC. The authors are now planning a multicenter controlled study comparing PBT and hepatectomy.

Hong et al. (2016) conducted a single-arm, phase II, multi-institutional study to evaluate the safety and efficacy of high-dose, hypofractionated PBT for HCC and intrahepatic cholangiocarcinoma (ICC). Eighty-three participants \geq 18 years with unresectable or locally recurrent HCC or ICC were included. With 42 HCC patients (95.5%) and 36 ICC patients (92.3%) having completed their prescribed dose, the median dose delivered was 58.0 GyE (in 15 fractions; range, 15.1 to 67.5 GyE). Of the 83 patients, 71 (85.5%) experienced at least one radiation-related toxicity event while in the study, most commonly fatigue (54/83, 65.1%), rash (51/83, 61.4%), nausea (25/83, 30.1%), or anorexia (21/83, 25.3%). Median follow-up among the 50 survivors was 19.5 months (range, 0.6 to 55.9 months). For patients with HCC, the 1-year and 2-year PFS rates were 56.1% and 39.9%, respectively. The 1- and 2-year OS was 76.5% and 63.2%, respectively. Three patients with HCC underwent successful liver transplantation, two of whom remain alive. For patients with ICC, 1-year and 2-year PFS rates were 41.4% and 25.7%, respectively; with 1-year and 2-year OS rates of 69.7% and 46.5%, respectively. The authors concluded that high-dose, hypofractionated PBT is safe and associated with high rates of LC and OS for both HCC and ICC. These data provide the strong rationale for RCTs of proton versus photon RT for HCC, and for chemotherapy with or without RT for ICC.

Bush et al. (2016) conducted a single-center, prospective RCT, comparing outcomes of 69 patients with newly diagnosed HCC who received either transarterial chemoembolization (TACE) or PBT as definitive or bridge therapy while awaiting transplantation. Thirty-three subjects were randomized to PBT, and 36 subjects were randomized to TACE. Patients randomized to TACE received at least 1 TACE with additional TACE for persistent disease. The PBT group had proton therapy delivered to all areas of gross disease to a total dose of 70.2 Gy in 15 daily fractions over 3 weeks. The median follow-up for all subjects was 28 months. The primary endpoint was PFS, with secondary endpoints including OS, local disease control, transplant outcomes, and toxicity including days of hospitalization after treatment. The 2-year OS for the entire group was 59%, with no significant difference between treatment assignments. Regarding local control and PFS between treatment groups, there was a trend toward improved 2-year local tumor control (88% vs 45%, $P=.06$) and PFS (48% vs 31%, $P=.06$) favoring the PBT group. For the entire group of study subjects, 22 went on to have liver transplantation. The 2-year OS after transplantation was 82% for the entire group, with no difference seen between proton and TACE groups. The authors concluded that this study indicates similar OS rates for PBT and TACE. While there is a trend toward improved local tumor control and PFS favoring proton therapy, it is too early to determine whether this trend will be maintained.

NCCN guidelines state that hypofractionation with photons or protons at an experienced center is an acceptable option for unresectable intrahepatic tumors. (2020)

A phase III randomized trial comparing PBT to radiofrequency ablation (NCT02640924) is in progress. For more information on this and other clinical trials studying PBT and HCC, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Intracranial Arteriovenous Malformations (AVM)

Zuurbier et al. (2019) updated a previously conducted systematic review (Ross, 2010) that aimed to determine the effectiveness and safety of the different interventions, alone or in combination, for treating brain AVMs in adults compared against either each

other, or conservative management, in RCTs. A search was conducted using the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials, the Cochrane Library, MEDLINE, OVID and Embase OVID. The search identified 14 eligible RCTs and of those, 13 were excluded (10 did not meet the inclusion criteria and 3 were still ongoing), and 1 RCT with 226 participants was included (Mohr, 2013). The study titled, A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) was an international, multi-center, randomized, controlled, open, prospective clinical trial comparing interventional treatment (endovascular, surgical, and/or radiation therapy) to conservative management for unruptured brain AVMs in adults. The primary outcome was death or dependence from any cause (modified Rankin Scale score ≥ 2), and secondary outcomes included symptomatic intracranial hemorrhage, epileptic seizure, symptomatic radiation necrosis detected by MRI, and quality of life (QOL). Data on functional outcome and death at 12 months of follow-up were provided for 218 (96%) of the participants. Intervention compared to conservative management increased death or dependency with a risk ratio (RR) of 2.53, 95% CI 1.28 to 4.98, and higher proportion of participants with symptomatic intracranial hemorrhage (RR 6.75, 95% CI 2.07 to 21.96). There was no difference in the frequency of epileptic seizures (RR 1.14, 95% CI 0.63 to 2.06). The authors reported that moderate-quality evidence from one RCT (of adults with unruptured brain AVMs) showed that conservative management was superior to intervention with respect to functional outcome and symptomatic intracranial hemorrhage during the 1-year period after randomization however, more RCTs are needed to confirm or refute these findings.

Hattangadi-Gluth et al. (2014) evaluated the obliteration rate and potential AEs of single-fraction proton beam stereotactic radiosurgery (PSRS) in patients with cerebral AVMs. From 1991 to 2010, 248 consecutive patients with 254 cerebral AVMs received single-fraction PSRS at a single institution. The median AVM nidus volume was 3.5 cc, 23% of AVMs were in critical/deep locations (basal ganglia, thalamus or brainstem) and the most common dose was 15 Gy. At a median follow-up time of 35 months, 64.6% of AVMs were obliterated. The median time to total obliteration was 31 months, and the 5- and 10-year cumulative incidence of total obliteration was 70% and 91%, respectively. On univariable analysis, smaller target volume, smaller treatment volume, higher prescription dose and higher maximum dose were associated with total obliteration. Deep/critical location was also associated with decreased likelihood of obliteration. On multivariable analysis, critical location and smaller target volume remained associated with total obliteration. Post-treatment hemorrhage occurred in 13 cases (5-year cumulative incidence of 7%), all among patients with less than total obliteration. Three of these events were fatal. The most common complication was seizure. The authors reported that this is the largest modern series of PSRS for cerebral AVMs and concluded that PSRS can achieve a high obliteration rate with minimal morbidity. Post-treatment hemorrhage remains a potentially fatal risk among patients who have not yet responded to treatment.

Hattangadi et al. (2012) evaluated 59 patients with high-risk cerebral AVMs, based on brain location or large size, who underwent planned two-fraction PSRS. Median nidus volume was 23 cc. Seventy percent of cases had nidus volume ≥ 14 cc, and 34% were in critical locations (brainstem, basal ganglia). Many patients had prior surgery or embolization (40%) or prior PSRS (12%). The most common dose was 16 Gy in 2 fractions. At a median follow-up of 56.1 months, 9 patients (15%) had total and 20 patients (34%) had partial obliteration. Patients with total obliteration received higher total dose than those with partial or no obliteration. Median time to total obliteration was 62 months, and 5-year actuarial rate of partial or total obliteration was 33%. Five-year actuarial rate of hemorrhage was 22% and 14% (n=8) suffered fatal hemorrhage. Lesions with higher AVM scores were more likely to hemorrhage and less responsive to radiation. The most common complication was headache. One patient developed a generalized seizure disorder, and two had mild neurologic deficits. The authors concluded that high-risk AVMs can be safely treated with 2-fraction PSRS, although total obliteration rate is low and patients remain at risk for future hemorrhage. Future studies should include higher doses or a multistaged PSRS approach for lesions more resistant to obliteration with radiation.

Ocular Tumors

Verma and Mehta (2016) conducted systematic review to identify studies on PBT and uveal melanoma. The search was conducted using PubMed, EMBASE, abstracts from meetings of the American Societies for Radiation Oncology and Clinical Oncology, and the Particle Therapy Co-Operative Group. Articles included addressed clinical outcomes of proton radiotherapy for ocular melanoma with the following headings: proton, proton radiation therapy, proton beam therapy, ocular melanoma, uveal melanoma, choroidal melanoma, eye melanoma, and were published from 2000 to 2015. Articles excluded were those without specific assessments on clinically relevant outcomes of proton radiotherapy for previously untreated melanoma of the eye, letters to the editor, direct commentary to other articles, and small reports (<25 patients). A total of 14 original investigations from 10 institutions were analyzed. Results revealed that the majority of tumors were choroidal and medium to large-sized, and received 50–70 Gy equivalent doses however, more recent data reported use of lower doses. The five-year local control rates exceeded 90% and remained high at 15 years. The 5-year overall survival rates ranged from 70–85%, and 5-year metastasis-free survival and disease-specific survival rates ranged from 75–90%, with more recent series reporting higher

values. With the removal of smaller studies, 5-year enucleation rates were consistently between 7 and 10%. Many patients (60–70%) showed a post-PBT visual acuity decrease but still retained purposeful vision (>20/200). Complication rates were variable but showed improvements compared with historical plaque brachytherapy data. The authors concluded that PBT has shown excellent oncological and ophthalmological outcomes, and these have been sustained in the long-term.

Hartsell et al. (2016) conducted a case series study to determine feasibility of treating patients with ocular melanoma using volumetric imaging and planning for PBT. Twenty six patients met eligibility criteria and all were able to complete and tolerate treatment. Visual outcomes were assessed on routine ophthalmologic follow-up over a median time frame of 31 months. Four patients had poor vision in the treated eye prior to PBT; 3 of those 4 patients had serous retinal detachment prior to treatment. None of those patients had significant improvement in visual acuity after treatment. Of the remaining 22 patients, 9 had visual acuity equal to pre-treatment acuity at the most recent follow-up visit, 4 had stable vision with a loss of 2 to 5 lines on the Snellen chart, and 8 patients had lost more than 5 lines of visual acuity. The visual acuity status for 1 patient was unknown prior to his death from metastatic melanoma. The treatment was well tolerated by patients with minimal acute toxicity. Relatively low mean doses to the anterior structures (ciliary body and lens) were maintained, even in patients with large tumors. The authors concluded that while they continue evaluating outcomes of these patients in a prospective manner, this treatment technique appears to be feasible with excellent early outcomes.

In the NCCN guidelines on uveal melanoma, particle beam therapy is noted as a common form of definitive RT for the primary tumor. It is considered appropriate as an upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. It should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and particle beam physicist. (2020)

Prostate Cancer

A Hayes report assessed multiple clinical studies published between 1983-2016 evaluating the efficacy and safety of PBT in patients with localized prostate cancer. The report concludes that the best available studies of PBT for localized prostate cancer have consistently found that most or nearly all patients remain free from cancer progression for 5 years or longer after treatment. These results are promising but none of the reviewed studies assessed the efficacy of PBT as the sole or primary therapy for prostate cancer relative to the efficacy of other common methods of RT. Six of the reviewed studies found that the safety of PBT as sole or primary therapy was usually similar to the safety of other common RT; however, these studies are of low quality since they were retrospective. Moreover, these 6 studies do not provide sufficient evidence of comparative safety since they were divided between evaluations of PBT relative to brachytherapy, conformal X-ray therapy, and IMRT. The other available studies do not provide clear evidence concerning the relative safety and efficacy of PBT for prostate cancer since these other studies evaluated it as an adjunct to X-ray therapy or did not compare it with another common RT. Additional well-designed studies are needed to establish the clinical role of PBT relative to other widely used therapies for localized prostate cancer. (2019)

Several single-institution studies report favorable clinical outcomes of PBT in prostate cancer. Henderson et al. (2017) reported 5-year outcomes of a prospective trial of image-guided accelerated hypofractionated proton therapy (AHPT) for prostate cancer from a single institution. Late radiation AEs/toxicities and freedom from biochemical and/or clinical progression (FFBP) were the outcome measurements for the 215 participants categorized as low and intermediate risk. Median follow-up was 5.2 years, with FFBP rates overall noted at 95.9%. For the subsets of low and intermediate risk, FFBP was 98.3% and 92.7%, respectively. Actuarial 5-year rates of significant (\geq grade 3) late radiation-related GI AEs/toxicities were 0.5%, and 1.7% for GU AEs.

Bryant et al. (2016) performed a single-center study on 1,327 men with localized prostate cancer who received image guided PBT between 2006-2010. The 5-year FFBP rates were 99% for low-risk, 94% for intermediate-risk, and 76% for high-risk patients. The authors concluded that PBT provided excellent control of disease with low rates of GU/GI toxicity. Large prospective comparative studies with longer follow-up times are necessary for a true comparison between PBT and other types of RT.

In a case-matched analysis, Fang et al. (2015) assessed prospectively collected toxicity data on patients with localized prostate cancer who received treatment with IMRT and PBT techniques and similar dose-fractionation schedules. A total of 394 patients were treated with either PBT (n=181) or IMRT (n=213). Patients were case-matched on risk group, age and prior GI and GU disorders, resulting in 94 matched pairs. The risks of acute and late GI/GU toxicities did not differ significantly after adjustment for confounders and predictive factors.

Mendenhall et al. (2014) reported 5-year clinical outcomes from 3 prospective trials of image-guided PBT for prostate cancer conducted at a single institution. From August 2006-September 2007, 211 patients (low risk n=89, intermediate risk n=82, and high risk n=40) were enrolled in one of the 3 trials. Dosages delivered were 78 cobalt gray equivalent (CGE) for low risk and 78 to 82 CGE for intermediate-risk. Participants with high risk disease received 78 CGE with weekly concomitant chemotherapy, followed by 6 months of androgen deprivation therapy (ADT). Five-year OS of 93%, 88%, and 86% were reported for low, intermediate, and high risk patients, respectively. FFBR rates for the same time period were 99% for both low and intermediate risk and 76% for high risk patients. There was a single instance of acute grade 3 GU toxicity. One acute grade 3 and 2 late grade 3 GI events throughout the entire group resulted in a 5-year incidence of 1%. Limitations to this study include overall study design and lack of a control group. The authors concluded that image-guided PBT was highly effective with minimal toxicities. While outcomes were favorable, the lack of control group limits interpretation of the studies and does not allow assessment of PBT outcomes compared to other forms of radiation therapy.

Yu et al. (2013) conducted a retrospective cohort analysis using data from the Chronic Condition Warehouse, a national database for Medicare fee-for-service claims from patients with specific conditions. The investigators identified patients who were age 66 and older with prostate cancer and treated with IMRT or PBT. To evaluate toxicity, each patient who received PBT was matched with two patients who received IMRT based on similar sociodemographic and clinical characteristics. Toxicity was reported at 6 months post-treatment and included 421 patients who received PBT matched to 842 patients who received IMRT, and at 12 months post-treatment and included 314 patients who received PBT matched to 628 patients who received IMRT. At 6 months, GU toxicity was significantly lower in patients who received PBT vs. IMRT (5.9% vs. 9.5%; OR=0.60, 95% CI=0.38 – 0.96, p=0.03). However, there was no difference at 12 months post-treatment (18.8% vs. 17.5%; OR=1.08, 95% CI=0.76–1.54, p=0.66). At 6 months and 12 months post-treatment, there was no difference in GI or other toxicities. The authors concluded that in a national sample of Medicare beneficiaries, patient who were treated with IMRT or PBT for prostate cancer had no difference in toxicity rates at 12 months post-treatment, and that additional longitudinal studies evaluating the effectiveness of PBT in comparison to IMRT are needed prior to widespread use of PBT for prostate cancer.

Sheets et al. (2012) evaluated the comparative morbidity and disease control of IMRT, PBT and conformal RT for primary prostate cancer treatment. Main outcomes were rates of GI and GU morbidity, erectile dysfunction, hip fractures and additional cancer therapy. In a comparison between IMRT and conformal RT (n=12,976), men who received IMRT were less likely to experience GI morbidity and fewer hip fractures, but more likely to experience erectile dysfunction. IMRT patients were also less likely to receive additional cancer therapy. In a comparison between IMRT and PBT (n=1,368), IMRT patients had a lower rate of GI morbidity. There were no significant differences in rates of other morbidities or additional therapies between IMRT and PBT.

Several large population-based cohort studies using Surveillance Epidemiology and End Results (SEER) data, have found greater GI toxicity with PBT than IMRT. Kim et al. (2011) reported that patients treated with RT are more likely to have procedural interventions for GI toxicities than patients with conservative management, and patients treated with PBT therapy experienced greater GI morbidity relative to IMRT patients. The elevated risk persisted beyond 5 years.

The NCCN Panel believes that photon and PBRT are both effective at achieving highly conformal RT with acceptable and similar biochemical control and long-term side effect profiles. No clear evidence supports a benefit or decrement of one treatment over another. Conventionally fractionated PBT can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise. (2019)

To further elucidate the clinical advantages and disadvantages between various types of radiation therapy used in prostate cancer, additional clinical trials are underway (NCT01617161, NCT00969111 and NCT03561220). For more information, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Clinical Practice Guidelines

American Urological Association (AUA)

In collaboration with the Society of Urologic Oncology (SUO) and ASTRO, the AUA guidelines for treating clinically localized prostate cancer discuss PBT as an option within the category of EBRT. The guidelines also state that PBT offers no clinical advantage over other forms of definitive treatment. (Sanda et al., 2017)

Skull-Based Tumors

Zhou et al. (2018) performed a meta-analysis to compare the effectiveness of photon therapy, PBT, and carbon ion therapy (CIT) for chordoma. Twenty-five studies were included, with results showing that the 3-, 5-, and 10-year OS rates were higher for stereotactic RT (SRT), PBT, and CIT than for conventional RT. The 10-year OS was higher for PBT than for SRT. The analysis revealed that particle therapy was more effective following surgery for chordoma than conventional RT. After 10 years, PBT was more beneficial than SRT. However, future studies should include more studies to enable accurate meta-analysis and a better exploration of prognosis.

The use of PBT to treat chondrosarcoma of the skull base after surgery is widely accepted, but studies demonstrating the need for PBT and its superiority in comparison to RT with photons are lacking. In a systematic review, Amichetti et al. (2010) reported that studies of PBT for skull-based chondrosarcoma resulted in LC ranging from 75% to 99% at 5 years. There were no prospective trials (randomized or non-randomized), but 4 uncontrolled single-arm studies with 254 patients were included. The authors concluded that PBT following surgical resection showed a very high probability of medium- and long-term cure with a relatively low risk of significant complications.

A systematic review of 7 uncontrolled single-arm studies concluded that the use of protons has shown better results in comparison to the use of conventional photon irradiation, resulting in the best long-term (10 years) outcome for skull-based chordomas with relatively few significant complications. (Amichetti et al., 2009)

NCCN guidelines for bone cancer states that specialized techniques, including particle beam RT with protons, should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing in patients with chondrosarcoma or chordoma. (2021)

NCCN guidelines on HNC state that use of proton therapy is an area of active investigation. In cancers of the oropharynx, nasopharynx, supraglottic larynx, paranasal/ethmoid sinus, maxillary sinus and salivary glands, as well as mucosal melanoma and other primary tumors of the head and neck, proton therapy can be considered when normal tissue constraints cannot be met by photon-based therapy. (2021)

Unproven Indications

Age-Related Macular Degeneration (AMD)

Evans et al. (2020) updated a previously conducted systematic review (Evans, 2010) that examined the effects of radiotherapy on neovascular AMD. A search was conducted using CENTRAL, MEDLINE, Embase, LILACS and three trials registers for randomized controlled trials in which radiotherapy was compared to another treatment, sham treatment, low dosage irradiation or no treatment in people with choroidal neovascularisation (CNV) secondary to AMD. Outcomes included best-corrected visual acuity (BCVA) (loss of 3 or more lines, change in visual acuity), contrast sensitivity, new vessel growth, quality of life and adverse effects at any time point. A total of 18 studies (n=2,430 people, 2,432 eyes) were included, and the radiation therapy with dosages ranging from 7.5 to 24 Gy. Three of these studies investigated brachytherapy (plaque and epimacular), the rest were studies of external beam radiotherapy (EBM) including one trial of stereotactic radiotherapy. The authors concluded that the evidence is uncertain regarding the use of radiotherapy for neovascular AMD. They stated that: 1) most studies took place before the routine use of anti-VEGF, and before the development of modern radiotherapy techniques such as stereotactic radiotherapy; 2) visual outcomes with epimacular brachytherapy are likely to be worse, with an increased risk of adverse events, probably related to vitrectomy; 3) the role of stereotactic radiotherapy combined with anti-VEGF is currently uncertain; and 4) further research on radiotherapy for neovascular AMD may not be justified until current ongoing studies have reported their results.

In a systematic review, Bekkering et al. (2009) evaluated the effects and side effects of PBT for indications of the eye. All studies that included at least 10 patients and that assessed the efficacy or safety of PBT for any indication of the eye were included. Five controlled trials, 2 comparative studies and 30 case series were found, most often reporting on uveal melanoma, choroidal melanoma and AMD. Methodological quality of these studies was poor. Studies were characterized by large differences in radiation techniques applied within the studies, and by variation in patient characteristics within and between studies. Results for uveal melanoma and choroidal melanoma suggest favorable survival, although side effects are significant. Results for choroidal hemangioma and AMD did not reveal beneficial effects from proton radiation. There is limited evidence on the effectiveness and safety of due to the lack of well-designed and well-reported studies.

A RCT by Zambarakji et al. (2006) studied 166 patients with angiographic evidence of classic choroidal neovascularization resulting from AMD and best-corrected visual acuity of 20/320 or better. Patients were assigned randomly (1:1) to receive 16-cobalt gray equivalent (CGE) or 24-CGE PBT in 2 equal fractions. Complete ophthalmological examinations, color fundus photography, and fluorescein angiography were performed before and 3, 6, 12, 18, and 24 months after treatment. At 12 months after treatment, 36 eyes (42%) and 27 eyes (35%) lost three or more lines of vision in the 16-CGE and 24-CGE groups, respectively. Rates increased to 62% in the 16-CGE group and 53% in the 24-CGE group by 24 months after treatment. Radiation complications developed in 15.7% of patients receiving 16-CGE and 14.8% of patients receiving 24-CGE. The authors concluded that no significant differences in rates of visual loss were found between the 2 dose groups.

Clinical Practice Guidelines

American Academy of Ophthalmology (AAO)

AAO preferred practice patterns state that RT is not recommended in the treatment of AMD. (2019)

Bladder Cancer

Takaoka and colleagues (2017) conducted a retrospective review to assess outcomes, prognostic factors and toxicities of PBT as a component of trimodal bladder-preserving therapy for muscle-invasive bladder cancer. Trimodal bladder-preserving therapy consisted of maximal transurethral resection of the bladder tumor, small pelvis (conventional) photon radiation, intra-arterial chemotherapy and PBT. Seventy patients with cT2-3N0M0 muscle-invasive bladder cancer were included who received treatment from 1990 to 2015 at a single institution. The OS and PFS rate, time to progression, predictive factors for progression and toxicities were analyzed. Progression was defined as when muscle-invasive recurrence, distant metastasis or upper urinary tract recurrence was observed. The patients' median age was 65 (range 36-85) years. The median follow-up period was 3.4 years (range 0.6-19.5 years). The 5-year cumulative OS rate, PFS rate and time to progression rate were 82%, 77%, and 82%, respectively. In univariate and multivariate analyses, tumor multiplicity and tumor size (≥ 5 cm) were significant and independent factors associated with progression (hazard ratio 3.5, 95% confidence interval 1.1-12; hazard ratio 5.0, 95% confidence interval 1.3-17; $P < 0.05$ for all). As for toxicity, 26 (18%) patients had grade 3-4 acute hematologic toxicities and 2 (3%) patients had grade 3 late GU toxicity. No patient had to discontinue the treatment due to acute toxicity. The authors concluded that trimodal therapy including both conventional and proton radiation was well tolerated and may be an effective treatment option for selected muscle-invasive bladder cancer patients. Further studies are needed to determine whether PBT is integral to this multi-modality therapy.

Miyanaga et al. (2000) conducted a small prospective uncontrolled clinical study to assess the efficacy and safety of PBT and/or conventional photon therapy for bladder cancer. The study involved 42 patients who received PBT to the small pelvic space following intra-arterial chemotherapy. At 5-year follow-up, the bladder was preserved in 76% of patients and 65% were free of disease. The disease-specific survival rate was 91%. Patients with large and multiple tumors were more at risk of cancer recurrence than patients with single, small tumors. Nausea and vomiting, irritable bladder and ischialgia were the main side effects.

NCCN guidelines do not address the use of PBT for treating bladder cancer. (2020)

Brain and Spinal Cord Tumors

Petr et al. (2018) assessed structural and hemodynamic changes of healthy brain tissue in the cerebral hemisphere contralateral to the tumor following conventional (photon) and proton radiation with concurrent chemotherapy. Sixty seven adult patients diagnosed with glioblastoma undergoing adjuvant conventional (n=47) or proton (n=19) radiotherapy with temozolomide after tumor resection underwent T1-weighted and arterial spin labeling magnetic resonance imaging. Changes in volume and perfusion before and 3-6 months after were compared between therapies. A decrease in gray matter (GM) and white matter (WM) volume was observed in patients receiving conventional radiation compared to the pre-RT baseline. In contrast, for the proton therapy group, no significant differences in GM or WM volume were observed. GM volume decreased with 0.9% per 10 Gy dose increase and differed between the radiation modalities. Perfusion decreased in conventional radiation therapy patients, whereas the decrease in proton therapy patients was not statistically significant. There was no correlation between perfusion decrease and either dose or radiation modality. The authors concluded that proton therapy may reduce brain volume loss compared to photon therapy, with decrease in perfusion being comparable for both modalities. As this was an uncontrolled retrospective study with a surrogate end-point (brain volume loss on imaging), prospective randomized trials are needed to compare the effect of proton and conventional radiotherapy on imaging and clinical outcomes.

Kabolizadeh et al. (2017) conducted a single-center, retrospective, case series to evaluate local control (LC), overall survival (OS), disease-specific survival, and distant failure in 40 patients with unresected chordoma and treated with photon/proton radiation therapy. Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). To characterize tumor response the soft tissue and bone compartments of the tumor were defined separately as the soft tissue target volume, bone target volume and combined total target volume. Twenty-seven patients had sacrococcygeal chordoma, and the remaining patients had mobile spine tumors, which included 9 cervical, 1 thoracic, and 3 lumbar. Thirty-nine patients underwent proton therapy only or predominantly proton therapy mixed with photons to limit the radiation dose to adjacent critical normal structures. Only 4 patients received either concurrent or neoadjuvant systemic treatments. The median age was 67 years (range, 36-94 years) and median follow-up, after completion of radiation therapy, was 50.3 months (range, 2-216.4 months). At 5-years, LC, OS, disease-specific survival, and distant failure were 85.4%, 81.9%, 89.4%, and 20.2%, respectively. Nineteen patients had complete sets of regular imaging scans (a total of 84 CT and MRI scans were reviewed) and of those, only 4 local failures had occurred at 34, 46, 78 and 82 months after treatment. The authors concluded that their results support the use of high-dose definitive radiation therapy in select patients with unresected spine and sacral chordomas, and that soft tissue target volume is the best indicator of tumor response. Limitations of this study include its design, the small number of patients with local failure and limited follow-up periods.

Indelicato et al. (2016) conducted descriptive analysis using data from a single-institution. In this prospective case series study, researchers sought to evaluate the effectiveness of definitive or adjuvant external beam proton therapy in patients with chordomas and chondrosarcomas of the spine. Outcomes of interest included distant metastases (DM), overall survival (OS), cause-specific survival, local control (LC) and disease-free survival (DFS). A total of 51 patients participated with a median age of 58 years (range, 22-83 years) and median follow-up of 3.7 years (range, 0.3-7.7 years). There were 34 patients with chordomas, and 17 patients with chondrosarcomas, which were all grade 2 or higher. The anatomic distribution was as follows: sacrum (n=21), cervical spine (n=20), and thoracolumbar spine (n=10). The median dose of radiation therapy was 70.2 Gy (range, 64.2-75.6 Gy). The 4-year LC, freedom from distant metastases, DFS, cause-specific survival, and OS rates were 58%, 86%, 57%, 72%, and 72%, respectively. A total of 25 patients experienced disease recurrence: 18 local recurrences, 6 local and distant recurrences, and 1 DM. In patients with a local relapse, the median time to progression was 1.7 years (range, 0.2-6 years). The median survival after local progression was 1.7 years (range, 0.1-4.9+ years). Regression analysis results showed that younger patients had a significantly higher risk for local reoccurrence and that patients whose initial management was only surgery also had a higher rate of reoccurrence however, these patients may represent a high-risk subset. The authors concluded that high-dose proton therapy controls more than half of spinal chordomas and chondrosarcomas and compares favorably with historic photon data. Local progression is the dominant mode of treatment failure and it may be reduced by treating patients at the time of initial diagnosis. Limitations of this study include its design, small sample size and small number of select events, which may have impacted the statistical validity of the regression analysis results.

Noel et al. (2002) conducted a retrospective review of 17 patients with meningioma to evaluate the efficacy and the tolerance of an escalated dose of external conformal fractionated RT combining photons and protons. Five patients presented a histologically atypical or malignant meningioma, 12 patients had a benign tumor that was recurrent or rapidly progressive. In 2 cases, RT was administered in the initial course of the disease and in 15 cases at the time of relapse. A highly conformal approach was used combining high-energy photons and protons for approximately 2/3 and 1/3 of the total dose. The median total dose delivered within gross tumor volume was 61 CGE (25-69). Median follow-up was 37 months (17-60). The 4-year LC and OS rates were 87.5 +/- 12% and 88.9 +/- 11%, respectively. Radiologically, there were 11 stable diseases and 5 partial responses. The authors concluded that in both benign and more aggressive meningiomas, the combination of conformal photons and protons with a dose escalated by 10-15% offers clinical improvements in most patients as well as radiological long-term stabilization. Limitations of this study include small sample size and study design.

NCCN guidelines for CNS cancers states that when toxicity is a concern during management of spinal ependymoma or medulloblastoma in adults, PBRT should be considered if available. (2020)

Several clinical trials studying PBT in patients with various types of brain tumors are active or recruiting. For more information, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Breast Cancer

DeCesaris (2019) conducted single-institution, retrospective cohort analysis to evaluate acute skin toxicity, i.e., radiation dermatitis (RD) or skin hyperpigmentation (SH) in patients with primary invasive breast cancer who underwent radiation therapy with either photon or proton radiation therapy. Skin toxicity was recorded using Common Terminology Criteria for Adverse

Events version 4.0 criteria and scored by treating physicians on a weekly basis. For each patient, the highest recorded grades of RD and SH were analyzed. A total of 86 patients received treatment with a median age of 53 years (range, 245 – 78 years) and median RT dose of 60 Gy (range, 45 – 70 Gy). Of those, 47 (55%) received photon beam therapy and 39 (45%) received proton beam therapy. Patients treated with proton beam radiation therapy had a statistically significant higher rate of grade ≥ 2 RD compared with patients who were treated with photon radiation therapy (69.2% vs. 29.8%, $p < 0.001$). There was no difference in the rates of grade 3 RD or SH between the modalities. The authors concluded that women who will be undergoing proton beam radiation therapy should receive counseling regarding its potential for grade ≥ 2 skin toxicities. Limitations of this study include its design, use of subjective assessments, and that during treatment optically stimulated luminescent dosimeters were not used to measure patients' radiation exposure.

Verma et al. (2017) conducted a single-institution retrospective cohort study to evaluate acute toxicity in patients with locally advanced breast cancer and receiving comprehensive regional nodal irradiation (CRNI) with adjuvant PBT from 2011–2016. PBT targeting the intact breast/chest wall and CRNI including the axilla, supraclavicular fossa, and internal mammary lymph nodes consisted of a 3-dimensional uniform scanning technique. In 2016, the institution transitioned to a pencil beam scanning (PBS) technique. The change in technique was driven by anticipated dosimetric advantages including decreased dose to the skin surface and to cardiopulmonary organs, and shorter planning and treatment delivery time. Toxicities were assessed weekly during treatment, one month following treatment completion, and then, every 6 months. A total of 91 patients were treated with a median follow-up period of 15.5 months. The most common toxicities were dermatitis and/or skin infections, but esophagitis and fatigue were also observed. Acute dermatitis of grades 1, 2, and 3 occurred in 23%, 72%, and 5%, respectively. Eight percent ($n=7$) required treatment breaks due to dermatitis and the median time to resolution of acute skin toxicity was 32 days. Grades 1, 2, and 3 esophagitis developed in 31%, 33%, and 0%, respectively. The authors concluded that PBT for breast cancer as part of CRNI appears to have toxicity rates comparable to prior published studies e.g., Cuaron et al. (2015) reported 71.4% of those who received PBT developed grade 2 dermatitis however, Bradley et al. (2016) reported 100% developed grade 2 dermatitis. While the use of PBT with CRNI may have dosimetric advantages, particularly to the heart and other organs at risk, toxicities observed with its use demonstrates the need for randomized controlled trials comparing PBT to other radiation modalities.

Verma et al. (2016a) performed a systematic review of clinical outcomes and toxicity of PBT for treating breast cancer. Nine original studies were analyzed, however the types of studies and the volume of patients in those studies were not specifically cited by the authors. Conventionally fractionated breast/chest wall PBT produced grade 1 dermatitis rates of approximately 25% and grade 2 dermatitis in 71%-75%. This is comparable or improved over the published rates for photons. The incidence of esophagitis was decreased if the target coverage was compromised in the medial supraclavicular volume, a finding that echoes previous results with photon RT. From the limited available data, the rate of grade 2 esophagitis ranged from 12% to 29%. Using PBT-based accelerated partial breast irradiation (PBI), the rates of seroma/hematoma and fat necrosis were comparable to those reported in the existing data. Radiation pneumonitis (RP) and rib fractures remain rare. PBT offers the potential to minimize the risk of cardiac events, keeping the mean heart dose at ≤ 1 Gy. However, definitive clinical experiences remain sparse. Results from clinical trials in progress, comparing protons to photons, will further aid in providing conclusions. Limitations to this review included a general lack of data and low number of participants in the available studies.

Bradley et al. (2016) conducted a prospective case series study to evaluate the clinical feasibility and potential benefits of PBT in breast cancer patients who were at risk for regional nodal disease. In this pilot study, the primary endpoint was cardiac V5, testing the hypothesis that PBT could reduce the volume of the heart receiving 5 Gy by $\geq 50\%$ when compared to CRT. The secondary endpoints included acute toxicity and other dosimetric parameters of target coverage and exposure to at-risk organs. PBT and CRT plans, targeting the regional nodes, were created for each patient. Patients were evaluated weekly while on RT, 4 weeks after RT was completed and at 6-month intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 18 women enrolled with a median age of 51.8 years (range, 42–73 years) and a median follow-up period of 20 months (range, 2–31 months). Ten of the women received only PBT and 8 received combination therapy of PBT and photon beam RT. All patients had improved heart and lung dose with PBT. The primary endpoint, which was to determine if PBT could reduce cardiac V5 by $\geq 50\%$, was achieved. Of the nine patients with left-sided breast cancer, the median cardiac dose decreased from 5.9 Gy with CRT to 0.6 Gy with PBT ($p=0.004$). In patients with right-sided breast cancer, the median cardiac dose decreased from 2.9 Gy with CRT to 0.5 Gy with PBT ($p=0.004$). No patients developed grade 4+ toxicities. Four (22%) patients developed grade 3 dermatitis and of these, 3 were treated with PBT and 1 was treated with combination PBT and CRT. All of the patients developed grade 2 dermatitis, which resolved within 1 month of the completion of therapy. However, 1 patient developed cellulitis and required a course of antibiotics. Additional acute grade 2 toxicities included: fatigue ($n=6$), esophagitis ($n=5$), nausea ($n=1$) and dyspnea ($n=1$). The authors acknowledged

that their rate of patients with grade 3 acute skin toxicity was not unexpected given the higher skin dose with PBT and concluded that PBT for regional node irradiation after mastectomy or breast conserving surgery offers a lower cardiac dose particularly for patients with left-sided breast cancer and without grade 4+ toxicities. Limitations of this study include its design, small sample size and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT. (DeCesaris 2019)

Cuaron et al. (2015) conducted a single-institution case series study to report dosimetry and early toxicity data in patients with breast cancer. Retrospectively collected data from consecutive patients diagnosed with non-metastatic breast cancer, no prior history of chest wall radiation and treated with PBT postoperatively were studied. Patients with unfavorable cardiopulmonary anatomy were usually referred to this institution. Post-lumpectomy patients with large breast size were not offered treatment due to a higher propensity for day-to-day measurement differences in the target position. Patients were evaluated weekly while on RT, 4 weeks after RT was completed, and at 12–24 week intervals thereafter. Toxicity was recorded using the Common Terminology Criteria for Adverse Events (CTCAE, v4.0). A total of 30 women were included in the study with a median age of 49 years (range, 29–86 years), cancer staging was as follows: 8 had stage II, 20 had stage III and 2 had chest wall recurrence. The median follow-up was 9.3 months (range, 2.3–18.6 months). With PBT, full coverage of the planned target volume was achieved, and it significantly spared the heart, lungs and contralateral breast. Of those with greater than 3 months of follow-up (n=28), 71.4% developed grade 2 dermatitis and of those, 28.6% experienced moist desquamation. Eight (28.6%) developed grade 2 esophagitis and 1 developed grade 3 reconstructive complications. The authors concluded that in this series of 30 patients, PBT achieved excellent coverage of the target volume while sparing the heart, lungs, and contralateral breast, that the treatment was well tolerated, and that additional studies assessing long-term outcomes and toxicity are needed. Limitations of this study include its design, exclusion of women with large breast size, and higher toxicity rates compared with other forms of RT, e.g., intensity modulated RT. (DeCesaris 2019)

Bush et al. (2014) performed a single center study of 100 subjects who received postoperative PBI using PBT after undergoing partial mastectomy with negative margins and axillary lymph nodes. After following these individuals for an average of 5 years, the researchers concluded that ipsilateral recurrence-free survival with minimal toxicity was excellent. While the authors acknowledged that cosmetic results may be improved with PBT over those reported with photon-based techniques, there was nothing in the study demonstrating that PBT outcomes were superior to the current standard of care.

NCCN guidelines do not address the use of PBT for treating breast cancer. (2020)

To further elucidate the clinical advantages and disadvantages between PBT and other types of radiation therapy used in breast cancer, additional clinical trials are underway, NCT02603341, NCT01245712, and NCT03391388, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Choroidal Hemangiomas

Hocht et al. (2006) conducted a single-center, retrospective study of 44 consecutive patients with choroid hemangiomas treated with photon therapy (n=19) or proton therapy (n=25). Outcomes were measured by visual acuity, tumor thickness, resolution of retinal detachment, and post-treatment complications. Mean follow-up was 38.9 months and 26.3 months, and median follow-up was 29 months and 23.7 months for photon and proton patients, respectively. Tumor thickness was greater in the photon group than in the proton group. In the collective groups, 91% were treated successfully, and there was no significant difference in the outcomes between the 2 groups. The authors concluded that RT is effective in treating choroidal hemangiomas with respect to visual acuity and tumor thickness, but a benefit of proton versus photon therapy could not be detected.

Three additional studies showed some improvement in tumor regression and visual acuity following PBT; however, these studies were small and retrospective in nature. (Chan et al., 2010; Levy-Gabriel et al., 2009; Frau et al., 2004)

Gastrointestinal (GI) Cancers

Verma et al. (2016b) conducted a systematic review to identify studies on PBT and gastrointestinal malignancies. The search included PubMed, EMBASE, and abstracts from meetings of the American Society for Radiation Oncology, Particle Therapy Co-Operative Group, and American Society of Clinical Oncology. A total of 39 original investigations were analyzed. For esophageal cancer, 12 studies were analyzed and several of those reported that PBT resulted in a significant dose reduction to intrathoracic OARs and is associated with reduced toxicity, postoperative complications while achieving comparable local control and overall survival. However, for some of the studies, contemporaneous comparison groups were lacking or comparisons were made between PBT and x-ray radiotherapy (XRT), which consisted of either 3D-CRT or IMRT rather than

IMRT only. For pancreatic cancer, 5 studies were analyzed. Survival for resected/unresected cases was similar to existing data where IMRT was used and nausea/emetesis were numerically lower than what had been reported among patients who received IMRT however, direct head-to-head comparisons were not made. For hepatocellular carcinoma, 10 studies were analyzed and these had the strongest evidence to support use of PBT. Those studies reported very low toxicities, and a phase III trial comparing PBT to transarterial chemoembolization (TACE) showed a trend toward better LC and PFS with PBT. For cholangiocarcinoma, liver metastases, and retroperitoneal sarcoma, survival and toxicity data is comparable to historical photon controls, and stomach and biliary system/gallbladder cancer studies consisted of case reports and small cohort experiences. The authors concluded that PBT offers the potential of lower toxicities without compromising survival or local control. However, there was limited high quality evidence for select gastrointestinal malignancies and that multi-institution, randomized controlled trials are needed.

NCCN guidelines do not address PBT in the treatment of gastric cancers. (2020)

Esophageal Cancer

Xi et al. (2017) conducted a single-center retrospective cohort study to evaluate outcomes of patients diagnosed with esophageal cancer (EC) and treated with PBT or IMRT. Outcomes included treatment-related toxicity, OS, PFS, locoregional failure-free survival (LRFSS) and distant metastasis-free survival (DMFS). Patients were followed every three months for the first year after radiation therapy, every 6 months for the following 2 years and then yearly until 5 years. A total of 343 patients were included and of those, 211 received IMRT and 132 received PBT. The median follow-up period for the IMRT group was 65.1 months (range, 19.4-115.3) and for the PBT group was 44.8 months (range, 11.9 – 110.3 months). The median radiation dose was 50.4 Gy in both the IMRT and PBT groups (ranges, 41.4-66.0 Gy and 45.0-63.0 Gy, respectively). There was no difference in treatment-related toxicities between the groups. The PBT group had better OS ($p=.011$), PFS ($p=.001$), and DMFS ($p=.031$) compared with the IMRT group. In subset analyses, patients with stage I/II disease had no differences in survival. In patients with stage III disease, those who received PBT had higher rates of OS (34.6% vs. 25.0%, $p=.038$) and PFS (33.5% vs. 13.2%, $p=.005$). The authors concluded that PBT was associated with improved OS, PFS and LRFSS, particularly in EC patients with advanced disease and that their results may suggest a benefit of PBT over IMRT. Limitations of this study include its design, that the type of radiation therapy each patient received was based on the multidisciplinary team and the patients' intent rather than randomization, there were differences in patient demographics and baseline characteristics between the groups, and that for some patients, accurate long term documentation was lacking. Prospective, randomized controlled studies are needed to clarify the role of PBT in EC.

Lin et al. (2017) conducted a multi-center retrospective cohort study of patients diagnosed with EC and treated with neoadjuvant chemoradiation. The purpose of this study was to assess the association between RT modality and postoperative outcomes. The outcomes included pulmonary, cardiac and wound complications, and length of stay (LOS), readmission and mortality. A total of 580 EC patients were included and of these, 214 (37%) received 3D-CRT, 255 (44%) received IMRT and 111 (19%) receive PBT. IMRT and PBT were associated with a reduced risk of pulmonary complications compared with 3D-CRT ($p=.001$), and PBT was trending toward being better than IMRT (OR 0.584, $p=.077$). Both IMRT and PBT were associated with a reduced risk of cardiac complications as were older age and history of coronary artery bypass grafting or atrial fibrillation. PBT was associated with a reduced risk of wound complications (OR 0.255, $p=0.006$, PBT vs. 3D-CRT; OR 0.276, $p=0.009$, PBT vs. IMRT) yet there was no difference between IMRT and 3D-CRT. Mean LOS was significantly associated with RT modality (13.2 days for 3D-CRT, 11.6 days for IMRT and 9.3 days for PBT ($p<0.0001$). There was no difference in 60-day readmission rates or deaths during the same hospitalization, or 30, 60 or 90-day postoperative mortality. The authors concluded that IMRT and PBT were associated with significantly reduced rates of postoperative complications compared to 3D-CRT, that these results may show an advantage of PBT over IMRT however, prospective randomized clinical trials will better establish the role of PBT in EC.

In a retrospective analysis, Wang et al. (2013a) reported that advanced radiation technologies such as IMRT or PBT significantly reduced postoperative pulmonary and GI complication rates compared to 3D-CRT in esophageal cancer patients. These results need to be confirmed in prospective studies.

Mizumoto et al. (2011) evaluated the efficacy and safety of hyperfractionated concomitant boost PBT in 19 patients with esophageal cancer. The overall 1- and 5-year actuarial survival rates for all 19 patients were 79% and 42.8%, respectively. The median survival time was 31.5 months. Of the 19 patients, 17 (89%) showed a complete response within 4 months after completing treatment and 2 (11%) showed a partial response, giving a response rate of 100% (19/19). The 1- and 5-year LC rates for all 19 patients were 93.8% and 84.4%, respectively. The results suggest that hyperfractionated PBT is safe and

effective for patients with esophageal cancer. Further studies are needed to establish the appropriate role and treatment schedule for use of PBT for esophageal cancer.

Mizumoto et al. (2010) evaluated the efficacy and safety of PBT for locoregionally advanced esophageal cancer. Fifty-one patients were treated using PBT with or without X-rays. All but one had squamous cell carcinoma. Of the 51 patients, 33 received combinations of X-rays and protons as a boost. The other 18 patients received PBT alone. The overall 5-year actuarial survival rate for the 51 patients was 21.1% and the median survival time was 20.5 months. Of the 51 patients, 40 (78%) showed a complete response within 4 months after completing treatment and seven (14%) showed a partial response, giving a response rate of 92% (47/51). The 5-year LC rate for all 51 patients was 38% and the median LC time was 25.5 months. The authors concluded that these results suggest that PBT is an effective treatment for patients with locally advanced esophageal cancer. Further studies are required to determine the optimal total dose, fractionation schedules and best combination of proton therapy with chemotherapy.

NCCN guidelines state that PBT is appropriate when treating esophageal and esophagogastric junction cancers in settings where dose reduction to organs at risk is necessary and cannot be achieved by 3D-CRT. Because data is early and evolving, patients should receive PBT within a clinical trial. (2020)

Gynecologic Cancers

The efficacy of PBT combined with photon radiation for the treatment of cervical cancer was investigated in a prospective uncontrolled study involving 25 patients (Kagei et al., 2003). In this study, 5-year and 10-year survival rates were similar to conventional therapies as reported in the literature. The 10-year survival rate was higher for patients with low stage (89%) compared with advanced stages (40%) of cervical cancer. The treatment caused severe late complications in 4% of patients.

NCCN guidelines do not address the use of PBT when treating any type of gynecologic cancer (i.e., Cervical Cancer (2021), Ovarian Cancer (2020), Uterine Neoplasms (2021) or Vulvar Cancer (2021)).

Several clinical trials are recruiting or in progress studying the use of PBT in multiple types of gynecologic cancer (e.g., cervical, ovarian, and uterine). For more information, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Head and Neck Cancers (HNC) not listed in the coverage rationale as proven

A 2019 Hayes report, Proton Beam Therapy for Treatment of Head and Neck Cancer, assessed multiple clinical studies evaluating the efficacy and safety of PBT in patients with HNC. The majority of the evidence included retrospective studies, data analyses, and systematic reviews. They noted there was some overlap of investigators and, possibly, overlap of patient groups as well. The report concludes that the study abstracts present conflicting findings regarding the use of PBT for treatment of HNC.

Seeking to improve LC rate and reduce late AEs, Takayama et al. (2016) evaluated therapeutic results and toxicities of PBT combined with selective intra-arterial infusion chemotherapy (PBT-IACT) in patients with stage III-IVB squamous cell carcinoma of the tongue. Between February 2009 and September 2012, 33 patients were enrolled. After 2 systemic chemotherapy courses and whole-neck irradiation (36 Gy in 20 fractions), participants were administered concurrent chemoradiotherapy comprising PBT for the primary tumor and the metastatic neck lymph node with weekly retrograde IACT of cisplatin with sodium thiosulfate by continuous infusion. The median follow-up duration was 43 months. The 3-year OS, PFS, LC rate, and regional control rate for the neck were 87%, 74.1%, 86.6%, and 83.9%, respectively. Major acute toxicities > grade 3 included mucositis in 26 cases (79%), neutropenia in 17 cases (51%), and dermatitis in 11 cases (33%). Late grade 2 osteoradionecrosis was observed in 1 case (3%). The authors concluded that PBT-IACT for stage III-IVB tongue cancer has an acceptable toxicity profile and showed good treatment results, and that this protocol should be considered as a treatment option for locally advanced tongue cancer. This study is limited by the lack of data comparing toxicity to conventional radiation therapy.

NCCN's HNCs guideline makes no mention of proton beam radiation therapy for cancer of the lip (mucosa), oral cavity, hypopharynx or glottic larynx. The guideline states that use of proton therapy is an active area of investigation, and that proton therapy may be considered when normal tissue constraints cannot be met by photon-based therapy in cancers of the oropharynx, nasopharynx, supraglottic larynx, paranasal/ethmoid sinus, maxillary sinus and salivary glands, as well as mucosal melanoma and other primary tumors of the head and neck. (2021)

Clinical Practice Guidelines

American College of Radiology (ACR)/ American Society for Radiation Oncology (ASTRO)

Regarding head and neck tumors, the ACR/ASTRO practice parameter states that PBRT reduces the dose delivered to critical normal structures in the head and neck region that may impact QOL, including optic nerves, optic chiasm, pituitary gland, brain, brainstem, spinal cord, salivary glands, pharyngeal constrictor muscles, oral cavity, and the emetogenic sites in the posterior fossa. (2018)

American Society for Radiation Oncology (ASTRO)

ASTRO's model policy supports the use of PBT in the treatment of malignant and benign primary CNS tumors, advanced (e.g., T4) and/or unresectable head and neck cancers, and cancers of the paranasal sinuses and other accessory sinuses. (2017) (Accessed February 17, 2021)

Lung Cancer

A Hayes report (2020) concluded that the best available studies of PBT for NSCLC do not provide sufficient evidence that PBT is safer or consistently more effective than CRT and IMRT in the treatment of NSCLC.

Liao et al. (2018) conducted a single-center randomized trial that compared outcomes of passive scattering proton therapy (PSPT) versus IMRT, both with concurrent chemotherapy, for inoperable non-small-cell lung cancer (NSCLC). The primary end point was the first occurrence of severe (grade ≥ 3) radiation pneumonitis (RP) or local failure (LF). Eligible patients had stage IIB to IIIB NSCLC (or stage IV NSCLC with a single brain metastasis or recurrent lung or mediastinal disease after surgery) and were candidates for concurrent chemoradiation therapy. Pairs of treatment plans for IMRT and PSPT were created for each patient. Patients were eligible for random assignment only if both plans satisfied the same prespecified dose-volume constraints for at-risk organs at the same tumor dose. Compared with IMRT (n=92), PSPT (n=57) exposed less lung tissue to doses of 5 to 10 Gy(RBE), which is the absorbed Gy dose multiplied by the relative biologic effectiveness (RBE) factor for protons; exposed more lung tissue to ≥ 20 Gy(RBE), but exposed less heart tissue at all dose levels between 5 and 80 Gy (RBE). The grade ≥ 3 RP was greater for PSPT than IMRT (6.5% for IMRT and 10.5% for PSPT) though the difference did not reach statistical significance; there was no difference observed in LF (10.9% and 10.5% for IMRT and PSPT, respectively). Exploratory analysis showed that the RP and LF rates at 12 months for patients enrolled before versus after the trial midpoint were 21.1% (before) versus 18.2% (after) for the IMRT group and 31.0% (before) versus 13.1% (after) for the PSPT group suggesting that that outcomes for proton therapy improved over the course of the trial as the investigators gained experience. The authors stated that findings from 2 ongoing trials (NCT01993810 and NCT01629498) will provide additional evidence of the efficacy of proton and photon therapies.

Chang et al. (2017) reported 5-year results of a prospective phase II single-institution study evaluating chemotherapy with concurrent high dose PBT in 64 patients with unresectable phase III NSCLC. 5-year OS, PFS, actuarial distant metastases and locoregional recurrence were 29%, 22%, 54%, and 28%, respectively. Acute and late toxic effects with PBT (compared to historical studies with 3D-CRT and/or IMRT) with chemotherapy were very promising. The authors concluded that the study demonstrated that concurrent PBT and chemotherapy was safe and effective in the long term, and that further prospective studies are warranted.

Chi et al. (2017) conducted a systematic review and meta-analysis to assess hypo-fractionated PBT's efficacy relative to that of photon SBRT for early stage NSCLC. Seventy two SBRT studies and 9 hypo-fractionated PBT studies (mostly single-arm) were included. PBT was associated with improved OS and PFS in the univariate meta-analysis. The OS benefit did not reach its statistical significance after inclusion of operability into the final multivariate meta-analysis, while the 3-year LC still favored PBT. Researchers concluded that although hypo-fractionated PBT may lead to additional clinical benefit when compared with photon SBRT, no statistically significant survival benefit from PBT over photon SBRT was observed in the treatment of early stage NSCLC.

Harada et al. (2016) conducted a single-institutional, open label, dose escalation phase I trial to determine the recommended dose of PBT for inoperable stage III NSCLC. Two prescribed doses of PBT were tested: 66 Gy RBE in 33 fractions and 74 Gy RBE in 37 fractions in arms 1 and 2, respectively. The planning target volume included the primary tumor and metastatic lymph nodes with adequate margins. Concurrent chemotherapy included intravenous cisplatin (60 mg/m²), day 1) and oral S-1 (80, 100 or 120 mg based on body surface area, days 1-14), repeated as 4 cycles every 4 weeks. Dose-limiting toxicity (DLT) was

defined as grade 3 (severe) toxicities related to PBT during days 1-90. Each dose level was performed in 3 patients, and then escalated to the next level if no DLT occurred. When 1 patient developed a DLT, 3 additional patients were enrolled. Overall, 9 patients were enrolled, including 6 in Arm 1 and 3 in Arm 2. The median follow-up time was 43 months, and the median PFS was 15 months. In Arm 1, grade 3 infection occurred in 1 of 6 patients, but no other DLT was reported. Similarly, no DLT occurred in Arm 2. However, one patient in Arm 2 developed grade 3 esophageal fistula at 9 months after the initiation of PBT. From a clinical perspective, the authors concluded that 66 Gy RBE is the recommended dose.

Oshiro et al. (2014) initiated a phase II study to evaluate the safety and efficacy of high-dose PBT with concurrent chemotherapy for unresectable or medically inoperable advanced NSCLC. Patients (n=15) were treated with PBT and chemotherapy with monthly cisplatin (on Day 1) and vinorelbine (on Days 1 and 8). The treatment doses were 74 Gy RBE for the primary site and 66 Gy RBE for the lymph nodes without elective lymph nodes. The median follow-up period was 21.7 months. None of the patients experienced Grade 4 or 5 non-hematologic toxicities. Acute pneumonitis was observed in 3 patients (Grade 1 in one, and Grade 3 in two), but Grade 3 pneumonitis was considered to be non-proton-related. Grade 3 acute esophagitis and dermatitis were observed in 1 and 2 patients, respectively. Severe (\geq Grade 3) leukocytopenia, neutropenia and thrombocytopenia were observed in 10, 7, and 1 patients, respectively. Late RP (grades 2 and 3) was observed in one patient each. Six patients (40%) experienced local recurrence at the primary site and were treated with 74 Gy RBE. Disease progression was observed in 11 patients, with the mean survival time being 26.7 months. The authors cited short follow up period as a limitation to this study. They concluded that high-dose PBT with concurrent chemotherapy is safe and useful in the multimodality therapy for unresectable NSCLC.

Sejpal et al. (2011) conducted a single-center, retrospective case series study to evaluate the use of PBT plus concurrent chemotherapy in patients with SNCLC. Outcomes included acute and subacute toxicity and were evaluated using Common Terminology Criteria (version 3.0) at least weekly during treatment, at 4-6 weeks after treatment, every 3 months for 2 years and then, every 6 months. Survival, time to progression and failure patterns were also collected. Comparisons between other radiation treatment modalities (IMRT and 3D-CRT, each with concurrent chemotherapy) were made using historical controls from the same center. A total of 202 patients were included in the analysis: 74 received 3D-CRT, 66 IMRT and 62 PBT. Median follow-up periods were 17.9 months (3D-CRT), 17.4 months (IMRT) and 15.2 months (proton). Median total radiation dose was higher in the PBT group at 74 Gy versus 63 Gy for the other groups. Despite the higher radiation dose in the PBT group, rates of severe (grade \geq 3) pneumonitis and esophagitis were lower (2% and 5%, respectively) compared with the other groups (3D-CRT, 30% and 18%; IMRT, 9% and 44%, respectively). Due to the short follow-up periods, tumor control and survival were not reported. The authors concluded that in this early and promising study, higher doses of PBT could be delivered to lung tumors with a lower risk of esophagitis and pneumonitis, and that additional clinical trials may further clarify the benefits and risks of PBT in patients diagnosed with SNCLC.

Pijls-Johannesma et al. (2010) conducted a systematic review to test the theory that RT with beams of protons and heavier charged particles (e.g., carbon ions) leads to superior results, compared with photon beams. The authors searched for clinical evidence to justify implementation of particle therapy as standard treatment in lung cancer. Eleven studies, all dealing with NSCLC, mainly stage I, were identified. No phase III trials were found. For PBT, 2- to 5-year LC rates varied in the range of 57%-87%. The 2- and 5-year OS and 2- and 5-year cause-specific survival rates were 31%-74% and 23% and 58%-86% and 46%, respectively. RP was observed in about 10% of patients. For CIT, the overall LC rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and cause-specific survival rates were 42% and 60%, respectively. Slightly better results (at 50% and 76%, respectively) were reported when using hypofractionation. The results with protons and heavier charged particles are promising. However, the current lack of evidence on the clinical effectiveness of particle therapy emphasizes the need to further investigate the efficiency of particle therapy. The authors concluded that until these results are available for lung cancer, CPT should be considered experimental.

NCCN guidelines state that advanced technologies such as PBT are appropriate when needed to deliver curative RT safely when treating NSCLC (2020). NCCN is silent on the use of PBT in the treatment of small cell lung cancer. (2021)

A phase III RCT comparing photon to proton chemoradiotherapy for patients with inoperable NSCLC (NCT01993810) is in progress. For more information, go to www.clinicaltrials.gov. (Accessed February 17, 2021)

Clinical Practice Guidelines

American College of Radiology (ACR)

ACR appropriateness criteria addressing nonsurgical treatment for locally advanced NSCLC states that while PBT may have the potential to spare critical normal tissues, more prospective studies are needed. (Chang, et al., 2014)

Lymphomas

Multiple small, lower quality studies have been published on the management of lymphomas with PBT, particularly focused on long term radiation toxicity (König et al., 2019; Horn et al., 2016; Sachsman et al., 2015; Hoppe et al., 2012). Early outcomes are encouraging, but larger prospective studies are needed to confirm long term efficacy.

NCCN guidelines for Hodgkin, B-cell, and T-cell lymphomas state that PBT may be appropriate, depending on clinical circumstances. It also states that advanced RT technologies, such as PBT, may offer significant and clinically relevant advantages in specific instances to spare important organs at risk and decrease the risk for late, normal tissue damage while still achieving the primary goal of LC. NCCN is silent on the use of PBT in the treatment of primary cutaneous lymphoma. (2020-2021)

Pancreatic Cancer

There is a lack of robust clinical evidence evaluating PBT for treating pancreatic cancer although research continues (Kim et al., 2018, Hong et al., 2014; Terashima et al., 2012; Hong et al., 2011). Further larger scaled prospective studies are warranted to determine the long-term safety and efficacy of this treatment modality.

NCCN guidelines do not address PBT in the treatment of pancreatic adenocarcinoma. (2021)

Numerous clinical trials are currently in progress studying the use of PBT in multiple types of GI cancer (e.g., esophageal, pancreatic, and retroperitoneal sarcoma). For more information, go to www.clinicaltrials.gov. (Accessed February 16, 2021)

Vestibular Tumors

In a critical review, Murphy and Suh (2011) summarized the radiotherapeutic options for treating vestibular schwannomas, including single-session stereotactic radiosurgery, fractionated conventional RT, fractionated stereotactic RT and PBT. The comparisons of the various modalities have been based on single-institution experiences, which have shown excellent tumor control rates of 91-100%. Early experience using PBT for treating vestibular schwannomas demonstrated LC rates of 84-100% but disappointing hearing preservation rates of 33-42%. The authors report that mixed data regarding the ideal hearing preservation therapy, inherent biases in patient selection and differences in outcome analysis have made comparison across radiotherapeutic modalities difficult.

The efficacy of PBT for the treatment of tumors of the vestibular system was assessed in 2 prospective uncontrolled studies involving 30 patients with acoustic neuromas (Bush et al., 2002) and 68 patients with vestibular schwannomas (Harsh et al., 2002). Fractionated PBT effectively controlled tumor growth in all patients with acoustic neuroma, and 37.5% of patients experienced tumor regression. Hearing was preserved in 31% of patients. The actuarial 5-year tumor control rate for patients with vestibular schwannomas was 84%; 54.7% of tumors regressed, 39.1% remained unchanged, and 3 tumors enlarged. The procedure caused some serious side effects in patients with vestibular schwannoma (severe facial weakness), but most side effects were either transient or could be successfully treated.

Combined Therapies

No evidence was identified in the clinical literature supporting the combined use of PBT and IMRT in a single treatment plan.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Radiation therapy is a procedure and, therefore, is not subject to FDA regulation. However, the accelerators and other equipment used to generate and deliver PBRT are regulated by the FDA. See the following website for more information (use product code LHN): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>. (Accessed February 17, 2021)

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Policy History/Revision Information

Date	Summary of Changes
11/01/2021	<ul style="list-style-type: none"> New Clinical Policy

Instructions for Use

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual[®] criteria, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.