CLINICAL GUIDELINES

Radiation Therapy

V1.0.2018

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Clinical guidelines for medical necessity review of radiation therapy services.

Please note the following:

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Dear Provider,

This document provides detailed descriptions of eviCore's basic criteria (also known as clinical guidelines) for radiation therapy arranged by diagnosis. They have been carefully researched and are continually updated in order to be consistent with the most current evidence-based guidelines and recommendations for the provision of radiation therapy from national medical societies and evidence-based medicine research centers. In addition, the criteria are supplemented by information published in peer-reviewed literature.

Our health plan clients review the development and application of these criteria. Every eviCore health plan client develops a unique list of CPT codes or diagnoses that are part of their radiation therapy utilization management programs. Health Plan medical policy supersedes the eviCore criteria when there is conflict with the eviCore criteria and the health plan medical policy. If you are unsure of whether or not a specific health plan has made modifications to these basic criteria in their medical policy for Radiation Therapy please contact the plan or access the plan's website for additional information.

While eviCore encourages participation in clinical trials when consistent with each health plan's policies, we want to clarify our position on the use of such standard arms outside of the research setting. The use of a control arm or standard arm in a Phase III clinical trial does not necessarily mean that other standard treatment techniques are not equally effective. Examples of multiple "standard" arms can easily be found in the treatment of prostate cancer where Intensity-Modulated Radiation Therapy (IMRT), 3-Dimensional (3-D), low dose implant or High Dose Rate (HDR) can be equally effective or breast cancer where standard whole breast fractionation or hypo-fractionation can be used. Indeed, national criteria such as National Comprehensive Cancer Network

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(NCCN) and American College of Radiology (ACR) Appropriateness Criteria often suggest more than one radiation technique.

It is eviCore's process to apply evidence-based criteria to the particular clinical characteristics in evaluating a case, and to certify the most appropriate regimen/modality. This regimen/modality may match one that is used as a "standard arm" in a federally funded clinical trial, or it may be one that is considered an "alternate standard". The alternate standard will be one supported by nationally published guidelines such as the NCCN, ACR Appropriateness Guidelines, or American Society for Radiation Oncology (ASTRO) Evidence-Based Guidelines, or supported by other acceptable peer-reviewed publications.

As such, eviCore will not automatically certify a case based solely on the fact that it matches the standard (control) arm of a clinical trial. This concept applies also to regimens/modalities listed by the NCCN or ACR as "acceptable" treatments for specific disease sites. Rather, we commit to working with the providing Radiation Oncologist to certify the most appropriate regimen/modality for a particular case.

eviCore healthcare works hard to make your clinical review experience a pleasant one. For that reason, we have peer reviewers available to assist you should you have specific questions about a procedure.

For your convenience, eviCore's Customer Service support is available from 7 a.m. to 7 p.m. Our toll free number is (800) 918-8924.

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Brachytherapy of the Coronary Arteries

POLICY

I. Coronary artery brachytherapy

A. Is medically necessary when used as an adjunct to percutaneous coronary intervention (PCI) for treatment of in-stent restenosis in a native coronary artery bare-metal stent or saphenous vein graft (SVG)
B. Intravascular brachytherapy (VBT) is considered medically necessary for recurrent drug-eluting stent in-stent restenosis
C. All other indications, are not covered because they are considered experimental, investigational, or unproven (EIU)

Key Clinical Points

Revascularization of obstructed arteries due to coronary artery disease (CAD) may be accomplished by PCI with balloon angioplasty, a minimally-invasive procedure in which a catheter with an inflatable balloon at the tip is inserted into the lumen of the artery and inflated, dilating the area of blockage. Coronary stents are implanted in most patients during PCI, resulting in lower rates of restenosis compared to balloon angioplasty alone. Several DES have been developed to minimize the incidence of restenosis, and represent approximately 70 to 90% of stent implantations. The choice of stent (bare metal vs. drug-eluting) depends on various factors, including lesion location and morphology, patient characteristics, and the patient's ability to adhere to the extended period of dual antiplatelet therapy required for drug-eluting stents. In-stent restenosis continues to be a significant problem with bare metal stents, and is thought to be caused by neointimal hyperplasia within the stent. Several mechanical treatments of in-stent restenosis were attempted, including balloon re-dilation, removal of in-stent hyperplasia by atherectomy, and repeated bare metal stenting. Brachytherapy was introduced as a method to treat in-stent restenosis by the delivery of gamma or beta radiotherapy via a catheter-based system. Brachytherapy affects the proliferation of smooth muscle cells that are responsible for restenosis, and may be used to treat in-stent restenosis of native coronary arteries and SVGs. The role of brachytherapy has diminished, however, and drug-eluting stents have emerged as the preferred method of treatment for in-stent restenosis. Brachytherapy may play a role in treatment of selected patients, however.

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Three brachytherapy devices received U.S. Food and Drug Administration (FDA) premarket approval (PMA). The Novoste™ Beta-Cath™ System (Novoste Corp., Norcross, GA) and the GALILEO™ Intravascular Radiotherapy System (Guidant Corp., Houston, TX) deliver beta radiation, while the Cordis Checkmate™ System (Cordis Corp., Miami, FL) delivers gamma radiation. Each operates in a similar fashion. A delivery catheter is placed in the coronary artery at the site of in-stent restenosis and a transfer device is connected to the catheter, delivering the radioactive seeds to administer radiation to the artery. After a specified period of time, the radioactive seeds are returned to the transfer device and removed. Although significant data was collected through the use of all of these devices, both the Checkmate™ and GALILEO™ systems have been discontinued by their respective manufacturers (2007) as DES are now most frequently used. The Beta-Cath™ System is now distributed by Best Vascular, Inc.

Literature Review

I. In-stent restenosis of native coronary arteries and SVGs

A. Several early multicenter trials of brachytherapy demonstrated the treatment benefits of intracoronary radiation for the treatment of in-stent restenosis:
   1. **IN**itial **H**yperplasia **I**nhibition with **B**eta **I**n-stent **T**rial [**INHIBIT**], Waksman et al. (2002)
   2. **ST**ents **A**nd **R**adiation **T**herapy [**START**], Popma et al. (2002)
   3. GAMMA-1 trial, Leon, et al. (2001)
   4. Coronary Radiation to Inhibit Proliferation Post Stenting [**SCRIPPS**], Teirstein, et al. (1997)
   5. **W**ashington **R**adiation for **I**n-**S**tent Restenosis **T**rial [**WRIST**], Ajani et al. (2002)

B. Ellis et al., for the TAXUS V ISR Investigators (2008), conducted a randomized study to evaluate two-year outcomes of treatment with a paclitaxel-eluting stent (PES) (n = 195) or brachytherapy (n = 201) in patients referred for PCI for bare metal stent in-stent restenosis. Between 9 and 24 months, ischemia-driven target lesion revascularization (TLR) tended to be required less in the PES group compared to the brachytherapy group (5.3. vs. 10.3%, p = .07). At 24 months, ischemia-driven TLR and ischemia-driven target vessel revascularization (TVR) were significantly reduced in the PES group compared to the brachytherapy group (10.1 vs. 21.6%, p = 0.003, and 18.1 vs. 27.5%, p = .03, respectively).There were no significant differences between the two groups in death, myocardial infarction, or target vessel thrombosis between 12 and 24 months, or cumulative to 24 months.

C. Holmes et al., for the SISR Investigators (2008) conducted a randomized trial to evaluate the safety and efficacy of sirolimus-eluting stents (SES) (n = 259) compared to vascular brachytherapy (VBT) (n = 125) for treatment of in-stent restenosis in a bare metal stent. At three years, survival free from TLR or TVR

was significantly improved with SES; freedom from TLR was 81.0% for SES vs. 71.6% for brachytherapy, p = 0.018; TVR was 78.2% for SES vs. 68.8% for brachytherapy, p = 0.022. Target vessel failure and major adverse cardiac events (MACE) were improved with SES but did not reach statistical significance. There was no statistically significant difference in definite or probable stent thrombosis between the two groups. Five-year follow-up of the SISR trial was published by Alli et al. in 2012. There were no differences in safety or efficacy outcomes for treatment of BMS restenosis with SES vs. VBT. There were no significant differences in survival free from TLR, TVR, or major adverse cardiac events between the two groups.

D. Drug-eluting stents were compared to beta-radiation for the treatment of in-stent restenosis in a case series conducted by Zavalloni et al. (2006). The first 68 patients (group I) were treated with brachytherapy using the Novoste Beta-Cath system. The latter 73 patients (group II) were treated with a Cypher™ sirolimus-eluting stent or a Taxus™ paclitaxel-eluting stent. Nine months following treatment, restenosis rates were 37.8% (28/74) for patients in group I and 14.9% (11/74) for patients in group II (p = .0028). A diffuse pattern of recurrence was more frequently seen after brachytherapy (20/74 vs. 6/74, p = .005). The "edge effect" following brachytherapy was associated with worse outcomes and accounted for most failures. Recurrence within the original restenotic stent was similar in both groups (12.9% vs. 14.9%, p = .8). Patients treated with drug-eluting stents for diffuse in-stent restenosis experienced more favorable clinical and angiographic outcomes compared to a similar cohort of patients treated with beta-brachytherapy.

E. The three devices described above received FDA approval for in-stent restenosis in native coronary arteries, and most published studies have focused on this indication. Brachytherapy has also been used to successfully treat in-stent restenosis in SVGs. The SVG-WRIST trial (Waksman, et al., 2002), a randomized, double-blind, placebo-controlled trial, evaluated the effect of intravascular gamma radiation in 120 patients with in-stent restenosis in saphenous vein grafts. Patients underwent balloon angioplasty, atherectomy, additional stenting or a combination of these procedures. If the intervention was successful, patients were randomly assigned in a double-blind fashion to intravascular treatment with a ribbon containing iridium-192 (n = 60) or nonradioactive seeds (n = 60). Revascularization and radiation therapy were successful in all patients. At six months, the restenosis rate was lower in the iridium-192 group (21%) than in the placebo group (44%). At 12 months, revascularization of the target lesion was lower in the iridium-192 group (17%) than in the placebo group (57%). The rate of major cardiac events at 12 months was also lower in the iridium-192 group (32%) than the placebo group (63%).

F. Rha et al. (2005) published a follow-up to the SVG-WRIST trial to determine whether the safety and efficacy of brachytherapy is durable. At 36 months,

target lesion revascularization (TLR), repeat percutaneous transluminal coronary angioplasty (PTCA) and TLR-major adverse cardiac events (MACE) remained significantly lower in the irradiated group, although TVR and TVR-MACE did not. The beneficial effect and efficacy of irradiation declined with time and manifested with late recurrences. The authors stated that saphenous vein grafts are known to degenerate over time, and when PCI is required, the clinical outcome of these patients is markedly impaired. The outcomes of patients in the SVG-WRIST trial are driven, therefore, by the restenotic process, with a high likelihood that graft failure was a result of progression of degenerative disease within the graft or within the native coronary arteries distal to the graft. The authors concluded that patients in the SVG-WRIST trial treated with brachytherapy had a marked reduction in the need for repeat TLR at 36 months, with sustained clinical benefit at three years despite late recurrences, which were more pronounced in the irradiated group.

II. Meta-analyses

A. A meta-analysis by Lu et al. (2012) was conducted to determine whether DES implantation remains favorable in large sample size and long-term follow-up when compared to intracoronary brachytherapy (ICBT) in patients with in-stent restenosis. The analysis included 1942 patients in twelve controlled trials (four randomized controlled and eight nonrandomized controlled trials). DES were significantly more effective in reducing TVR ($p = 0.009$) and binary restenosis ($p < 0.00001$) compared to ICBT at a midterm follow-up of six to twelve months. There were no significant differences in cardiac death, MI, and late stent thrombosis at midterm follow-up. At a follow-up of 24 to 36 months, there continued to be no significant difference in cardiac death ($p = 0.59$) or MI ($p = 0.65$), although a statistically significant difference was found in TVR ($p = 0.005$) in favor of DES.

B. Oliver et al. (2008) conducted a meta-analysis of randomized trials assessing the outcome of brachytherapy or drug-eluting stents for the treatment of in-stent restenosis. The analysis included 14 studies/3103 patients. Neither treatment had any effect on mortality or rate of myocardial infarction. At intermediate follow-up, brachytherapy reduced the rate of revascularization, binary restenosis, and late loss compared to balloon angioplasty and selective bare metal stents alone. MACE rates were lower in patients treated with brachytherapy at both intermediate and long-term follow-up. Drug-eluting stents reduced the rate of revascularization, MACE, and binary restenosis compared to brachytherapy, but follow-up was limited to nine months. The authors concluded that vascular brachytherapy improves the long-term outcome of angioplasty compared with bare metal stents alone in the treatment of in-stent restenosis, and drug-eluting stents appear to provide similar results during short-term follow-up.

C. Uchida et al. (2006) conducted a meta-analysis of randomized controlled trials comparing intracoronary gamma- and beta-radiation therapy to placebo for in-stent restenosis. The authors assessed the effectiveness of brachytherapy and of the two radiation sources, and also evaluated the performance of the procedure in native coronary arteries and SVG. Five randomized controlled trials that compared brachytherapy to placebo in 1310 patients were reviewed. There was considerable between-study variance, and diabetes was found to be a significant factor in this variance. In multivariate meta-regression analyses adjusted for diabetes and lesion length, neither gamma radiation source nor SVG was a significant factor for the between-study variance ($p = 0.675$ and 0.433, respectively). Neither procedure in SVG (gamma radiation) nor difference in radiation source (beta or gamma) in native coronary arteries was a significant factor in brachytherapy effectiveness compared to placebo. Intracoronary brachytherapy was effective compared to placebo at mid-term follow-up.

D. Additional proposed indications include:
   1. Intracoronary brachytherapy has been proposed as a treatment for new stenosis of native coronary arteries and SVG, as well as restenosis of native coronary arteries and SVG at the unstented site of a previous PCI
   2. Brachytherapy has also been evaluated as a method of primary prevention of restenosis after stent implantation for de novo lesions.
   3. VBT may be used for recurrent drug-eluting stent in-stent restenosis. Recent studies have shown that VBT is safe with low recurrence rates at one year post procedure. It is considered to be a safe short-term method of restoring patency although repeat intervention will be eventually medically necessary. In a study of 186 patients with 283 lesions, Negi et al (2016), unstable angina was treated with balloon angioplasty followed by VBT. In 99% of cases treatment was delivered without adverse effects. Similarly, Ohri et al. (2016), reported on 134 patients with 141 treated lesions as well as a control group of 37 patients. This study confirmed the safety and usefulness of the procedure in a high risk population. Additional investigation was recommended.

E. In the BetAce randomized trial, Ribichini et al. (2006) evaluated brachytherapy for prevention of in-stent restenosis after angioplasty of de novo lesions in patients with high plasma angiotensin converting enzyme (ACE). Elevated plasma ACE levels have been proposed to increase the risk of in-stent restenosis. Thirty-one patients (33 stenoses) were randomized to stent implantation (control group), and 30 patients (31 stenoses) were randomized to brachytherapy and stented angioplasty. Following angioplasty, in-stent minimal lumen diameter (MLD) was similar in both groups. At 6 months, MLD had decreased in the control group to 1.74 ± 0.8 mm, compared to 2.25 ± 1.05 mm in the brachytherapy group. The mean in-stent diameter was 2.3 ± 0.8 in

the control group vs. 2.9 ± 1.05 in the brachytherapy group, and the restenosis rate was 37.5% in the control group vs. 17.9% in the brachytherapy group. At six months, a higher need for TVR was seen in the control group (35.5%) than in the brachytherapy group (13.3%). The authors concluded that this study confirms that patients with high plasma ACE levels are exposed to an increased risk for in-stent restenosis and that the preventive use of brachytherapy in these patients reduced neointimal formation and increased MLD.

F. Ferrero et al. (2007) reported five-year follow-up of the BetAce trial, analyzing the incidence of death, myocardial infarction (MI), and ischemia-driven target vessel revascularization (TVR). The incidence of stent thrombosis was slightly higher in the brachytherapy group (10%) than in the control group (6.5%). This difference was not statistically significant. Although there was a significantly higher need for TVR in the control group at six months, the difference lost its significance at 12 months and five years because of a late catch-up phenomenon in the brachytherapy group, with a higher incidence of edge stenosis and stent occlusion. Five-year event-free survival rank for death, MI and TVR was 43% in the brachytherapy group compared to 45% in the control group (p = .95). The occurrence of additional ischemic events in both groups equalized the long-term clinical outcomes. The authors stated that intracoronary beta radiation at the time of stent implantation only transiently prevents excessive neointimal proliferation that leads to stenosis recurrence in the first year after treatment. The late catch-up phenomenon, along with the natural progression of the atherosclerotic disease in other segments, is responsible for the loss of the clinical benefit of brachytherapy in the long term.

G. Syeda et al. (2006) conducted a double-blind, randomized trial of beta brachytherapy for prevention of restenosis after stent implantation in native coronary de novo lesions. Eighty-nine diabetic patients (106 lesions) were randomly assigned to treatment with beta radiation or placebo treatment. Angiographic analysis at nine months demonstrated a late lumen loss of 0.7 ± 0.9 mm in the brachytherapy group vs. 1.2 ± 0.8 mm in the control group at the injured segment, 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the radiated segment, and 0.9 ± 1.0 vs. 1.3 ± 0.7 mm at the target segment. Binary restenosis rates were significantly lower in the brachytherapy group in all subsegments. TVR for restenosis was necessary in nine lesions (17.6%) in the brachytherapy group vs. 18 (34%) in the placebo group. Late thrombosis occurred in four brachytherapy patients after premature discontinuation of antiplatelet therapy, resulting in a MACE rate of 37.2%, compared to 38.6% in the placebo group. The authors concluded that, in diabetic patients with de novo coronary lesions, intracoronary radiation after stent implantation significantly reduced restenosis. This clinical benefit was reduced, however, by the frequent occurrence of new thrombosis.

III. Professional societies/organizations

A. A guideline update for PCI published by the American College of Cardiology (ACC), American Heart Association (AHA) and the Society for Cardiovascular Angiography and Interventions (SCAI) (Smith et al., 2005) states that vascular brachytherapy has been successful in treating restenosis occurring within stents, while other adjunctive therapies, such as the cutting balloon, rotary ablation, excimer laser and restenting have shown mixed results. The ACC/AHA/SCAI guideline states that brachytherapy can be useful as a safe and effective treatment for in stent restenosis (Class IIa recommendation). A Class IIa recommendation indicates that there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment but that the weight of evidence is in favor of usefulness/efficacy. No changes to this recommendation were made in focused updates to the PCI guideline published in 2007 and 2009.

B. A 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) PCI guideline (Wijns et al.) does not include recommendations for brachytherapy. The background of the guideline references studies demonstrating superiority of DES over brachytherapy.

C. Guidelines for PCI issued by the European Society of Cardiology (ESC) state that brachytherapy proved to be the only evidence-based nonsurgical treatment for in-stent restenosis. The guideline also states that a prolonged intake of clopidogrel for one year after radiation is necessary. The ESC guideline recommends brachytherapy for the treatment of in-stent restenosis in native coronary arteries as a Class 1A recommendation. Brachytherapy for treatment of in-stent restenosis of a saphenous vein bypass graft is considered as a Class 1B recommendation. Class I indicates evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful and effective. Level of evidence A indicates that data is derived from multiple randomized clinical trials or meta-analyses, while level of evidence B indicates data is derived from a single randomized clinical trial or large non-randomized studies (Silber et al., 2005).

D. Guidelines on Myocardial Revascularization developed by The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) state that currently, intracoronary brachytherapy is of very limited use: restenosis rates have declined and in-stent restenoses after BMS are treated by DES or CABG.

IV. Summary

Prior to the widespread use of drug-eluting stents, in-stent restenosis following percutaneous coronary intervention (PCI) was a significant clinical problem, frequently resulting in the need for repeat revascularization procedures. Intracoronary brachytherapy was shown to be an effective treatment for in-stent restenosis of native coronary arteries or saphenous vein grafts. Brachytherapy procedures have decreased in frequency, however, and drug-eluting stents have emerged as the treatment of choice in the majority of cases. Brachytherapy may still play a role in the treatment of in-stent restenosis in selected patients, however.

There is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of brachytherapy for expanded indications, including treatment for new stenosis of native coronary arteries and SVGs; restenosis of native coronary arteries and SVGs at the unstented site of a previous PCI; or as primary prevention of restenosis after stent implantation for de novo lesions.

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Hyperthermia

POLICY

I. The use of hyperthermia and concurrent radiation therapy treatment is medically necessary for any of the following:

A. Superficially recurrent melanoma
B. Chest wall recurrence of breast cancer
C. Recurrent cervical lymph nodes from head and neck cancer

Treatment of the above conditions will be approved in the absence of both of the following:

A. Metastatic disease for which chemotherapy or hormonal therapy is being given concurrently or planned
B. Evidence of tumor recurrence exceeding 4 cm in depth

When hyperthermia is indicated, no more than 10 hyperthermia treatments delivered twice weekly at 72-hour intervals should be utilized.

II. The use of intraluminal, endocavitary, interstitial, regional deep tissue hyperthermia exceeding 4 cm in depth, and whole body hyperthermia is considered experimental, investigational, or unproven (EIU)

Key Clinical Points

After initial enthusiasm for the use of hyperthermia in the late 1970s, interest waned with the publication of studies showing little or no benefit in the mid-1980s. Later review of the negative findings disclosed that the critical temperature necessary for hyperthermic cell death, 42 to 43 degrees centigrade (C), was either poorly measured or poorly maintained in these studies. Point measurements rather than volume mapping of thermal gradients were relied upon in planning these hyperthermia studies.

Renewed interest in the use of hyperthermia began to emerge in both Europe and the United States (US) in the 1990s. Research from Duke University, Northwestern University, University of Southern California, Stanford University, Washington University, as well as centers in Holland, Germany, Norway, Austria, Italy, and Switzerland have contributed substantially to the emergence of hyperthermia as a useful treatment modality when combined with radiation therapy.

Currently, in the US, the Food and Drug Administration (FDA) has approved hyperthermia for use in the treatment of cancer when combined with radiation therapy

for the "…palliative management of certain solid surface and subsurface malignant tumors (i.e. melanoma, squamous or basal cell tumors, adenocarcinoma, or sarcoma) that are progressive or recurrent despite conventional therapy." The National Cancer Center Network (NCCN) recommends "…that the use of hyperthermia be limited to treatment centers with appropriate training, expertise and equipment..." The NCCN Panel on Breast Cancer concluded that it was a controversial Category 3 recommendation in the treatment of local or regional recurrent breast cancer.

Following FDA approval, Medicare approved coverage for local hyperthermia when used together with radiation therapy. A National Coverage Determination (NCD 110.1) was issued by Medicare (CMS) in December 1984 and remains unchanged. It states, "Local hyperthermia is covered under Medicare when used in conjunction with radiation therapy for the treatment of primary or metastatic cutaneous or subcutaneous superficial malignancies. It is not covered when used alone or in connection with chemotherapy." Coding for this treatment is recognized and published in the current 2010 ACR/ASTRO guide.

Although research into hyperthermic treatments at depths greater than 4 cm is ongoing in the US, it is currently recognized only as investigational as are intraluminal, endocavitary, and interstitial applications.

On May 15, 2009, the FDA granted humanitarian use devise (HUD) status to the BSD-2000 and on November 18, 2011, the FDA granted humanitarian device exemption (HDE) to the BSD-2000 for the treatment of cervical cancer patients ineligible for chemotherapy (treatment population less than 4,000). This is the only approval for deep heating, and only actual costs incurred in the research may be billed. Other applications for deep heating are pending for both BSD and Medifocus devices.

In the US, only the BSD-500 has FDA commercial clearance for superficial heating (less than a 4 cm depth). This is currently the only device approved for reimbursement. It operates at the microwave range of 915 MHz with different applicators and power setting ranging from 20 to 250 watts. The standard recommended treatment regimen for use with radiation therapy is a "…total of 10 hyperthermia treatments delivered two times per week at 72-hour intervals, with each heat treatment preceded or followed by a standard prescribed dose of ionizing radiation within 30 minutes of the heat treatment." A sustained intratumoral temperature of 42.5 degrees C for 60 minutes is recommended.

The FDA granted per-market approval for the Sonotherm® 1000 Ultrasound Therapy System on September 29, 1989. This approval was for hyperthermia to treat tumors at a depth of 8 cm. Although FDA approval was granted, the device remains in clinical study and is designated EIU.

There are three clinical sites in which randomized studies have documented the benefit of hyperthermia given in conjunction with radiotherapy.

1. Melanoma – 134 metastatic or recurrent lesions of malignant melanoma in 70 patients were randomly assigned to receive radiation therapy (three fractions of 8 or 9 Gy over 8 days) alone or followed by hyperthermia (43 degrees C for 60 minutes). Beneficial local effect was 28% for radiation alone, and 46% for combined treatment. Toxicity was not higher with hyperthermia (Overgaard, 1995)

2. Breast – Five randomized trials were combined to report the benefit of combined treatment for superficial localized breast cancer. The control rate for radiation therapy alone was 41%, while that for combined treatment was 59%. The greatest effect was observed in patients with recurrent lesions in previously irradiated lesions where further irradiation was limited to low doses (Vernon, 1996)

3. Head and neck metastatic lymph nodes – a randomized study of 44 nodes in 41 patients confirmed the improved five-year actuarial nodal control of the combined treatment arm. In addition, the study reports a statistically significant in survival at five years, and no increased toxicity from combined modality therapy (Valdagni, 1994)

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Image-Guided Radiation Therapy (IGRT)

POLICY

IGRT is a method by which image guidance is applied to place the isocenter for the upcoming treatment appropriately. This technology typically is applied for an individual undergoing Intensity-Modulated Radiation Therapy (IMRT). However, in some cases in which the isocenter is the main concern, IGRT occasionally can be used with three-dimensional (3D) conformal radiation therapy (3DCRT). The American Society for Radiation Oncology (ASTRO) together with the American College of Radiology (ACR) have published practice guidelines regarding IGRT (Potters et al., 2010). In addition, in their 2017 Radiation Oncology Coding Resource, ASTRO has addressed IGRT in detail.

Historical methodology of using port films to confirm patient set-up and block placement has not been replaced by IGRT. For example, the Coding Resource states "…guidance and tracking are not indicated…" when "…replacing "port check" imaging when target localization is not medically necessary." Outside of treatment procedures requiring only isocenter placement, port films and/or verification simulations are still the appropriate modalities. If the isocenter placement is the primary concern, i.e. for IMRT, then IGRT is typically the method utilized. This does, however, imply the target can be localized with the specific IGRT modality requested, i.e., stereoscopic imaging for target localization, computed tomography (CT) guidance for field placement or ultrasound (US) guidance for field placement (Weiss et al., 2011). In the event no target is localized, blocking and patient set-up is accomplished through typical alignment of bony structures using portal imaging; appropriate coding for port films would apply.

Effective 1/1/2015, IGRT techniques are covered under two different coding systems. CPT® code 77387 is for billing in the Hospital Outpatient Prospective Payment System (HOPPS) and for those non-Medicare health plans that accept this definition. It may be necessary to check with the individual health plan directly before billing this code for this purpose. Also, the new IMRT treatment delivery CPT® codes (77385 and 77386) include IGRT guidance and tracking, when performed. The technical component of IGRT (77387-TC) is packaged into the IMRT service with which it is performed and is not reported separately. In the Medicare Physician Fee Schedule (MPFS) setting, as well as the Healthcare Common Procedure Coding System (HCPCS) setting, the G-Code system has replaced CPT® codes. G6001 replaces CPT® code 76950, G6002 replaces CPT® code 77421, and G6017 replaces CPT® code 0197T. In contrast to the HOPPS reporting, IGRT is not bundled into IMRT for MPFS and HCPCS and is reported separately.

Respiratory motion management may be clinically appropriate for treating some cancers, including lung cancer and some cases of breast cancer (deep inspiration breath hold [DIBH]). Respiratory tracking by continuous localization systems or four-dimensional CT (4D-CT) are now included in CPT® code 77387. This code is for billing in the HOPPS and for those non-Medicare health plans that accept this definition. It may be necessary to check with the individual health plan directly before billing this code for this purpose. In the MPFS setting as well as the HCPCS setting, the G-Code G6017 has replaced CPT® code 0197T. In the hospital-outpatient setting, G6017 is considered image guidance and is packaged into the primary service payment. For all other purposes, this code is considered carrier-priced and may be accepted or refused by different health plans and Medicare contractors.

In IGRT-approved cases, only one method or technique of IGRT is allowed daily.

CPT® codes 77370 and 77470 should not be billed based on the use of IGRT.

I. IGRT during IMRT

IGRT is considered medically necessary when IMRT has been approved and is being utilized.

II. IGRT during 3DCRT

IGRT in conjunction with 3DCRT is medically necessary in the following circumstances:

A. When the planning target volume (PTV) is in close proximity to a previously irradiated area
B. Treatment of the hepatobiliary tract
C. Treatment of head and neck cancer
D. Treatment of Hodgkin's and Non-Hodgkin's Lymphoma
E. Treatment of lung cancer
F. Treatment of prostate cancer
G. Treatment of esophageal cancer
H. Treatment of gastric cancer
I. Treatment of pancreatic cancer
J. Treatment of pelvic cancers (i.e. rectal cancer) when the individual is in the prone position on a belly board
K. During breast boost when using photons
L. During external beam-based accelerated partial breast irradiation (APBI)
M. During treatment of breast cancer when a DIBH technique is being used
N. During the boost to the bladder
O. Preoperative or postoperative treatment of sarcomas

III. IGRT during SRS/SBRT

For Stereotactic Body Radiation Therapy (SBRT), the IGRT codes may not be billed separately because by American Medical Association (AMA) definition they are bundled and included in the daily treatment codes. In addition, the IGRT codes may not be billed separately with Stereotactic Radiosurgery (SRS) as stated in the ASTRO coding guide.

IV. IGRT and brachytherapy

In brachytherapy cases, imaging is medically necessary to verify source position in all but the simplest of cases. The images may also be used to perform dosimetry calculations. Use of applicable simulation and/or field verification codes is appropriate, such as CPT® Code 77280.

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Neutron Beam Therapy

POLICY

I. Neutron beam radiotherapy is medically necessary for salivary gland cancers that are inoperable, recurrent, or are resected with gross residual disease or positive margins.

II. All other indications are not covered because neutron beam radiotherapy is experimental, investigational, or unproven (EIU).

Key Clinical Points

Neutron beam radiotherapy differs from other forms of radiation particle treatment such as protons or electrons as neutrons have no electrical charge. The treatment effects are the results of the neutron mass producing dense radiation energy distributions. This effect is high energy linear transfer (LET) and may offset the negative effects of low oxygen tension in tumors, leading to increased rate of control in hypoxic tumors.

Currently, the number and location of neutron facilities in the United States is quite small. This has limited research and has resulted in a lack of substantial information on its clinical effectiveness, although it has been tried in soft tissue sarcoma, prostate cancer, pancreas, colon, and lung cancers amongst others. The lack of data and comparative trials limits its designation to EIU, with the exception of salivary gland cancers. The most recent advance in neutron treatment has been the development of Intensity Modulated Neutron Therapy (IMNRT) at the Wayne State Facility which may permit biologic dose escalation compared to IMRT while maintaining reasonable toxicity rates. The use of this technique is highly experimental at this time.

The effectiveness of neutrons as treatment of choice in the treatment of salivary gland tumors was most recently confirmed by Stannard et al. (2013) with the treatment of 335 patients at IThemba Labs. The patients were either unresectable or had gross macroscopic residual disease. Localregional control was 60.6% at 5 years and 39.1% at 10 years. Disease specific survival was 66.8% at 5 years and 53.7% at 10 years. A recent publication by Davis, et al. (2016) reported a 6 year overall survival of 58% in 140 patients, with the most common subtype being adenoid cystic carcinoma and the submandibular gland being the most common site. The current standard neutron dose was reported as 1.15 neutron Gray (nGy) 4 times per week for 4 weeks (total 18.4 nGy) equivalent to 60-70 Gy over 6 to 7 weeks with conventional photon radiation.

Neutrons do have limitations, especially at the skull base, which can result in an increased complication rate. Recent studies at the University of Washington (Douglas et. al, 2008; Rockhill and Laramore, 2016) have focused on reducing the neutron contribution at the superior portion of the tumor in skull based tumor using SRS, Gamma Knife, as a boost. The 40 month actuarial control rate was 82% compared to a historical control rate of 39% with neutrons alone.

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Proton Beam Therapy

POLICY

Proton Beam Therapy (PBT) is considered medically necessary for the treatment of the following tumors:

I. Chordomas and chondrosarcomas of the base of the skull, localized and in the postoperative setting
II. Uveal melanoma, when PBT is considered preferential compared to brachytherapy
III. Select cases of localized unresectable hepatocellular carcinoma (HCC) (see discussion in Key Clinical Points)
IV. Stage IIA seminoma

Prostate Cancer

I. In the treatment of newly diagnosed prostate cancer, PBT is considered not medically necessary
II. In the treatment of prostate cancer after prostatectomy, PBT is considered experimental, investigational and/or unproven (EIU)

PBT is experimental, investigational and/or unproven (EIU) for all other tumors.

PBT in combination with photon therapy for any tumor is experimental, investigational and/or unproven (EIU).

Key Clinical Points

PBT is a form of external beam radiation therapy (EBRT) also known as charged particle therapy. Proton beam therapy provides the opportunity of achieving dose escalation and decreasing toxicity by delivering physical dose to a narrowly defined region, while avoiding normal tissue. The potential benefit is to improve local control, improve survival, and decrease toxicity.

While PBT has been used in individuals in the United States since the mid–1950s, and although it has been shown to be effective in some malignancies, there is insufficient data clearly demonstrating its benefit over conventional forms of radiation therapy (Brada et al., 2009).

In addition to the American Society for Radiation Oncology (ASTRO) evidence-based review of PBT, there are other systematic reviews of PBT which also conclude that rationale for PBT is often associated with a low level of evidence according to standard health technology assessment and evidence-based medicine criteria (Brada et al., 2007; Olsen et al., 2007). In a 5-year update of a systematic review of PBT, De Ruysscher, et al. (2012) state that "… from the many retrospective and the few prospective series, we still cannot conclude that protons or C-ions are truly superior to

X-rays…" and that "…except for rare indications such as childhood cancer, the gain from introducing proton therapies into clinical practice remains controversial."

Further, the impact of inter- and intrafraction motion, tissue heterogeneity and variability in relative biological effectiveness (RBE), among other factors, on the outcomes of proton beam therapy is not understood fully.

As an example, a recent retrospective analysis (Gunther et al., 2015) compared outcomes in pediatric patients who underwent proton therapy and intensity-modulated radiation therapy (IMRT) for ependymoma and found increased rates of post-radiation magnetic resonance imaging (MRI) changes, and neurologic deficits from brainstem necrosis in those who underwent proton therapy vs. IMRT. These findings demonstrate the need for further comparative research examining clinical differences between proton and photon therapy.

Therefore, for many clinical indications, the use of proton beam therapy is considered experimental, investigational, or unproven (EIU). Requests for proton beam therapy will be considered on a case-by-case basis.

I. Chordomas and chondrosarcomas of the skull base

These rare primary malignant tumors of the skull base are treated primarily by surgery and postoperative radiotherapy. There is extensive data on the use of PBT for the treatment of these tumors postoperatively, although there are no randomized trials and no evidence of the superiority of PBT over conventional therapy in these tumors. A recent systematic review of all published cases of chordoma (416 patients) treated with proton radiotherapy revealed a local control of 69% and 5 year overall survival (OS) of 80% (Amichetti et al., 2009). While comparison to older historical data of conformal photon radiotherapy may imply some benefit to PBT, more current Stereotactic Radiosurgery (SRS) outcomes compare more favorably with PBT results. However, based on the rare nature of these tumors, their location adjacent to critical CNS structures, and the documented efficacy of PBT, treatment of these tumors with PBT is considered medically necessary.

II. High-grade gliomas

Currently, there is very limited and insufficient clinical data in the medical literature documenting the outcomes of proton beam radiation in this setting. For example, Mizumoto et al. (2015) published their results of using proton beam therapy in the treatment of a GBM. In this study, 23 patients were treated post-operatively with standard photons (x-rays) to a dose of 50.4 Gy with a concurrent boost of 46.2 GyE using proton beam therapy. The 1- and 2-year survival was 78% and 43% respectively. Median survival was 21 months. It is noted that 6 patients developed radiation necrosis (who all survived at least 4 years without evidence of recurrence, but in whom the performance status had declined by 10-30%). The authors conclude that the studied regimen "has a high potential to improve survival in GBM patients…" and that "although radiation necrosis is inevitable in the treated area, it may be controllable with necrotomy and

bevacizumab administration." At the present time, the results of this study cannot be used to support proton beam therapy as the dose used is significantly higher than what is considered a standard of care (i.e. 66 Gy), and the rate of symptomatic brain necrosis is higher than with customary doses and techniques. Further, this study utilized both photons and protons.

In a retrospective dosimetric study of 12 patients with high-grade gliomas (HGGs) treated with intensity-modulated proton therapy (IMPT) and compared to volumetric-modulated arc therapy (VMAT) and 3D conformal radiotherapy (3D), Adeberg et al. (2016) found that "target coverage was comparable for all three modalities" with the use of proton beam therapy resulting in significant reductions in the mean dose to the whole brain, brain stem, pituitary gland and contralateral hippocampus." The authors further state that "this can potentially reduce the dose- and volume-related side effects of treatment…" However, no evidence of reduction in side effects has been demonstrated.

In an abstract, Ramakrishna et al. (2016) developed passive scatter proton beam therapy plans for 19 patients recently treated with IMRT. The authors demonstrated similar target coverage using protons compared to IMRT and not unexpectedly a lower mean V5, V10, V12 and V20 for uninvolved brain. Further, proton beam therapy resulted in lower mean hippocampal V5 and V10 relative to IMRT. The authors however, conclude that "the overall potential clinical benefit of these dosimetric advantages in glioblastoma patients remains to be determined."

Though such studies show the potential for a benefit of proton beam therapy in the treatment of GBMs, there remains insufficient clinical publications documenting the benefits, risks or efficacy of proton beam therapy. Studies to evaluate any benefit of proton beam therapy are ongoing, including a randomized phase II trial, NCT01854554, Glioblastoma Multiforme (GBM) Proton vs. Intensity Modulated Radiotherapy (IMRT). Therefore, until such data is published and until there is clear data documenting the clinical outcomes of proton beam therapy in the treatment of glioblastoma multiforme, proton beam therapy remains unproven.

III. Benign CNS tumors

Meningiomas have been treated with PBT with good outcomes, but there is no evidence that this treatment is superior to conventional therapy (Boskos et al., 2009). Pituitary adenomas, craniopharyngiomas, arteriovenous malformations, and acoustic neuromas have also been treated with PBT; but conventional techniques and relatively safe doses of radiation also yield excellent results. (Barker et al., 2003; Bush et al., 2002; Luu et al., 2006; Murphy et al., 2011; Ronson et al., 2006; Rowe et al., 2007; Weber et al., 2003). There is insufficient clinical evidence in this setting that PBT is associated with superior control rates or a decrease in secondary malignancies compared to treatment with conventional fractionated radiation therapy or radiosurgery techniques. The ASTRO emerging technology committee report on proton therapy specifically states "…more clinical

data (published clinical trials) are needed to fully establish the role of PBT in CNS tumors." Until such data are available, PBT is considered EIU in the treatment of benign CNS tumors.

IV. Uveal melanoma

PBT is effective in the treatment of these tumors with local control rates of over 95%, 85% cause-specific survival, and eye preservation rate of 90% with reasonable vision retained in approximately 50% of individuals. Intermediate tumors are treated just as effectively with brachytherapy, and the superiority of PBT in these tumors has not been demonstrated. For large uveal melanomas, PBT has been associated with a lower rate of secondary enucleation. Based on the extensive and excellent data on the use of protons in uveal melanomas, PBT is considered medically necessary, particularly in an individual who is not an optimal candidate for brachytherapy (Char et al., 2002; Conway et al., 2006; Desjardins et al., 2006; Egger et al., 2003; Lumbroso-Le Rouic et al., 2006).

V. Prostate cancer

IMRT is the most commonly used technique of EBRT for the treatment of prostate cancer. Currently, the evidence does not support any definitive benefit to PBT over IMRT in the treatment of prostate cancer (Efstathiou et al., 2009). There are no published patient-reported outcomes for prostate cancer patients treated with IMRT versus PBT.

Since IMRT and/or brachytherapy are considered the standard of care, any discussion on PBT must be compared to these modalities. The table below shows recent outcome data in prostate cancer using standard modalities.

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Table 1

Trial	Boost Modality	Planning Technique	High Dose Arm	5-Year Control	10-year Control	Gastrointestinal Toxicity	
						≥ G2	≥ G3
PROG 95-09 (Zietman et al., 2010)	protons	3D	79.2 Gy	91%	83%	17%	1%
ACR phase 2 03-12 (Coen et al., 2011)	protons	3D	82 Gy	Not reported yet	Not reported yet	26%	7%
Single institution MSK (Spratt et al., 2013)	xrays	IMRT	86.4 Gy		98.8% (7 year)*	4.4%	0.70%
MSK LDR – seeds (Kollmeier et al., 2013)	seeds	Brachytherapy	>100 Gy		97% (8 year)**	3%	
MSK HDR brachytherapy (Kotecha et al., 2013)	Ir-192	IMRT	>100 Gy		95% (7 year)***	1%	0.40%

*control at 7 years is 100%, 97.7%, 85.6% and 67.9% for very low risk, low risk, intermediate risk and high risk patients
**control for low risk is 97% and for intermediate risk is 94%
*** 7-year prostate specific antigen (PSA) relapse-free survival (RFS) for low risk, intermediate risk and high risk is 95%, 90% and 57%

While not meant to make an exact comparison, the point of the table is to show the very high local control rates and low toxicity rates against which PBT will ultimately need to be compared in order for PBT to be considered a standard therapy for early prostate cancer.

A Surveillance, Epidemiology and End Results (SEER)-Medicare analysis evaluated the comparative effectiveness of IMRT, proton therapy, and conformal radiation therapy for prostate cancer. In the comparison between IMRT and proton therapy, IMRT patients had a lower rate of gastrointestinal morbidity. There were no other significant differences regarding toxicities between IMRT and proton therapy (Sheets et al., 2012). Another analysis of early toxicity compared 421 patients treated for prostate cancer with proton therapy and 842 matched case controls treated with IMRT within the SEER-Medicare database. There was a statistically significant decrease in genitourinary toxicity at 6 months with proton therapy, however this difference disappeared by one year. There were no other significant differences in toxicity between the two techniques. Costs were approximately 75% higher with proton therapy (Yu et al., 2013).

Three prospective single arm studies at the University of Florida found a five-year rate of biochemical freedom from progression at 99%, 99%, and 76%, respectively,

in patients with low, intermediate, and high risk disease (Mendenhall et al., 2014). A prospective study performed by the University of Florida examined quality of life data in patients treated with proton therapy and IMRT for prostate cancer and found no significant differences in quality of life (QOL) summary score between the two modalities (Hoppe, 2014).

In 2013 ASTRO stated, "At the present time, ASTRO believes the comparative efficacy evidence of proton beam therapy with other prostate cancer treatments is still being developed, and thus the role of proton beam therapy for localized prostate cancer within the current availability of treatment options remains unclear." The National Comprehensive Cancer Network (NCCN) Guidelines include ASTRO's current model policy statement, "Proton beam therapy for primary treatment of prostate cancer should only be performed within the context of a prospective clinical trial or registry." The ASTRO Choosing Wisely® Campaign also states that "…there is no clear evidence that proton beam therapy for prostate cancer offers any clinical advantage over other forms of definitive radiation therapy".

As PBT is significantly more costly than IMRT, coverage for newly diagnosed prostate cancer may depend upon the applicable health plan benefit definition of medical necessity. Where that definition limits coverage to the most cost-effective equivalent treatment, the use of PBT for the treatment of newly diagnosed prostate cancer is deemed not medically necessary.

In the treatment of prostate cancer after prostatectomy, PBT is considered EIU.

VI. Lung cancer

Radiation therapy is used as a sole modality in the treatment of medically inoperable stage I non-small cell lung cancer (NSCLC). In stage III NSCLC lung cancer radiation therapy is used in conjunction with chemotherapy with or without surgery as definitive treatment. It is also used in limited stage small cell lung cancer (SCLC) with chemotherapy and in palliative settings. There is limited data on the use of PBT in lung cancer and the very significant concern of accurately delivering the high dose Bragg Peak region of protons directly into the target when there is organ motion.

Eight PBT case series were identified in the assessment that included a total of 340 patients. No comparative studies, randomized or nonrandomized, were found. In stage I lung cancer, recent results of SBRT has yielded excellent control rates of over 90%, with low toxicity in peripheral lesions. While there have been several single institution PBT series, the results are similar to that of SBRT. A recent indirect meta-analysis reviewed in the assessment found a non-significant difference of nine percentage points between pooled two-year overall survival estimates favoring SBRT over PBT (Grutters et al., 2010). The non-significant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of single-arm studies on SBRT and PBT, it is unclear if this

indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT. The assessment noted that adverse events reported after PBT generally fell into the following categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods and lack of information about rating criteria and grades. The report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC.

All PBT studies examining lung cancer are case series; there are no completed studies directly comparing PBT and SBRT. Analyses of these studies included several quality issues such as, failure to use an independent assessor of patient-reported adverse events and were lacking in details on several aspects of the PBT treatment regimens. The PBT studies were similar in patient age, but there was great variability in percent within stage IA, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. In the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain.
In stage III lung cancer, there are also theoretic advantages to PBT, especially in terms of decreasing toxicity. At this time, there are only three published clinical trials (phase I and II) on PBT for locally advanced NSCLC. This is insufficient to consider PBT standard therapy for lung cancer (Chang et al., 2011; Hoppe et al., 2012; Jiang et al., 2012). A phase III trial comparing proton beam radiation therapy vs. photon beam radiotherapy is currently accruing patients (RTOG 1308). Therefore, at this time, PBT is considered EIU in the treatment of lung cancer.

VII. Hepatocellular carcinoma (HCC)

In HCC, proton beam treatment may play a role in unresectable cancers that are not amenable to other forms of treatment including:

A. Ablative techniques (Radiofrequency, Cryosurgery, Alcohol injection, Microwave)
Several ablative techniques have been used both in the operable and definitive setting. For select lesions, generally under 3 cm in size that are well localized, definitive treatment may be considered. Contraindications to ablation include lack of anatomic accessibility, size, number, and location near abdominal organs, major ducts, and blood vessels. A complication reported with ablation is the development of tumor rupture with lesions located on the hepatic capsule or tumor seeding along the track with subcapsular and poorly differentiated lesions. Local control rates in the range of 90% at two years have been reported for ablative techniques.

B. Arterial treatments (Selective Internal Radiation Therapy [SIRT], also known as Transarterial Radioembolization [TARE]; Transarterial Chemoembolization [TACE]; or Trans-arterial Embolization [TAE])

These techniques require selective catheterization of the hepatic arterial supply to the tumor-involved liver segments. As HCC is a hypervascular tumor, there is preferential blood blow as compared to the normal hepatic parenchyma. Indications for these procedures include multiple tumors, generally 4 or more in number, lesions greater than 3 to 5 cm, lesions without vascular invasion or extra-hepatic spread. Absolute contraindications include decompensated cirrhosis, jaundice, clinical encephalopathy, refractory ascites, hepatorenal syndrome, extensive tumor replacement of both lobes, portal vein occlusion or severely reduced flow, hepatofugal flow and renal insufficiency. Relative contraindications include tumor size greater than 10 cm, severe cardiovascular or pulmonary disease, varices at high risk of bleeding or bile duct occlusion. In clinical trials TACE appears superior to TAE. SIRT/TARE provide high doses of radiation to tumor capillary beds. Yttrium-90 beta radiation, delivered by SIR-Spheres®- or TheraSphere®-labeled microspheres, delivers preferential high doses of radiation and tends to spare normal hepatic tissues. Full discussion of the indications and contraindications to SIRT/TARE may be found in the separate eviCore Clinical Guideline, Radioactive Yttrium-90 Microspheres.

In addition to the contraindications listed above, all arterial therapies must take into account their effect on liver function as embolic-, chemo-, or radiation-liver disease or dysfunction can result in severe morbidity or death. Bilirubin greater that 3 mg/dl for TACE/TAE and 2 mg/dl for SIRT/TARE are considered strong relative contraindications unless segmental treatment is being performed.

C. EBRT (IMRT, 3DCRT, and SBRT)
Conformal radiation techniques such as 3DCRT generally have played a palliative role in the treatment of HCC. Yet, HCC is a radiosensitive tumor and highly conformal external beam techniques such as IMRT or 3DCRT should be considered in a definitive manner in inoperable tumors not amenable to other treatments. Great care must be given in considering the individual's liver function, Hepatitis B carrier status, prior transarterial or other treatments or other treatments, portal vein thrombosis, and Childs-Pugh score. A dose volume constraint to be considered is for the mean liver dose (liver minus gross tumor volume) to be less or equal to 28 Gy in 2 Gy fractions. The University of Michigan has demonstrated that tumoricidal doses from 40 Gy to 90 Gy delivered in 1.5 Gy BID treatments along with hepatic-infused chemotherapy could result in a one year local control rate of 81% and survival rate of 57% in an individual who was unresectable and without portal vein

thrombosis. Studies for conformal RT and TACE have also been done in Asia showing improved survival for the combination.
SBRT is considered the mainstay of the radiation effort to control inoperable HCC. Current indications for the use of SBRT include 3 or fewer tumors without evidence of vascular or organ invasion and away from hollow organs, such as the bowel or stomach, as perforation and hemorrhage are significant complications. Sufficient hepatic reserve as evidenced by a Childs-Pugh A score is extremely important as safety data are considered limited in Childs-Pugh B or those with poor liver reserve. Some controversy has existed over the size of eligible lesions with initial restriction to lesions of up to 5 cm now being expanded to larger lesions. RTOG 1112 eligibility criteria include up to 5 lesions with no one lesion exceeding 15 cm, with a total maximum sum of all lesions not exceeding 20 cm. Current optimal dose recommendations are 50 Gy in 5 treatment fractions with a mean liver dose of 13.0 Gy and an additional organ constraint of liver Veff < 25%. If these constraints are not met, dose reductions from this optimal dose down to 30 Gy for a mean lung dose (MLD) of 16 Gy are recommended. Optimal and acceptable dose volume constraints to critical organs may be found in the RTOG 1112 study.
SBRT has proven itself both as effective bridge therapy 1) for an individual with HCC and cirrhosis prior to transplant and 2) in individual who is inoperable, both as an initial treatment and for an individual who is ineligible or incompletely treated by other methods. Excellent local control rates at 1 to 2 years ranging from 70 to 90% have been reported on initially treated patients and a 61% 2 year survival rate has been reported in patients previously treated with TACE.

D. PBT

PBT for HCC is an emerging technology which, according to the NCCN, may have a role in certain clinical circumstances. The unique dosimetric advantages of heavy charged particle radiation (Bragg Peak) offer significant potential advantages in sparing hepatic parenchyma compared to traditional photon techniques. This theoretical advantage is still the object of on-going studies in this country. A multi-institutional Phase II study in the Journal of Clinical Oncology, published in February of 2016, demonstrated a two-year HCC local control rate of 94.8%. Treatment was given with a hypofractionated regimen of 67.5 Gy equivalent in 15 fractions to a patient population that included previously treated patients and those with tumor vascular thrombosis. On-going Phase III studies are in progress. However, a meta-analysis of 70 studies demonstrated a decided advantage of charged particle treatment as compared to traditional radiation but found no difference when comparing charged particle treatment to SBRT.

The larger PBT series are from Japan suggesting excellent local control rates and modest 2- to 5-year survival rates. Four retrospective (360 patients) and two prospective studies (64 patients) of hypofractionated PBT in patients with hepatocellular cancer show results similar to those achieved with SBRT. (Fukumitsu et al., 2009; Hashimoto et al., 2006; Hata et al., 2005; Hata et al., 2006; Hsiung-Stripp et al., 2001; Koyama et al., 2003; Kozak et al., 2007; Macdonald et al., 2001; Sugahara et al., 2005; Sugahara et al., 2010; Zhang et al., 2008; Zurlo et al., 2000). In an individual with unresectable hepatocellular cancers who is not optimally treated with radiofrequency ablation or SBRT, PBT is medically necessary.

If a letter or minutes from a multi-disciplinary tumor board meeting documenting the medical necessity for the use of PBT (as opposed to the other techniques previously described) is not available, requests for the use of PBT for HCC must include **all** of the following:

1. A consultation note from Interventional Radiology documenting the contraindications as listed above to the use of ablative or transarterial techniques **and**
2. Documentation of the inability to maintain the mean normal liver dose (liver minus gross tumor volume) to less than 28 Gy in 2 Gy fractions with 3DCRT or IMRT **and**
3. Documentation of the inability to use SBRT delivering a minimal therapeutic dose of 30 Gy in 5 fractions per the constraints of RTOG 1112 or due to the presence of more than 5 lesions or the inability to maintain 700 cc of normal function liver tissue to a dose of 15 Gy or less with 3 to 5 fractions of SBRT **and**
4. Documentation of no evidence or minimal evidence of extra-hepatic disease **and**
5. Documentation of tumor size not exceeding 16 cm in nominal diameter with the ability to maintain a normal function liver volume of 700 cc with proton treatment **and**
6. The ability to deliver a full hypofractionated proton treatment regimen of not less than 50 GyE in 22 fractions.

In an individual with HCC who is not acceptably treated with 3DCRT, IMRT, ablative, transarterial or SBRT techniques in the curative setting, PBT requests will be considered on a case-by-case basis.

VIII. Head and neck cancers

The ASTRO Emerging Technology Committee (ETC) has reported there was insufficient evidence to support the use of PBT in head and neck cancer. Results of the few ongoing randomized studies are not yet available or insufficiently mature to draw definitive conclusions.

NCCN guidelines address radiation techniques for head and neck cancer stating "…advanced radiation therapy technologies such as IMRT, Image-Guided Radiation Therapy (IGRT) and PBT may offer clinically relevant advantages in

specific instances to spare important organs at risk (OARs)…and decrease the risk for late, normal tissue damage…". Though clinical data describing PBT and late toxicity is limited, there continues to emerge clinical and dosimetric data describing the potential benefits in the short-term.

For example, in results published in abstract form, Hutcheson et al. (2013) documented less toxicity and need for g-tube placement with the use of IMPT (intensity modulated proton therapy) in 26 HPV/p16+ patients with oropharyngeal carcinoma. The authors conclude that "preliminarily, IMPT may out-perform IMRT for acute dose-limiting and functional toxicities." Such data has led to the development of clinical trials comparing proton beam therapy to IMRT such as NCT01893307. Additional clinical data has been well described in a review published by Holliday and Frank (IJROBP, 2014).

Though PBT holds promise for the treatment of head and neck cancers, there remains insufficient data to consider it medically necessary. Therefore, requests will be considered on a case-by-case basis. This includes patients being treated with curative intent, who have a good performance status and have sufficiently long life expectancy where best effort IMRT (or other appropriate technique) is unable to safely achieve target coverage or meet normal structure tolerances. In some cases that have been previously irradiated to full dose, retreatment of localized recurrent head and neck tumors may also benefit from the unique properties of PBT. In all such situations, medical review is required. Evidence that competing techniques are unsafe for the specific request is to be supplied.

IX. Seminoma

The risks of radiation induced second malignancy in seminoma are well documented. The current NCCN Guideline Version 2.2017 continues to mention the increased risk of second cancers arising in the stomach, kidney liver and bowels in patients treated with radiation therapy. They caution against the use of IMRT in the treatment of seminoma as the radiation doses to these organ (integral dose) is increased compared to 3DCRT fields used in anterior and posterior fashion. However, it must be recognized that use of anterior/posterior fields whether 2D or 3D are the very technique which has been the subject of these reports. IMRT might theoretically make it worse.

A brief review of the literature outlines the risk. Lewinshtein, Gulati et al (J Urology, 2012) used SEER data between 1973 and 2000. They found a 19% increase in secondary primary malignancies in seminoma patients exposed to radiation therapy as compared to the general population including pancreas, non-bladder urothelial, bladder, thyroid and others. The risk lasted 15 years from the time of initial diagnosis. An accompanying editorial in the journal noted an increased incidence of seminoma during the last 4 decades with improved survival, which makes the issue of radiation-induced malignancies of increasing concern. Indeed, the NCCN noted that the routine use of adjuvant therapy for Stage I seminoma is not warranted as the risk of recurrence is low compared to the potential harms of adjuvant therapy.

Travis et al., reported twice on this issue in 1997 and 2005. They identified risks of lung, bladder, pancreas, stomach and other organs, noting that secondary primary cancers are a leading cause of death in men with a history of testicular cancer. The risk may extend as long as 35 years. Patients treated with radiation therapy had the highest risk of developing cancer especially when treated at a young age. Among organs treated in a radiation field, stomach, large bowel, pancreas and bladder stood out for the development of a later cancer.

Given these findings, radiation is no longer used in early seminoma but there remains a population of patients with more advanced disease that may benefit. Although this population of patients is relatively small as 80% of seminoma, totaling approximately 8600 cases a year, is diagnosed in Stage I, the relative doses of radiation and increased field sizes pose a problem. Dose modeling by Mazonakis et al., published in 2015 showed that medically necessary abdominopelvic irradiation increased the risk for induction of secondary malignancies by as much as 3.9%.

The use of protons brings a distinct advantage in lowering radiation dosed to the population at risk. Kramer, et al., writing in the International Journal of Radiation Oncology Biology Physics in 2012 showed that proton plans could reduce mean doses to the stomach to 119 cgy vs 768 cgy for photons as well as having meaningful reductions in doses to bladder and pancreas with a subsequent theoretical expected decrease in cancers.

Based on the above information documenting a higher risk of secondary malignancy unique to seminoma, the use of proton beam treatment is considered medically necessary.

X. Secondary malignancies

There has been a suggestion that there may be a lower risk of second malignancies with PBT compared to IMRT. A larger volume of normal tissue is exposed low dose radiation with IMRT, and this higher integral dose theoretically could cause a higher rate of second malignancies. There is a large body of data discussing the theoretic risks and benefits of PBT with respect to second malignancies, based on dosimetry and modeling (Athar et al., 2009; Brenner et al., 2008; Moteabbed et al., 2012; Shih et al., 2010; Zacharatou et al., 2008). Both sides of the argument can be supported based on this data. It is best summed up by a comprehensive review from the NIH published in June 2013. The publication concluded that "…to date, no observational studies have directly assessed the second cancer risks after IMRT or proton therapy. Until sufficient follow-up is available to conduct such studies, assessment of the risks relies on risk projection studies or theoretical models." (Berrington de Gonzales et al., 2013)

There is also a publication from the Massachusetts General Hospital (MGH) proton facility that looks at the risk of second malignancies in their patient population (Chung et al., 2013). The authors admit to several significant limitations of their study, including having lost 26% of the patients to follow-up. While their data shows

a lower risk of second malignancies in the proton group (5.2%) compared to a National Cancer Institute SEER database matched with a photon control group (7.5%) at a median follow-up of 6.7 years, their conclusion of the study is that "…these findings are reassuring that the risk of second tumors was at least not increased when using protons compared with photons…" and that "…given the limitations of the study, the reduced second tumor rate in the proton cohort that we observed should be viewed as hypothesis generating." There is also debate about the reliability of the SEER database matched cohort in determining the risk of second malignancies from photon therapy.
In an editorial published by Bekelman et al. (2013), the authors state "…most of the excess of second cancers in the photon therapy cohort occurred in the first 5 years after treatment…" and that "…for the key period of interest for radiation-related solid malignancies, 5 or more years after treatment, the incidence rate was nearly identical…" between photons and proton beam therapy.

A publication by Zelefsky et al. (2013) from Memorial Sloan-Kettering Cancer Center on the rate of second malignancies after treatment of prostate cancer with radical prostatectomy, brachytherapy and external beam radiotherapy yielded a different outcome related the conventional radiotherapy. Two thousand six hundred fifty-eight (2658) patients treated over 3 years were followed over 10 years. The study found that, when adjusted for age and smoking history, the incidence of second malignancies after radiotherapy was not significantly different from that after radical prostatectomy.

Regarding the risk of second malignancy after cranial irradiation with SRS, a study with 5000 patients showed no increased risk (Kollmeier et al., 2013). The authors conclude, "Pragmatically, in advising patients, the risks of malignancy would seem small, particularly if such risks are considered in the context of the other risks faced by patients with intracranial pathologies requiring radiosurgical treatments."

As a result of the available published data, the use of proton beam is considered not medically necessary solely to reduce the risk of a secondary malignancy. An exception, however, will be considered for those with stage IIA seminoma (see discussion above).

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Radiation Therapy for Bladder Cancer

POLICY

I. Non-muscle invasive bladder carcinoma (stages Ta, Tis, T1)

A. In the treatment of newly diagnosed non-muscle invasive bladder carcinoma, the use of radiation therapy is considered not medically necessary
B. In the treatment of recurrent non-muscle invasive bladder carcinoma in patients who are medically inoperable, the use of radiation therapy will be considered on a case-by-case basis

II. Muscle-invasive bladder carcinoma (stages T2-T4)

A. In an individual undergoing bladder preservation, the use of up to 37 fractions of 3D conformal radiation (3DCRT) is considered medically necessary. The use of Intensity-Modulated Radiation Therapy (IMRT) will be considered on a case-by-case basis
B. In the preoperative setting (i.e. prior to planned cystectomy), the use of radiation therapy will be considered on a case-by-case basis
C. In the postoperative setting (i.e. following cystectomy), the use of up to 33 fractions of 3DCRT is considered medically necessary in those who have pT3-T4 disease, positive lymph nodes and/or positive surgical margins

III. Palliation

A. In the palliative treatment of bladder carcinoma, the use of up to 20 fractions of 3DCRT is considered medically necessary

Key Clinical Points

For non-muscle invasive (stages Ta, Tis, T1) bladder carcinoma (NMIBC), treatment includes transurethral resection of bladder tumor (TURBT) often followed by intravesical therapy (Babjuk, 2013; Brausi 2011). In patients with high-risk non-muscle invasive bladder cancer, radiation has been evaluated. However, its use in this group of patients is not well defined. For example, in a retrospective study of 141 patients with high-risk T1 bladder cancer, radiation alone or combined with chemotherapy was found to be a "…reasonable alternative to intravesical treatment or early cystectomy..." (Weiss, 2006). On the other hand, in a randomized control trial of 210 patients with pT1G3 bladder cancer, radiation therapy was found to be equivalent to more conservative treatment (Harland, 2007). Further, NCCN currently does not endorse the use of radiation therapy for non-muscle invasive bladder cancer (NCCN v3.2017). As such, the use of radiation is considered not medically necessary for the treatment of non-muscle invasive bladder cancer.

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For an individual with muscle-invasive bladder cancer, treatment options include cystectomy or definitive chemoradiation as part of a bladder preserving approach (Gakis, 2013). An ideal candidate for bladder preservation includes one with tumors < 5 cm, a visibly complete TURBT, absence of associated carcinoma *in situ*, and no evidence of ureteral obstruction (Milosevic, 2007). NCCN also indicates that "…concurrent chemoradiotherapy or radiation therapy alone is most successful for patients with hydronephrosis and without extensive carcinoma *in situ*…"

Radiotherapy with concurrent cisplatin is the most common bladder sparing approach used to treat muscle-invasive bladder cancer. Following TURBT, 40 to 45 Gy is given to the whole pelvis using 3DCRT. Afterwards, repeat endoscopy is performed to examine the tumor response. If residual disease is seen, then a cystectomy is recommended. If a complete response is noted, then an additional 20 to 25 Gy is delivered with cisplatin. This approach demonstrated a 5-year survival of 49% when examined prospectively in RTOG 89-03 (Shipley, 1998). In a phase III randomized trial, concurrent chemoradiation improved 5-year disease-free survival (DFS) from 54% to 67% ($p = 0.01$) (James, 2012). Furthermore, approximately 80% of long-term survivors will maintain an intact bladder with this approach (Mak, 2014; Rodel, 2002). While several phase II prospective studies have examined alternative radiation fractionation schemes, none has demonstrated a clinically meaningful benefit compared to standard once a day fractionation schedules (Hagan, 2003; Kaufman, 2000). Recently, anti-PD-L1 immunotherapy with agents such as atezolizumab (Tecentriq) was approved for the treatment of advanced bladder cancer for patients who are unable to received cisplatin. However, the use of radiation therapy with these agents is considered investigational, experimental, and unproven (EIU) at this time. Definitive radiotherapy alone is considered for an individual with no evidence of metastatic disease who cannot undergo a cystectomy or concurrent chemoradiation.

In the preoperative setting, there remains insufficient data to determine the benefit of radiation therapy. For example, in an intergroup trial of 140 patients with invasive bladder cancer or recurrent superficial high-grade cancer, preoperative radiation (20 Gy in 5 fractions) was not associated with a survival advantage at five years (Smith, 1997). On the other hand, several publications have suggested a benefit to preoperative radiation in patients with high stage disease (Parsons, 1988; Cole, 1995). Further, recent NCCN Guidelines® state, "…for invasive tumors, consider low-dose preoperative radiation therapy prior to segmental cystectomy…" though this is a category 2B recommendation. Given the available data, the use of radiation in the preoperative setting will be considered on a case-by-case basis.

In the postoperative setting, the role of radiation is more defined. Data from retrospective series demonstrate higher local recurrence rates in patients with T3-T4 disease, positive nodes or positive surgical margins (Herr, 2004). The benefit of postoperative radiation and reducing local recurrence and improving disease-free survival has been shown in several studies (Bayoumi, 2014; Zaghloul, 1992; Nasr

2015). Further, recent NCCN guidelines recommend consideration of postoperative pelvic radiation for patients with pT3/pT4 pN0-2 disease. As a result, the use of radiation in the postoperative setting is considered medically necessary for an individual with pT3-T4 disease, positive lymph nodes and/or positive surgical margins.

In an individual with evidence of metastatic disease, palliative radiation is medically necessary, up to 20 fractions using 3D techniques.

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Radiation Therapy for Bone Metastases

POLICY

I. Up to 10 fractions of radiation planned using a complex isodose technique is considered medically necessary in the palliative treatment of bone metastases.

II. Techniques

A. Complex isodose technique: This planning technique is medically necessary for the majority of individuals requiring palliative treatment for bone metastases (CPT 77307). One or 2 gantry angles can usually produce the appropriate dose distribution. More than 1 phase (i.e. a conedown) is rarely medically necessary. In rare circumstances where there exists significant extraosseous component or where higher doses are justified, up to 3 gantry angles and use of complex blocking may be medically necessary.

B. Three-dimensional (3D) Conformal Radiation Therapy (3DCRT) and Intensity-Modulated Radiation Therapy (IMRT): Use of conformal radiation therapy techniques including 3DCRT and IMRT generally are not medically necessary for the treatment of bone metastasis. 3DCRT will be considered when there is a significant complex extraosseous component to the target volume. 3DCRT and IMRT will be considered only in cases where overlap with previous radiotherapy fields is likely to cause complications.

C. Stereotactic Body Radiosurgery (SBRT): SBRT is considered not medically necessary in the initial treatment of bone metastases. In addition to 3DCRT and IMRT, SBRT will be considered in cases that require treatment to a portion of the spine that has been previously irradiated. In other scenarios, SBRT will be considered on a case-by-case basis. For oligometastatic disease, please refer to the eviCore Radiation Therapy for Oligometastases Clinical Guideline.

III. Radium-223 (Xofigo®) is medically necessary for the treatment of castration-resistant prostate cancer for an individual with all of the following:

A. Skeletal (bone) metastases

B. No evidence of visceral metastases or bulky regional lymph nodes greater than 3 cm on imaging performed within the past 30 days

C. Who has received and exhausted all medical- or surgical-ablative hormonal treatments. The individual may be kept on his ablative hormonal treatment to maintain a castrate level in accordance with NCCN® guidelines.

D. Medically- or surgically-castration resistant prostate cancer, as defined by
   1. A serum testosterone level of less than < 50 ng/dL **and either**
      a. Sequential rise of prostate specific antigen (PSA) levels **or**

b. Worsening of existing bone metastases or development of new bone metastases on a bone scan performed within the past 60 days despite androgen-deprivation treatment

Xofigo® is administered intravenously once a month for 6 months.

Concurrent chemotherapy with Xofigo® is considered experimental, investigational, or unproven (EIU).

Key Clinical Points

Bone is a common site of metastatic cancer. Photon techniques are the mainstay of treatment for symptomatic bone metastases. Local field radiotherapy is highly effective in relieving pain and preventing fractures and is typically associated with minimal side effects. Eighteen trials assessing fractionation and dose of radiotherapy for painful bone metastases have been published (Hartsell et al., 2003; Wu et al., 2003). Randomized trials comparing single fraction of 8 Gy with multiple fraction radiotherapy regimens (20 to 30 Gy in 5 to 10 fractions) reveal similar overall response rates. Pain relief is typically achieved 1 to 4 weeks after treatment and the duration of response is 12 to 24 weeks. In a pooled analysis of patients with bone metastases, approximately one-third of patients will have complete pain relief and an additional one-third of patients will have partial relief of pain, irrespective of the dose-fractionation used. ROTG trial 9714 included 949 patients who were randomly assigned between 8 Gy in a single dose or 30 Gy in 10 fractions. Pain response rates were similar with 8 Gy in 1 fraction compared with 30 Gy in 10 fractions (66% in each group). A British trial (Yarnold et al., 1999) randomized 765 patients with painful bony metastases to 8 Gy as a single fraction, 20 Gy in 5 fractions, or 30 Gy in 10 fractions. There were no differences in pain endpoints among the groups. A Dutch trial (van der Linden et al., 2004) randomized 1171 patients with bone metastases to 8 Gy in 1 fraction or 24 Gy in 6 fractions and found no difference in pain relief or toxicity. While retreatment was higher with patients treated with a single fraction (18% vs. 9%), a reanalysis revealed this was because physicians were only more willing to treat after a single fraction. The study concluded that with or without the effect of retreatment, single fraction and multi-fraction radiation provided equal palliation.

The American Society for Radiation Oncology (ASTRO) Choosing Wisely® campaign has recommended not to use extended fractionation schemes (> 10 fractions) for palliation of bone metastases. It also states that, "…strong consideration should be given to a single 8 Gy fraction for patients with limited prognosis or with transportation difficulties." The NCCN guidelines for prostate non-vertebral metastases also state that, "…8 Gy as a single dose should be used instead of 30 Gy in 10 fractions."

Photon techniques as sole therapy have been used most commonly for the treatment of spinal cord compression. Corticosteroids are initiated immediately prior to radiation. A total dose of up to 30 Gy in 10 fractions may be appropriate in an individual predicted to

have more extended life span, although shorter dose schedules including single and 5-fraction treatment have been employed with similar outcome. One trial (Maranzano et al., 2005) randomized patients with cord compression with a short life expectancy to 8 Gy x 2 (16 Gy total dose) or 5 Gy x 3 followed by 3 Gy x 5 (30 Gy total dose). It found no significant difference in outcomes between the two schedules.

Surgery may be appropriate to establish a diagnosis, if uncertain, in an individual with acceptable performance status where bony retropulsion is likely to be the primary cause of neurologic deficit, in one with rapid deterioration of neurologic function or with high grade cervical cord compression, and can be considered more generally based on the results of a randomized trial comparing surgery and post-operative radiotherapy versus radiotherapy alone. Vertebral body resection and radical decompressive surgery with postoperative radiotherapy was found to be superior to radiotherapy alone in the only randomized trial of spinal cord compression conducted to date (Regine et al., 2003). Patients with a single site of cord compression and a minimum three-month life expectancy were enrolled. The trial was stopped early after 101 patients were enrolled. Patients who received surgery plus conventional radiation therapy retained the ability to walk significantly longer (126 days vs. 35 days with conventional radiation therapy alone). In a total of 32 patients who could not walk at the time of enrollment, 56% of those who received surgery and conventional radiation therapy recovered the ability to walk versus 19% who received conventional radiation therapy alone. Functional scores, maintenance of continence, and use of steroids and narcotics were all improved in patients undergoing decompressive surgery versus radiotherapy alone. Survival was slightly better in patients undergoing surgery (median 4.2 months vs. 3.3 months, $p = 0.08$). An individual with neurologic deficit and life expectancy of at least 3 months should be considered for surgery based on the results of this phase III study.

The ASTRO Task Force on radiotherapy for bone metastases published its guidelines in 2011. The task force clearly states that dosing and target volume have yet to be fully defined for SBRT and that SBRT should be considered investigational. Further, the task force states that SBRT should not be the primary treatment of vertebral bone lesions causing spinal cord compression. For recurrent painful lesions, the task force recommends that SBRT should be limited to clinical trials. The summary of the task force is that SBRT "…holds theoretical promise in the treatment of new or recurrent spine lesions… [and that]…its use be limited to highly selected patients and preferably within a prospective trial."

I. Radiation fractionation and technique

The ACR Appropriateness Criteria® panel recommends fractionation schedules ranging from a single 8 Gy fraction to 30 Gy in 10 fractions for the palliation of long bone involvement, whereas 35 Gy in 14 or 15 fractions and 40 Gy in 20 fractions is considered less appropriate due to the protracted length of therapy. A shorter course of radiation offers equivalent palliation and increased convenience for the individual and caregivers. CT simulation, to include accurately the involved

vertebrae and account for body habitus in conventional radiation therapy dose calculation is most desirable. Fluoroscopic simulation is regarded as a reasonable alternative. An individual with spinal involvement may be considered for treatment using 20 Gy in 5 fractions or 30 Gy in 10 fractions. An individual who requires more than 10 fractions for the treatment of bone metastases will require discussion with an eviCore radiation oncologist for authorization.

Complex techniques are medically necessary for the majority of individuals requiring palliative treatment for bone metastasis. According to ACR Appropriateness Criteria®, conformal radiotherapy techniques, including IMRT and protons, generally are not medically necessary for the treatment of bone metastases. Furthermore, Complex simulation, planning, and treatment charges do not apply in most cases. One study (Pope et al., 2013) found no clinical benefit among patients who underwent Complex or 3D planning for bone metastases. Therefore, 1 or 2 gantry angles can usually produce the appropriate dose distribution. Due to the palliative nature of the treatment, and the dose fractionations utilized, construction of a dose volume histograms of normal structures or of gross tumor volumes is not medically necessary and unlikely to significantly affect the treatment delivered. More than 1 phase (i.e. a conedown) is rarely medically necessary. In rare circumstances where there exists a significant extraosseous component or where higher doses are justified, up to 3 gantry angles and use of complex blocking may be medically necessary.

In cases of reirradiation of painful bone metastases, a phase III study (Chow, et al., 2014) randomized 425 patients between receiving 8 Gy vs. 20 Gy in multiple fractions. It found no difference in pain response to treatment, and that a single fraction of radiation was associated with less toxicity. Based on these results, reirradiation can be delivered safely with Complex techniques, and the use of SBRT in this setting to non-vertebral lesions is not medically necessary.

II. Management of oligometastases

Please refer to the eviCore Radiation Therapy for Oligometastases Clinical Guideline.

III. Radiopharmaceutical therapy

Radium-223 (Xofigo®) is an alpha emitter that targets areas of increased bone turnover in osteoblastic or sclerotic metastases. A phase III study examined patients with castration resistant prostate cancer with two or more bone metastases and no visceral metastases and randomized them to Radium-223 or matching placebo. It found improved overall survival (OS) for patients who received Radium-223 with a survival 14.9 months vs. 11.3 months ($p < .001$) in

those who received best standard of care. The targeted nature of Radium-223 with alpha particles of short range minimizes myelosuppression and has limited effects on the normal tissue. Based on these results, Radium-223 is medically necessary for the treatment of castration resistant prostate cancer with bone metastases but no visceral metastases and is administered intravenously once a month for 6 months.

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Radiation Therapy for Brain Metastases

POLICY

I. In considering optimal treatment for an individual with brain metastases, several prognostic factors must be considered. Risk factors for early death include:

A. Karnofsky performance status (KPS) ≤ 70
B. Age > 65 years
C. Tumor histology in order of prognosis (1. best prognosis→ 5. worst prognosis)
   1. Breast Her2+
   2. Non-Small Cell Lung Cancer (NSCLC)
   3. Melanoma
   4. Colorectal
   5. Breast Her2-
D. Number of brain metastases
E. Systemic disease status (new/stable vs. progressive)
F. Neurologic symptoms (present vs. absent)
G. Extracranial tumor burden (none vs. oligometastatic vs. widespread)

II. Whole brain radiotherapy (WBRT)

A. For an individual with most of the risk factors listed above, up to 10 fractions of WBRT is medically necessary. For an individual with a better prognosis, up to 15 fractions of WBRT is medically necessary
   1. WBRT is limited to 2 fields planned using a complex isodose technique (77307). Three-dimensional (3D) conformal planning, intensity-modulated radiation therapy (IMRT), and image guided therapy (IGRT) are not medically necessary

III. Stereotactic radiosurgery (SRS)

A. Initial treatment with SRS for brain metastases is medically necessary when the following conditions are met:
   1. No lesion is greater than 5 cm
   2. The individual has a KPS > 70
   3. Primary histology is not germ cell, small cell, or lymphoma
   4. Systemic disease is under control or good options for systemic treatment are available
   5. All lesions can be treated in a single treatment plan in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS). Note that **all** lesions present on imaging must be targeted as a single episode of care. If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met.

B. In an individual who has received prior SRS, retreatment with SRS is medically necessary when the following conditions are met:
   1. New lesions (no lesion is greater than 5 cm) are present with evidence of controlled systemic disease
   2. The individual has a KPS > 70
   3. Primary histology is not germ cell, small cell, or lymphoma
   4. The individual has not been treated with more than two episodes of radiosurgery in the past 9 months
   5. All lesions can be treated in a single treatment plan with a single fraction (for SRS) or up to 5 fractions (for fractionated SRS). Note that **all** lesions present on imaging must be targeted as a single episode of care. If this cannot be accomplished in a maximum of 5 fractions, each fraction must be billed as 3D conformal or IMRT, depending on the planning, as the definition of SRS is not met.
   6. Life expectancy > 6 months
   7. Submission of recent consultation note and recent restaging studies

C. In an individual who has received prior WBRT, SRS may be medically necessary if the individual's KPS is > 70, systemic disease is under control, and life expectancy > 6 months

D. Post-operative SRS is considered not medically necessary.

Key Clinical Points

I. Whole brain radiation therapy (WBRT)

The median survival following the diagnosis of metastatic disease involving the brain is generally four to six months. Many patients develop brain metastases late in the course of their disease when progressive extracranial disease dictates survival. The clinical response rate, degree of response, and duration of response depend on the extent of tumor and the severity of initial neurologic deficits.

The use of alternative fractionation schedules during WBRT has been studied in patients with brain metastases and in those undergoing prophylactic cranial radiation (Borgelt et al., 1980, Le Péchoux C et al, 2009; Murray et al., 1997; Wolfson et al., 2011). These studies have not shown any improvement in neurocognitive outcomes with alternative schedules. Shorter course regimens are appropriate for patients at increased risk of early death, such as those with a poor performance status and progressive systemic disease. Whole brain radiation using 30 Gy in 10 fractions is considered medically necessary in the treatment of brain metastases. For patients with an improved prognosis and few risk factors for early death, 37.5 Gy in 15 fractions can be considered medically necessary. In patients

with a poor performance status, a shorter course of radiation using 20 Gy in 5 fractions should be utilized.

The use of whole brain radiation for individuals who are eligible for treatment with SRS to all brain metastases has changed. A recent meta-analysis in 2014 analyzed 5 randomized studies and found the addition of whole brain radiation with SRS vs. SRS or surgery alone decreased the risk of intra-cranial progression by 53% but did not improve overall survival (Soon, 2014). A recent large randomized study conducted by the Alliance group came to similar conclusions. This study randomized patients to SRS with whole brain radiation or SRS alone and found higher rates of cognitive deterioration in patients who received whole brain radiation (92% vs 64%). Similarly, it found improved intracranial tumor rates (85% vs 50% at one year) but no improvement in overall survival with whole brain radiation (HR 1.02, 95% CI 0.75-1.38) (Brown, 2016). Furthermore, in 2014, ASTRO released its second Choosing Wisely® recommendations, which stated "Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases. (www.choosingwisely.org/astro-releases-second-list)". Therefore, in individuals who can undergo routine surveillance, WBRT is not considered medically necessary as adjunctive therapy following treatment with SRS.

In patients who have undergone surgical resection, post-operative WBRT was associated with a three-fourths relative risk reduction in recurrence (absolute risk reduction 18%) and was associated with decreased risk of death from neurologic causes (Patchell et al., 1998). Therefore, postoperative whole brain radiotherapy can be recommended for individuals who undergo resection of a solitary metastasis and who have controlled extracranial disease.

Whole brain radiotherapy involves the use of two lateral opposed fields, with or without the use of custom blocking. Radiation planned using a complex isodose technique is considered medically necessary for the majority of patients requiring whole brain radiation therapy. Due to the palliative nature of the treatment, and dose delivered, construction of a dose volume histogram is not medically necessary. In cases where the patient has received prior radiation 3D planning techniques will be considered.

One strategy to reduce the neurocognitive decline following whole brain radiation is the use of memantine. A single randomized study found a decrease in cognitive decline in patients who were started on memantine compared to observation, (hazard ratio 0.78, 95% CI 0.62 to 0.99).

A phase II study (RTOG 0933) examined whether hippocampal avoidance whole brain IMRT was associated with a decrease in neurocognitive decline. It found a mean decline in the Hopkins Verbal Learning Test of 7% at four months which compared favorably to historical comparison value of 30%. Overall survival was 6.8 months. This approach is now being investigated in an ongoing phase 3 randomized study. Confirmatory results of this approach are needed as there are limitations when comparing the results of RTOG 0933 to historical controls. Including that the improved survival seen on 0933 could explain the improvement in neurocognitive decline. Furthermore, the delivery of hippocampal radiation is technically challenging as shown in an analysis that found 24% of cases submitted to RTOG 0933 had unacceptable deviations when the contours were submitted for pretreatment review (Gondi, 2015). Therefore, hippocampal sparing whole brain radiation is considered investigational.

II. Stereotactic radiosurgery (SRS)

Radiosurgery delivers a high dose of radiation to a treatment volume using multiple convergent beams. The target is defined by high-resolution stereotactic imaging. To assure quality of patient care the procedure involves a multidisciplinary team consisting of a neurosurgeon, radiation oncologist, and medical physicist." The adjective "stereotactic" describes a procedure during which a target lesion is localized relative to a fixed three-dimensional reference system, such as a rigid head frame affixed to a patient, fixed bony landmarks, a system of implanted fiducial markers, or other similar system. This type of localization procedure allows physicians to perform image-guided procedures with a high degree of anatomic accuracy and precision. Stereotactic Radiosurgery (SRS) typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system. Current guidelines state that radiosurgery for brain metastases should be delivered in a single fraction. More than a single fraction of radiosurgery is not medically necessary in the treatment multiple brain metastases. Consideration for multiple sessions of radiosurgery, up to 5, will be considered on a case by case basis after peer to peer discussion or review of a patient specific rationale for the use of multiple fractions.

Selection criteria for radiosurgery are similar to those for surgical resection, i.e. patients with solitary metastases, tumor size, tumor location, good performance status, and limited or responsive extracranial disease (Andrews, 2004; Kocher, 2011; Soon, 2014; Yamamoto, 2014). In tumors, up to 3cm in size, radiosurgery is associated with a local control of approximately 70% at one year (Kocher, 2011). A recent prospective nonrandomized study revealed radiosurgery could be utilized in the treatment of up to 10 brain metastases with similar efficacy and no increase

in toxicity as long as the cumulative volume < 15 mL. Therefore, radiosurgery is medically necessary in the initial management of patients with brain metastases who meet the following conditions, 1. No lesion is greater than 3 cm, 2. The individual has a KPS > 70, 3. Systemic disease is under control or good options for systemic treatment are available, 4. All lesions can be treated in a single fraction (for SRS) or up to 5 fractions (for fractionated SRS).

Following radiosurgery alone, approximately 25-50 % of patients will develop new metastases within the first year (Ayala-Peacock, 2014; Gorovets, 2017). Treatment options for new metastases include further radiosurgery or whole brain radiation therapy. Factors predicting for recurrences within the brain include age, histology, increasing number of brain metastases, and increasing extracranial disease burden (Gorovets, 2017). The primary drawback with the use of radiosurgery upfront is the increased risk of distant failure in the brain (Kotecha, 2017). Patients who present with early and extensive distant failure in the brain and those with limited survival are better treated with whole brain radiation therapy. About 40% of patients will require whole brain radiation within 6 months of initial treatment with radiosurgery. In patients who do experience further recurrence in the brain following radiosurgery it is critical to risk stratify this cohort to determine who will benefit from further radiosurgery vs. whole brain radiation (Gorovets, 2017). Risk stratification includes taking into the following prognostic factors: 1) Age, 2) Number of metastases, 3) Primary histology in order of worsening prognosis (Breast Her 2+, Other, NSCLC, Melanoma, Colorectal cancer, Breast Her2-), 4) Presence of neurologic symptoms, 5) Systemic disease status, 6) Extracranial burden (none, oligometastatic, widespread), and 7) Distant intracranial recurrence ≤ 3 months.

Therefore, further treatment with radiosurgery, in a previously treated patient will be considered medically necessary in those who meet the following conditions: 1) New lesions (no lesion is greater than 5 cm) are present in absence of systemic progressive disease, 2) The individual has a KPS > 70, 3) The individual has not been treated with more than two episodes of radiosurgery in the past 9 months, 4) All lesions can be treated in a single treatment plan with a single fraction (for SRS) or up to 5 fractions (for fractionated SRS), 5) Expected survival > 6 months and if a previously treated lesion has recurrence (and necrosis is not considered likely) and more than 6 months has elapsed since initial treatment (NCCN).

In addition, submission of the consultation note and recent restaging studies will be required for review to verity that the indidual's systemic disease is controlled, life expectancy, history of previous treatments, and performance status.

A. Postoperative SRS

1. MD Anderson Cancer Center (MDACC)
   Mahajan et al. (2017) reported a phase III randomized trial (NCT00950001) of 132 patients with 1 to 3 completely resected brain metastases treated with postoperative SRS or observation. Patients were excluded if the tumor cavity was greater than 4 cm, the unresected brain metastases were no greater than 3 cm, there was prior history of brain radiation, presence of leptomeningeal disease, a prior history of resection of any brain metastases, incomplete resection, poor performance status (KPS < 70), and small cell lung malignancies (1 vs. 2 to 3), histology (melanoma vs. other), and preoperative tumor size (< 3 cm vs. > 3 cm).

   At 12 months, the use of SRS was associated with improved freedom from local recurrence (73% vs. 43% in observation, p = 0.015) with no statistically significant increase in distant brain metastases or time to whole brain radiation. Median overall survival (OS) was similar (17 months for the SRS group vs. 18 months for the observation group). In a post-hoc analysis, patients with an initial tumor diameter of 2.5 cm or less was associated with a 91% 12-month freedom from local recurrence rate, whereas those with a tumor > 2.5 cm had a local control rate of 40 to 46%. In multivariate analysis, predictors for time to local recurrence were SRS and metastases size. For overall survival, only stable disease (compared to progressive disease) was a significant predictor.

2. N107C/CEC.3
   Brown et al. (2017) reported on a phase 3 trial randomizing patients to SRS or WBRT to the resection cavity after resection (total or subtotal) of brain metastases. Patients eligible included those with one resected brain metastasis (with a resection cavity under 5 cm) with up to an additional 3 unresected metastases (each under 3 cm). It is noted that in both groups, SRS was given to the unresected metastases. Patients were excluded if there was prior cranial radiation, leptomeningeal metastases, lesions, within 5 mm of the optic chiasm or within the brain stem or germ cell, small-cell, or lymphoma histologies. Patients were stratified according to age, duration of extracranial disease control, number of brain metastases, histology, and diameter of resection cavity and treatment center. The primary endpoints were cognitive deterioration free survivial (CDFS) and OS.

   One hundred ninety-four (194) patients were included in the study with a medial follow up of 11.1 months. It is noted that of the 98 patients assigned3 to SRS, 5 did not receive treatment, 1 did not have baseline testing done, 11 died prior to 3 months, 20 did not complete cognitive assessment at 3 months, 13 died between 3 and 6 months, 1 was lost to

follow up between 3 and 6 months, and 16 did not complete cognitive assessment at 6 months.

The authors reported that the median CDFS was longer following SRS than WBRT (3.7 months vs. 3.0 months, p <0.0001). When conducted a stratified analysis, the median CDFS was longer following SRS than WBRS (3.7 months vs. 3.1 months, p < 0.0001).

Cognitive deterioration at 6 months was lower in the SRS group vs. WBRT (52% vs. 85%). However, about ½ of the patients enrolled (54 [SRS] and 48 [WBRT]) were available for analysis at this time.

Median OS was not statistically different between the two groups (12.2 months for SRS vs. 11.6 months for WBRT). It is noted, however, that brain metastases was the cause of deat in 87% of SRS patients vs. 73.1% in those receiving WBRT (p value not provided).

Local control and distant brain control were worse in the SRS group. For example, surgical bed control was significantly worse with SRS at 6- and 12-months (80.4% and 60.5% vs. 87.1% and 80.6% respectively). Local control was significantly worse with SRS at 3-, 6-, and 12-months (84.7%, 69.4%, and 61.8% vs. 96.7%, 92.5%, and 87.1% respectively). Distant brain control was significantly worse with SRS at 6- and 12-months (72.1% and 64.7% vs. 94.6% and 89.2% respectively). SRS was associated with a shorter time to intracranial progression as compared to WBRT (6.4 months vs. 27.5 months, p < 0.0001). Twenty percent (20%) of patients in the SRS group received WBRT as salvage therapy.

With respect to quality of life measurements, a clinically significant improvement was noted more frequently in the SRS group as compared to the WBRT group for physical well-being at 6 months. On the other hand, there was no difference in functional independence change from baseline at 6 months. The authors conclude that ”SRS in the postoperative setting is a viable treatment option…and should be considered one of the standards of care as a less toxic alterntive to WBRT.”

When considering treatment options following surgical resection of brain metastases, the data published by Brown et al. (2017) provide some insight. CDFS was improved by approximately 2 weeks; however, at the expense of a significantly higher risk of surgical bed relapse, local relapse, and distant brain relapse. The clinical relevance of this in unclear though there

appears to be a higher rate of death due to brain metastases in the SRS group. As such, the use of SRS in the postoperative setting is considered not medically necessary.

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Radiation Therapy for Breast Cancer

POLICY

I. Whole breast irradiation following breast-conserving surgery

A. For an individual with stage T1-2N0 disease, the use of a hypofractionated regimen is preferred. This includes the use of up to 16 fractions of three-dimensional conformation radiation therapy (3DCRT) to the whole breast and up to 8 fractions of electrons or photons as a boost to the surgical bed.

B. The use of up to 28 fractions of 3DCRT to the whole breast and, if needed, regional nodes is medically necessary. The use of up to 8 fractions of electrons or photons as a boost to the surgical bed is medically necessary.

C. Note that the boost to the surgical bed is planned using either a complex isodose technique (CPT®77307) or electrons (CPT®77321). A brachytherapy boost is not medically necessary. The use of AccuBoost® is considered experimental, investigational and/or unproven (EIU).

D. The use of Intensity Modulated Radiation Therapy (IMRT) for treatment of the whole breast will be considered on a case-by-case basis.

II. Accelerated partial breast irradiation (APBI) following breast conserving surgery

A. The use of up to 10 fractions of 3DCRT, IMRT or high dose rate (HDR) brachytherapy (intracavitary, interstitial or electronic) is medically necessary. The use of AccuBoost® is considered experimental, investigational and/or unproven (EIU).

III. Intraoperative radiation therapy (IORT)

The use of single fraction IORT at the time of breast conserving surgery will be considered for select node-negative individuals with invasive cancer in accordance with ASTRO guidelines (Correa et al., 2017)

A. Electron-beam IORT is considered medically necessary in a node-negative individual 50 years of age or older with invasive cancer and negative surgical margins

B. Consideration will be given for low-energy x-ray IORT (INTRABEAM®) when limited to a node-negative individual 50 years of age or older with invasive cancer and negative surgical margins who is enrolled in a prospective clinical trial or registry. However, coverage is dependent on the member's policy language as it relates to clinical trials and registries. The use of electronic brachytherapy for IORT is considered experimental, investigational and/or unproven.

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C. In an individual who is found to have adverse pathologic features, supplemental radiation using up to 28 fractions of 3DCRT is considered medically necessary

IV. Post-mastectomy radiation is medically necessary in an individual with positive axillary lymph node(s), a primary tumor greater than 5 cm or positive or close (< 1 mm) surgical margins

A. The use of up to 30 fractions of 3DCRT to the chest wall and, if needed, regional nodes is medically necessary
B. The use of up to 8 fractions of electrons as a boost is medically necessary.
C. The use of IMRT will be considered on a case-by-case basis.

V. Palliation

A. The use of up to 25 fractions of 3DCRT is considered medically necessary

Key Clinical Points

Early stage breast cancer is typically treated with mastectomy with or without radiotherapy to the chest wall, or breast local excision followed by radiotherapy. Indications for post-mastectomy radiotherapy are controversial but include the presence of multiple positive axillary lymph nodes, positive or narrow margins (< 1 mm), or large primary tumor size (> 5 cm). Radiotherapy is indicated for most women after local excision of ductal carcinoma in situ (DCIS) or invasive carcinoma. In some women over the age of 70 who have been diagnosed with invasive breast cancer, radiation therapy may be safely omitted, especially if they have comorbidities.

Primary therapy for women with metastatic breast cancer (M1 stage) is systemic therapy. However, if there is symptomatic breast or chest wall disease, a short course of radiotherapy may alleviate symptoms. In most cases, short course hypofractionated (HF) treatment (i.e., 10 fractions) is appropriate. It is not appropriate to deliver more than 20 fractions in that setting (or 25 fractions if a boost is included). Evidence is limited with regard to the role of locoregional radiotherapy for M1 stage disease in the absence of symptomatic locoregional disease. Locoregional radiation therapy may be appropriate for women who initially present with metastatic disease but after surgery and/or chemotherapy are found to have no clinical evidence of disease.

Most women with early stage breast cancer are treated with a five- to seven-week course of conventional radiation therapy. Use of simple devices for positioning (e.g., angle board) is usually adequate. The five- to seven-week course of treatment is based on dose-fractionation considerations that might decrease long-term side effects and provide optimal local control of disease. More than 30 fractions (or 38 fractions when a boost is utilized) are not medically necessary.

Hypofractionated whole breast irradiation (HF-WBI)

Several randomized trials have confirmed the efficacy of a hypofractionated regimen in the adjuvant treatment of breast cancer. For example in the Ontario trial, Whelan et al. (2010) randomized 1234 women with invasive carcinoma, negative axillary nodes and negative margins to 50 Gy in 25 fractions or to 42.5 Gy in 16 fractions to the whole breast. At 10 years, the hypofractionated regimen was not inferior to standard fractionation with respect to recurrence, survival or toxicity.

In the START-B trial, 2215 women with stage pT1-3a, pN0-1 invasive carcinoma were randomized to 50 Gy in 25 fractions or to 40 Gy in 15 fractions. At a median follow up of 6 years, there was no statistical difference in the rate of locoregional recurrence (LRR) between the groups (Yarnold et al., 2008). At a median follow up of 9.9 years, there remained no difference in LRR. The hypofractionated regimen was associated with higher rates of disease-free survival (DFS) and overall survival (OS) as well as reduced rates of breast shrinkage, telangiectasia and breast edema.

In an ASTRO evidence-based guideline, the task force stated that hypofractionated and conventionally fractionated regimens were "…equally effective for in-breast tumor control and comparable in long-term side effects…" for patients who were at least 50 years old with pT1-2N0 disease, who had not received chemotherapy and maintained homogeneity within the breast. For individuals who did not meet these criteria, the task force did not reach consensus, which "…should not be interpreted as a contraindication to its use." (Smith et al., 2011)

Such consensus and data led to ASTRO stating, "Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules." in their initial Choosing Wisely® campaign. (ASTRO, 2013).

Given the evidence supporting a hypofractionated regimen for an individual 50 years of age and older with pT1-2N0 breast carcinoma, the use of such a regimen is preferred.

Boost radiotherapy has been shown to improve local control, particularly in younger women. A boost to the tumor bed is recommended in an individual at higher risk for local failure (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). Electron beam or photon fields are most commonly used. Typical boost regimens after conventionally-fractionated WBI give total doses of 10 to 16 Gy at 2 Gy per fraction. It is appropriate to give up to an additional 4 fractions for a boost after HF-WBI when a boost is felt to be indicated.

An electron field is the simplest and most available technique used for delivering the boost. Women with deep-seated tumor beds or very large breasts often require treatment with photon boosts, which may consist of two or more fields.

Interstitial brachytherapy was commonly used for performing the boost during the development of breast-conserving therapy. While the use of brachytherapy in giving the boost is recognized in the NCCN guidelines®, it does not improve tumor control compared to external-beam boosts and results in worse cosmesis. Other brachytherapy techniques (such as the MammoSite® balloon brachytherapy system) and intraoperative radiotherapy (IORT) have also been used to perform the boost, but again they have not been shown to be superior to external-beam boosts, and they may have added toxicities. One prospective trial (Wong et al., 2014) of 52 patients treated at the Mayo Clinic with an intraoperative electron boost found difficulty in wound healing in 2 patients who had additional surgery later and 1 patient who developed significant fibrosis after aspiration of a symptomatic seroma. Therefore, the use of interstitial or intracavitary brachytherapy or IORT as a boost is not medically necessary and generally will not be reimbursed. For chest wall and regional nodal irradiation, the NCCN Guidelines® state that the appropriate dose is 50 Gy, given as 1.8 to 2 Gy fraction size, with or without the addition of a scar boost of 10 Gy given at 2 Gy per fraction, for a total dose of approximately 60 Gy. All dose schedules are given 5 days per week.

The acute side effects of radiation and the cosmetic result can be affected by inhomogeneities of dose within the breast, which, if the simplest methods are applied, can be significant given the irregular shape of the breast. Therefore, many methods can be applied to “compensate” for the shape of the breast and improve dose homogeneity by altering the fluence of radiation as it exits the treatment machine. A Complex planning method utilizes tungsten wedges, which are devices placed in the head of the machine to increase the fluence at the base of the breast and decrease the fluence anteriorly, where the tissue is thinner. However, this technique takes into account only the shape of the breast in one plane, and not the entire breast, and has been shown to be associated with more temporary acute skin reactions as compared to more sophisticated 3D techniques.

3D methods include real-time modulation of the beam to improve the dose distribution, including forward-planned 3DCRT with segments to modulate the fluence (also referred to as “step-and-shoot”), forward-planned electronic compensation method, and inverse-planned IMRT. Inverse planning requires dedicated software for IMRT planning in order to calculate and optimize the fluence to the outlined target and spare surrounding organs, which are also outlined. This approach requires trained personnel, individual-specific treatment delivery verification (i.e., comparison of calculated and measured doses in a solid-water phantom), and specific delivery equipment. Forward-planned 3D radiotherapy with segments can be performed with a 3D planning system. The treatment plan consists of several fields with different weights at the same gantry position (called segments). One study (Cardinale et al., 2007) compared the dose inhomogeneity within the breast and dose to heart and lung with inverse-planned IMRT and 3D segments (typically up to 5 fields total and 2 gantry angles) and found no significant differences. A recent study found no difference in normal tissue exposure from forward-planned 3D radiotherapy and IMRT plans. A study of 358 patients (Pignol

et al., 2008) found no differences in acute toxicity whether the forward-planning technique was used as compared with inverse planning ($p = 0.31$).

There are several advantages of forward-planned 3D compensation using a limited number of segments compared to inverse-planned IMRT. Forward planning requires less beam-on time, so that scatter to non-target tissues is minimized, which is especially important in young women or smokers, who may have a small increased risk of contralateral breast cancer or lung cancer years after radiotherapy, respectively.

Forward-planned 3D radiotherapy is widely available. Facilities that perform inverse-planned IMRT would have the equipment and personnel to perform forward-planned 3D radiotherapy, although the converse is not necessarily true. The forward-planning techniques are an extension of 3DCRT. Inverse-planning IMRT for breast cancer thus has no documented advantage over the forward planning step-and-shoot technique and as mentioned above, results in less beam-on time. Therefore, although IMRT is an acceptable method of breast irradiation, IMRT treatment planning is not medically necessary. In lieu of IMRT, the appropriate 3D radiotherapy will be considered medically necessary. An exception will be made when a physician requests the use of multiple-gantry angle IMRT in an individual with left-sided breast cancer in whom forward-planned tangential fields result in excessive dose to the heart. The requesting physician will need to state that plans and dose-volume histograms comparing the IMRT and forward-planned treatment plans have documented a superior result. (The treating physician should be encouraged to use deep inspiration breath hold techniques or prone positioning if available, as these usually give greater sparing of the heart than multiple-gantry angle IMRT. However, not all centers have such capabilities, and these approaches cannot be used for all individuals because of the need to treat regional nodes, individual ability to follow commands for breath holding, etc.). IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

Accelerated Partial Breast Irradiation (APBI) is an emerging technique in which the target of the radiation is only a portion of the breast with the greatest likelihood of harboring residual cancer cells after lumpectomy. The technique is called “accelerated” because it is given twice daily for five days, sparing the patient the inconvenience of daily radiation therapy for up to 7 weeks. Treatment is given in a “hypofractionated” fashion, with higher doses per fraction, which can be associated with greater delayed toxicity. This is considered medically necessary, because a smaller volume of breast tissue is being treated. However, brisk skin reactions can occur soon after the course of treatment and late skin changes and soft tissue fibrosis could potentially affect the cosmetic result or make the interpretation of future mammography more difficult.

There are several techniques of APBI:

1. Interstitial technique in which multiple needles are placed percutaneously and catheters are threaded into the breast (Brachytherapy)
2. Intracavitary single catheter balloon catheter, in which a device is placed into the surgical cavity (Brachytherapy)
3. Intracavitary multiple catheter device – single device with multiple catheter channels inserted into surgical cavity (Brachytherapy)
4. Multiple coplanar or non-coplanar field photon technique
5. Single fraction IORT using electrons or photons

Several single-institution, non-randomized studies using the multicatheter technique have shown low local recurrence rates that are comparable to standard photon technique. Data on newer techniques are not yet as mature but show comparable results at shorter follow-up.

There is no consensus on exactly which individuals are appropriate candidates for APBI. An ASTRO task force on this subject encouraged individuals to participate in clinical trials. If not eligible for trials, it is recommended that individuals who may be suitable for APBI are women 60 years and older who are not carriers of a BRCA1/2 mutation treated with primary surgery for a unifocal T1N0 estrogen receptor- (ER) positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype, not be associated with extensive intraductal component (EIC) or lobular carcinoma in situ (LCIS), and margins should be negative. This was adopted for the most recent NCCN guidelines®. However, other groups such as the ABS and the American Society of Breast Surgeons (ASBrS) have promulgated more liberal guidelines in the past (age 45 years old or greater, invasive ductal carcinoma (IDC) or DCIS, total tumor size (IDC and DCIS) 3 cm or smaller, negative microscopic excision margins, and pathologically-negative axillary lymph nodes). Further, many experts have contested the correctness of the ASTRO guidelines, with an increasing number of studies showing low failure rates in patients who do not meet these criteria, comparable to that of similar patients treated with WBI (e.g., from the William Beaumont Hospital group). Therefore, selection criteria for an individual for the use of APBI have not been established. Until there is firmer consensus in the community, it is reasonable to allow reimbursement for APBI when an individual is treated within the guidelines of any of the major professional groups.

The ASTRO and NCCN Guidelines® state that appropriate schemes for APBI are 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day. Other fractionation schemes are currently under investigation. Therefore up to 10 fractions (whether photon or brachytherapy) for APBI is considered medically necessary.

The Axxent® electronic brachytherapy (Xoft Inc, Fremont, CA) is a novel way of delivering APBI. Electronic brachytherapy delivers HDR radiation without radioactive

isotopes. In lieu of radioactive isotopes, the electronic brachytherapy system uses a miniature 50 kV xray tube, measuring 2.2 mm in diameter as a radiation source. The xray source can be turned off and on as necessary. The low energy of the xray source allows delivery in minimally shielded settings.

For treatment, the surgeon inserts a balloon applicator into the lumpectomy cavity. The balloon is inflated with saline. The catheter is connected to a robotic controller. At the time of treatment, a protective xray shield is placed over the breast. The miniature xray source travels into the catheter into the inflated balloon. The xray tube is encased in a sheath. Water is pumped through the xray sheath to cool the source. After the delivery of the treatment, the xray source is turned off and withdrawn through the catheter. Treatments are typically delivered in 10 fractions, twice daily. The dose-distribution is very similar to that achieved by HDR brachytherapy.

A study by Mehta et al. (2010) included 44 women treated with Axxent® electronic brachytherapy. Eligibility included age > 49, completely resected IDC (< 2 cm) or DCIS (< 2 cm), lymph node negative, with negative margins of at least 1 mm. The prescribed dose was 3.4 Gy, prescribed to 1 cm beyond the balloon surface. Follow up was 6 months in 43 patients. Four grade 3 toxicities were reported, including pain, blistering and moist desquamation. The study demonstrated that the Axxent® system delivered the planned dose of radiation successfully and was well tolerated.

The ASTRO emerging technology committee report on electronic brachytherapy (EBT) (Park et al., 2010) stated that, "…advantages of electronic brachytherapy over existing technologies are as yet unproven in terms of efficacy or patient outcomes…EBT is currently an unregulated treatment delivery modality for cancer therapy, with minimal clinical data available from small single institution studies, none with any significant follow-up."

Although the clinical data on this technology is limited, it appears very likely that it will result in results equivalent to those using HDR brachytherapy for APBI, which is reimbursed. Therefore, electronic brachytherapy will be approved for use.

AccuBoost® Non-Invasive Image-Guided Breast Brachytherapy (NIIGBB) (Advanced Radiation Therapy, Inc., Billerica, MA) is a method of IGRT that incorporates a real-time image guidance mammography-based system to deliver noninvasive brachytherapy. The breast is immobilized using moderate compression. Digital mammography provides localization of the target volume. Custom applicators, ranging from 4 to 8 cm in diameter, are designed to deliver a highly collimated beam, which are used with an HDR remote afterloading system. The applicators are mounted on mammography paddles, centered on the target to deliver HDR IR-192 along two intersecting orthogonal axes sequentially. To use AccuBoost®, the tumor bed must be visible on mammogram, the planning target volume (PTV) must be less than or equal to 8 cm, and the breast must be compressible to a plate separation less than or equal to 7 cm.

Sioshansi et al. (2011) conducted a study of dose modeling of NIIGBB, compared with electron beam and 3DCRT partial breast radiation. This study modeled the NIIGBB dose distributions as a point source. Dose volume comparisons were evaluated in eight patients and compared to 3DCRT and electron boost simulations. Patient eligibility required a clearly defined target cavity identified on CT, >/= 5 mm distance between the posterior aspect of the cavity and the chest wall, and a breast that could be compressed in </= 8 cm. The authors reported that the NIIGBB PTVs were significantly less than those of the 3DCRT and electron boost, allowing for more normal tissue sparing. Because NIIGBB directs radiation parallel to the chest wall, there is negligible dose delivered to the chest wall and lung. NIIGBB, compared to electrons and 3DCRT, resulted in lower maximum dose to the skin (60% and 10% respectively), and chest wall/lung (70 to 90%).

There is, as yet, little clinical information available on the long-term results in patients treated with this technique. A multi-institutional study showed acceptable rates of acute skin toxicity and a high rate of excellent or good cosmetic results at 6 months. In a study from Tufts Medical Center (Leonard et al., 2012), the cosmetic results and skin and subcutaneous toxicities were similar in 18 matched pairs of patients with more than 6 months follow-up treated with either AccuBoost® or a conventional electron boost. This device has also been used for APBI, again with very limited follow-up of small numbers of patients. Given the paucity of data regarding the use of NIIGBB, particularly on local control, additional research is necessary prior to widespread approval of NIIGBB outside of a clinical trial. NIIGBB is considered investigational.

IORT

The use of IORT for the treatment of breast cancer has been evaluated in two prospective randomized clinical trials, TARGIT-A which utilized low-energy x-rays and ELIOT, which utilized electrons.

TARGIT-A

In the TARGIT-A trial, patients 45 years or older with unifocal invasive ductal carcinoma (preferably less than 3.5 cm) were randomized to receive IORT (to the lumpectomy bed) or external beam radiation therapy (EBRT) to the whole breast (with or without a boost). Those receiving IORT were stratified by timing of the IORT (pre-pathology versus post-pathology) and by facility. For pre-pathology patients randomized to IORT, supplemental EBRT to the whole breast (without a boost) was given when pathology from the lumpectomy revealed either invasive lobular carcinoma, extensive intraductal component or another adverse criterion (i.e. high-grade, lymphovascular invasion, nodal involvement). In this setting, IORT was considered the boost. The primary outcome evaluated was local control in the conserved breast.

Initial results were published in 2010 at which time data was presented on 2232 patients, 862 who had a median follow up of 4 years and 1514 who had a median follow up of 3 years. Of the 1113 patients randomized to IORT, 996 received the allocated treatment. Of the 1119 patients randomized to EBRT, 1025 received the allocated

treatment. At four years, there was no significant difference in the estimate of local recurrence between IORT and EBRT (1.2% versus 0.95%, p = 0.41). It is noted that in the pre-pathology IORT group, 14.2% of patients received supplemental EBRT.

In a more recent update published in 2014, a total of 3451 patients randomized to IORT and 1730 patients randomized to EBRT were evaluated. Within the IORT group, 2298 were randomized prior to the lumpectomy (pre-pathology strata) and 1153 were randomized after lumpectomy (post pathology strata). Median follow-up of the 3451 patients who had received IORT was two years and five months. 2020 patients had a median follow up of four years and 1222 patients had a median follow-up of five years (note that only 611 patients (18%) had 5-year follow up). At five years, the risk for local recurrence with IORT was significantly higher as compared to EBRT (3.3% versus 1.3%, p = 0.042). When considering the pre-pathology strata, the risk of local recurrence was 2.1% with IORT versus 1.1% (p = 0.31). This contrasts with the post pathology strata where the recurrence was 5.4% with IORT versus 1.7% with EBRT (p = 0.069). Based on this data, the authors conclude that "TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to postoperative external beam breast radiotherapy."

In response to this publication, several authors have criticized the statistical analysis. For example, Cuzick (2014) states "…there are several major deficiencies in the analysis…" including "…the misuse of the non-inferiority criterion…" which "…clearly fails.." as the '…Kaplan-Meier estimates… establish a 2% superiority of external beam radiotherapy (p = 0.04) and a CI extending beyond 2.5%.'" Cuzick further states the "…protocol clearly states that the primary analysis population includes all randomized patients. However, the report concentrates on the prepathology group."

Haviland et al. (2014) stated that "…assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point. This analysis, including the non- inferiority test statistic, is therefore unreliable." The authors conclude that "…the TARGIT-A trial remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment."

Finally, Silverstein et al. (2014) indicated that "…the results of the TARGIT-A trial, with a median follow-up (FU) of 29 months, is still well below the median time when breast recurrences can be expected, especially since more than 90 % of TARGIT-A women were estrogen receptor positive, and at least 65 % received adjuvant hormonal therapy, a treatment well-known to delay recurrences in ER + women." In addition, they note that "…overall breast recurrence rates in the TARGIT group also exceeded rates in the EBRT group, a difference at borderline statistical significance (p = 0.053)." They conclude that "…with 29 months of median follow-up, the TARGIT data are still immature and risk-adapted IORT with 50-kV X-rays is still too early in follow-up to select the subset of women whose local control will be within their noninferiority criteria margin

of 2.5%. Until the data are more mature, 50-kV patients should be treated under strict institutional protocols."

ELIOT

In the ELIOT trial, 1305 patients 48 years or older with tumors 2.5 cm or smaller were randomized to receive IORT with electrons or EBRT. Patients were stratified by tumor size (<1.0 cm vs. 1.0 to 1.4 cm vs. ≥1.5 cm). The primary endpoint was the occurrence of ipsilateral breast tumor recurrences (IBTR), which included true local relapse plus new ipsilateral breast tumor. Median follow for all patients was 5.8 years.

Results revealed that there was a significantly greater occurrence of IBTR in the IORT group compared to the EBRT group at five years (4.4% versus 0.4%, p = 0.0001). The five-year rate of true local recurrence (occurring in the index quadrant) was also significantly higher in the IORT group compared to the EBRT group (2.5% versus 0.4%, p = 0.0003). The rate of new ipsilateral breast carcinoma was also significantly higher in the IORT group compared to the EBRT group (1.9% versus 0%, p = 0.0001). Finally, it was noted that the IORT group developed a significantly higher rate of axillary or other regional lymph node metastases (1% versus 0.3%, p = 0.03). At five years, overall survival did not differ between the two groups.

In a multivariate analysis of the IORT group, tumor size greater than 2 cm, presence of four or more positive lymph nodes, a poorly differentiated tumor and triple negative subtype was associated with nearly twice the risk of IBTR. The risk of IBTR at five years was 11.3% if any one of these unfavorable characteristics was present versus 1.5% in those without these features (p < 0.0001). It is noted that this group of patients with a low risk of IBTR is similar to that of the "suitable" APBI group as defined by ASTRO.

ASTRO CONSENSUS STATEMENT

ASTRO recently released an Evidence-Based Consensus Statement for APBI. In this statement, the authors recommend that patients "…be counseled that in 2 clinical trials the risk of IBTR was higher with IORT."

With respect to IORT using electrons, the authors state that "ELIOT has a median of 5.8 years follow up (n = 1305). However, ELIOT patients with invasive cancer fitting the 'suitability' criteria had a very low rate of IBTR. Among these patients, the 5-year occurrence of IBTR was approximately 1.5%, pointing out the importance of patient selection." Hence the recommendation that "…electron beam IORT should be restricted to women with invasive cancer considered "suitable" for PBI."

With respect to IORT using low-energy x-rays, the authors recommend that "…low-energy x-ray IORT for PBI should be used within the context of a prospective registry or clinical trial, per ASTRO Coverage with Evidence Development (CED) statement. When used, it should be restricted to women with invasive cancer considered 'suitable' for partial breast irradiation based on the data at the time of this review."

When further detailing their recommendations, the authors note that "…the five-year IBTR risk is based on the overall short follow up of the TARGIT trial, which limits precision of the five-year risk estimates. Although there was no statistically significant difference in IBTR risk for patients treated with IORT versus WBI in the TARGIT prepathology subgroup, the task force thought greater weight should be placed on evaluation of the efficacy of IORT in the prespecified primary analysis population that included all patients." Given this and the concern of "…misuse of the noninferiority criterion…," the authors "…felt low-energy x-ray IORT should continue to be used within the context of a prospective registry or clinical trial to ensure long-term local control and toxicity outcomes are prospectively monitored." In addition, "…given the increased risk of IBTR, the task force advised that low-energy x-ray IORT, when used, be confined to patients with the lowest risk of IBTR, specifically those in the 'suitable' group."

In response to the Consensus Statement, Small et al. reiterated that the "TARGIT-A trial specified stratification between pre- and post-pathology before randomization…" and that "…the panel's recommendations regarding IORT should have acknowledged the results for the pre-specified analysis for the primary end-point of IORT treatment in the whole trial (n = 3451, a difference of 2 % p = 0.04), as well the pre-pathology stratum (n = 2298, a difference of 1% p = 0.31).

CONCLUSION

Electron beam IORT is considered medically necessary for a node-negative individual with invasive cancer when used in accordance with the updated ASTRO Evidence-Based Consensus Statement for APBI.

As guidelines indicate that low-energy x-ray IORT (INTRABEAM®) should be used in the context of a prospective registry or clinical trial, coverage will depend on the member's policy language as it relates to clinical trials and registries.

As there remains limited data on the use of electronic brachytherapy for IORT, as the dose distribution differs from INTRABEAM® and as the Consensus Statement did not address the use of electronic brachytherapy for IORT, its use is considered experimental, investigational and/or unproven.

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Radiation Therapy for Cervical Cancer

POLICY

I. Brachytherapy alone, for IA1, is medically necessary for any of the following:

A. Medically inoperable
B. Surgical refusal
C. Invasive carcinoma diagnosed only by microscopy without evidence of a gross lesion; microscopic lesions with stromal invasion 3.0 mm or less in depth and a horizontal spread of 7.0 mm or less without lymphatic or vascular space involvement.

II. Pelvic radiation alone for stages IB or IIA is medically necessary for any of the following:

A. External beam photon radiation therapy
   1. Preoperative
   2. Definitive treatment when additional brachytherapy cannot be performed and the individual is inoperable
   3. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement
B. Intensity-Modulated Radiation Therapy (IMRT)
   1. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement

III. Pelvic radiation and brachytherapy for stages IA1 with lymphovascular space invasion (LVSI), IA2, IB, IIA, IIB, IIIA, IIIB or IVA are medically necessary for any of the following:

A. External beam photon radiation therapy with brachytherapy
   1. Microscopic lesions with stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread with lymphovascular space invasion
   2. All microscopic lesions with stromal invasion more than 3.0 mm
   3. All clinically visible lesions confined to the cervix with or without extension to the parametria, pelvic sidewall(s), lower third of vagina, or causing hydronephrosis or nonfunctioning kidney
   4. Tumor invading the mucosa of the bladder or rectum, and/or extends beyond the true pelvis
   5. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement.

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B. IMRT
   1. As postoperative treatment for positive surgical margins, positive pelvic nodes, vaginal margins less than 0.5 cm, extensive lymphovascular or capillary involvement

IV. External beam photon radiation therapy, IMRT, and brachytherapy are medically necessary for palliative therapy in an individual with or without evidence of distant metastases

A. In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be medically necessary. In this scenario, treatment is typically delivered with Complex or 3D conformal radiation therapy (3DCRT), up to 4 gantry angles, 1 phase, and up to 15 fractions. IMRT may be medically necessary when previous external beam photon radiation therapy or brachytherapy has been given.

V. External beam photon radiation therapy, IMRT, and brachytherapy are medically necessary for the treatment of loco-regional recurrence in an individual without evidence of distant metastases

A. When salvage radiotherapy is attempted to an isolated local/regional recurrence without evidence of distant metastatic disease, treatment is typically 3DCRT, up to 4 gantry angles, and up to 30 fractions. Two phases may be medically necessary, with or without brachytherapy. IMRT may be considered based on clinical presentation and anatomic location. Stereotactic Body Radiation Therapy (SBRT) may be considered based on a history of previous radiation to the same or abutting region and inability to deliver therapeutic doses of radiation with other techniques.

Key Clinical Points

Within the United States in 2017, 12,820 new cases of cervical cancer are projected resulting in approximately 4,210 deaths. The prognosis of individuals with cervical cancer is markedly affected by the extent of disease at the time of diagnoses.

I. Brachytherapy (internal radiation)

Brachytherapy is an important component of the radiation therapy regimen in the curative treatment of cervical cancer. Brachytherapy may be given by either Low Dose Rate (LDR) or High Dose Rate (HDR) techniques. Dose recommendations are available in the literature of the American Brachytherapy Society. It is recognized that disease presentations and anatomic deformity may result in less than optimal dosimetry using conventional radiation applicators, and that supplementary interstitial brachytherapy may be required on an individual basis to achieve optimal therapeutic effect.

The type of implant may include tandem and ovoids, tandem alone, ovoids only, interstitial, or vaginal cylinder only. For LDR therapy, up to 2 interstitial or intracavitary applications are considered medically appropriate. For HDR interstitial therapy, when 1 application is used, up to 5 fractions may be appropriate. When 2 applications are used, up to 3 fractions may be appropriate. For HDR tandem and ovoids, up to 6 applications may be appropriate. For HDR vaginal cylinder, up to 3 applications may be medically necessary.

Electronic/kilovoltage brachytherapy will be approved for a vaginal cylinder. Electronic/kilovoltage brachytherapy for other gynecologic devices, such as a tandem and colopostats is considered experimental, investigational, or unproven (EIU) for the treatment of cervical cancer.

II. Postoperative external beam photon radiation therapy / IMRT

The use of postoperative radiation treatment in this setting will depend on the type of surgery performed (simple or radical hysterectomy) and the surgical findings. Surgical findings of clinical relevance include the size of the primary tumor, depth of stromal invasion, and presence of lymphovascular invasion. Positive pelvic and/or para-aortic nodes, surgical margins, and involvement of the parametrium are also important. Chemotherapy generally is given concurrently in these situations as well. When indicated, postoperative radiation therapy typically is delivered using up to 30 fractions. Either IMRT or 3DCRT may be used as postoperative treatment for positive surgical margins, positive pelvic nodes, surgical margins less than 0.5 cm, extensive lymphovascular or capillary involvement. An intracavitary boost may be clinically appropriate in the setting of positive surgical findings. IMRT may also be used for pelvic and/or para-aortic radiation treatment when surgical lymph node sampling or dissection is positive for metastatic disease.

III. Management of the para-aortic nodes

The treatment of para-aortic nodal regions may be indicated in the following clinical situations:

A. Positive para-aortic lymph nodes on surgical staging if lymph nodes are less than 2 cm and are below L3
B. Positive para-aortic lymph nodes on surgical staging and all macroscopic para-aortic nodes are removed
C. Recurrent disease without evidence of distant metastases
D. Positive pelvic and/or para-aortic lymph nodes on Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) scan. Pathologic confirmation is recommended if technically feasible.

When treatment of the para-aortic nodes is indicated, treatment may be concurrent or sequential. External beam photon radiation therapy, IMRT, and brachytherapy, are considered medically appropriate. For concurrent treatment, up to 6 gantry angles are approved, and a conedown (additional phase) may be appropriate. For sequential treatment, up to 6 gantry angles, 1 conedown, and up to 28 additional fractions may be appropriate. If judged clinically necessary by the radiation oncologist and supported by dosimetry analysis, IMRT may be used in lieu of 3DCRT to reduce doses to critical organs including the kidneys, small bowel, liver and spinal cord. IMRT may also be used concurrently or sequentially for this treatment.

IV. IMRT

The use of IMRT routinely is not appropriate for the definitive treatment of cancer of the intact cervix, as studies have demonstrated difficulty in daily reproducibility and dosimetry. The cervix has been shown to move as much as 2 cm on a daily basis (Lim et al., 2009; Lim et al., 2011; National Comprehensive Cancer Network [NCCN] Guidelines Version 2.2015 Cervical Cancer; Small et al., 2008; Welsh et al., 2007). Devices for the immobilization of the cervix are considered experimental at this time. Significant and rapid tumor shrinkage seen in cervical cancer can also affect IMRT distributions. Thus, as recommended by NCCN, certification of IMRT treatment involving the intact cervix is restricted to individuals participating in IRB protocols. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/NCCN.

There is solid evidence that the risk of severe small bowel injury after conventional radiotherapy for postoperative patients with gynecologic cancer is 5 to 15% (Corn et al., 1994; Gallagher et al., 1986). IMRT is considered medically necessary when doses to critical organs can be meaningfully reduced compared to 3DCRT. RTOG 0418 showed that postoperative pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance. A similar result for cervical cancer is expected from this trial. Multiple dosimetric studies and smaller clinical studies have demonstrated that dose to the small bowel can be decreased using IMRT and should impact on the risk of small bowel injury (Jhingran et al., 2012; Klopp et al., 2010; Salama et al., 2006).

The major concern at RTOG was the ability of multiple institutions to safely implement IMRT programs for pelvic RT in gynecologic patients. The conclusion of RTOG 0418 is that this can be done. Preliminary data from RTOG 0418 in 40 cervical cancer patients receiving postoperative IMRT and chemotherapy was reported by Klopp et al. in abstract form and showed 0% grade 4 hematologic

toxicity with IMRT compared to 18% with conventional treatment, p = 0.002 with a median of 32 months, 2-year disease-free survival (DFS) and overall survival (OS) were 86.9% and 94.6%, comparing favorably to an intergroup postoperative study of concurrent chemoradiation with conventional RT in high risk early stage cervical cancer patients reported by Peters et al. (2000) where 3-year progression-free survival (PFS) and OS was 84% and 88%. Recently a report on 34 patients from Memorial Sloane-Kettering Cancer Center (MSKCC) in intermediate and high-risk cervical cancer receiving postoperative chemotherapy and concurrent IMRT showed a 3- and 5-year OS of 91% and PFS of 91.2% with a 44-month median follow up. There were only 2 locoregional failures, 1 vaginal and 1 pelvic (Folkert et al., 2013). These data suggest that with the tighter margins of IMRT local control can be maintained with a decrease in toxicity. Additionally, the use of IMRT may be considered when co-morbid medical conditions and/or surgical history may significantly increase risk to critical organs. It is recommended that all IMRT treatments be accomplished with photon beams not exceeding 10 MV to reduce integral neutron dose in this highly curable population.

V. Palliative therapy

In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be medically necessary. In this scenario, treatment is typically delivered with Complex or 3DCRT, up to 4 gantry angles, 1 phase, and up to 15 fractions. IMRT may be medically necessary when previous external beam photon radiation therapy or brachytherapy has been given. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

VI. Loco-regional recurrence

When salvage radiotherapy is attempted, treatment is typically 3DCRT, up to 4 gantry angles, and up to 30 fractions. Two phases may be medically necessary, with or without brachytherapy. IMRT may be considered based on clinical presentation and anatomic location. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

VII. Chemotherapy

Randomized trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy, while one trial examining this regimen demonstrated no benefit. The patient populations that benefit include FIGO stages 1B1 to IVA cervical cancer treated with primary radiation therapy and FIGO stages I to IIA disease with poor prognostic factors (metastatic disease in

pelvic lymph nodes, parametrial disease, or positive surgical margins) at primary surgery, who then go on to receive adjuvant chemoradiation. Although the positive trials vary in terms of the stage of disease and incorporate varying radiation treatment regimens with chemotherapy schedules of cisplatin alone or combined with fluorouracil, the trials demonstrate significant survival benefit for this combined approach. Based on these results, strong consideration should be given to the incorporation of concurrent chemotherapy with radiation therapy in women who require radiation therapy for the treatment of cervical cancer.

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Radiation Therapy for Endometrial Cancer

POLICY

Treatment options for a fully surgically staged individual:

I. Postoperative brachytherapy (alone) is medically necessary for any of the following:

A. Stage IA with adverse risk factors (G1, G2, G3)
B. Stage IA without adverse risk factors (G2, G3)
C. Stage IB (G1, G2, G3)
D. Stage II (G1, G2)

II. Pelvic external beam photon radiation therapy (alone) is medically necessary for either of the following:

A. Medically inoperable
B. Postoperative for any of the following:
   1. Stage IA (G2, G3) with adverse risk factors
   2. Stage IB (G3) without adverse risk factors
   3. Stage IB (G1, G2, G3) with adverse risk factors
   4. Stage II (G1, G2, G3)
   5. Stage IIIA and Stage IIIB vaginal or parametrial involvement (combination with brachytherapy preferred)
   6. Stage IIIC1 with positive pelvic nodes and negative para-aortic nodes (G1, G2, G3)

III. Postoperative pelvic external beam photon radiation therapy and brachytherapy are medically necessary for any of the following:

A. Stage IA with adverse risk factors (G2, G3)
B. Stage IB without adverse risk factors (G3)
C. Stage IB with adverse risk factors (G1, G2, G3)
D. Stage II (G1, G2, G3)
E. Stage IIIA (G1, G2, G3)
F. Stage IIIB
G. Stage IIIC1 positive pelvic but negative para-aortic nodes

IV. Para-aortic lymph node radiation treatment with pelvic external beam photon radiation therapy with or without brachytherapy is medically necessary for either of the following:

A. Stage IIIC1 (involvement of only pelvic nodes)
B. Stage IIIC2 (involvement of para-aortic lymph nodes with or without pelvic nodes) documented at surgery or by image-guided biopsy

V. Tumor directed radiation therapy is medically necessary for any of the following:

A. Stage IVA (tumor invading bladder and/or bowel mucosa) or Stage IVB (distant metastases including inguinal nodes, intra-peritoneal disease, lung, liver or bone metastases) following a debulking surgical procedure with no evidence of gross residual disease or microscopic abdominal disease
B. Recurrence
C. Palliation including primary and/or metastatic disease sites

VI. Electronic/kilovoltage brachytherapy

A. Electronic/kilovoltage brachytherapy is considered medically necessary when utilizing a vaginal cylinder
B. Electronic/kilovoltage brachytherapy for other gynecologic devices, such as a tandem and colopstats is considered experimental, investigational, or unproven (EIU) for the treatment of endometrial cancer.

Key Clinical Points

Within the United States in 2017, 61,380 new cases of uterine malignancy are projected resulting in projected 10,920 deaths. Uterine cancers represent the most common female genital tract malignancy. Endometriod (tumors resembling the lining of the uterus; adenocarcinomas) are the most prevalent subtype. Serous papillary carcinoma is not covered under this criteria.

The staging definitions used in the creation of the treatment criteria may be found in the 7th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The treatment options for treatment of cancer of the endometrium are defined by stage of disease, grade of the cancer, completeness of surgical staging and the presence of adverse risk factors. Complete surgical staging is defined as total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO), peritoneal lavage for cytology, dissection of pelvic and para-aortic lymph nodes and careful inspection and palpation of abdominal organs including but not limited to diaphragm, liver, peritoneal surfaces of the abdomen, pelvis, bowel and omentum. Adverse risk factors include advancing age, lymphovascular extension, tumor size, lower uterine involvement classified as cervical glandular involvement (newly classified as Stage I). For cases that are not completely surgically staged, radiologic imaging plays an important role in selecting a treatment strategy.

For surgically staged Stage IA with or without adverse risk factors, all individuals regardless of pathologic grading may be observed as per NCCN Guidelines®. Observation may also be employed for individuals with Stage IB G1, G2, and G3 disease without risk factors as well as individuals with G1 and G2 Stage IB disease with risk factors. Should treatment rather than observation be decided upon for these same groups, radiation techniques are stratified in the preceding guideline statements. With

more advanced clinical state and/or radiological presentations, more extended external beam photon radiation fields with or without brachytherapy may be medically necessary.

In advanced disease, the increased utilization of adjuvant chemotherapy has called into question the magnitude of the added benefit of adjuvant radiation therapy. We are awaiting the results of some recent trials that may help to answer some of these questions. Gynecologic Oncology Group (GOG) trial 249 randomized high risk early-stage patients to pelvic external beam photon radiation therapy or intravaginal external beam photon radiation therapy and chemotherapy. GOG 258 is comparing surgical Stage III or IVA patients to concurrent tumor directed external beam photon beam radiation therapy/chemotherapy to chemotherapy alone and PORTEC-3 is comparing concurrent pelvic external beam photon radiation therapy/chemotherapy to pelvic external beam photon beam radiation therapy alone in high risk surgical Stage IB-III patients. The early-stage endometrial cancer study by Aalders et al. (1980) updated by Onsrud, et al. (2013) of 568 patients with a median follow up of 20.5 years suggested no statistical difference in overall survival (OS) between women treated with vaginal brachytherapy alone versus those treated with vaginal brachytherapy and external beam radiation. Patients younger than age 60 who received external beam treatment did not have a survival benefit but did suffer an increase risk of secondary cancers with subsequent increased mortality.

For all other stages and those with positive radiologic imaging, surgical restaging or pathologic confirmation of more advanced disease is recommended (image directed biopsy). Individuals then enter the fully surgically staged treatment recommendations with their newly assigned stage.

Palliation/Recurrence: Either brachytherapy or pelvic external beam photon radiation therapy alone or combined treatment may be considered based on the clinical presentation. In the non-curative setting and where symptoms are present, palliative external beam photon radiation therapy may be appropriate. In this scenario, treatment is typically delivered with Complex or three-dimensional conformal therapy (3DCRT), up to 4 gantry angles, 1 phase, and up to 15 fractions. When salvage radiotherapy is attempted for recurrence, treatment is typically 3DCRT, up to 4 gantry angles, and up to 35 fractions. Two phases may be appropriate, and the use of brachytherapy may be appropriate. Intensity-Modulated Radiation Therapy (IMRT) may be considered based on clinical presentation and anatomic location.

Treatment Discussion

I. Brachytherapy

Current guidelines for the use of brachytherapy in the treatment of endometrial cancer with High Dose Rate (HDR) from the American Brachytherapy Society may be found in the International Journal of Radiation Oncology Biology & Physics (Nag

et al., 2000). Additional information is available from the American Brachytherapy Society Survey (Small et al., 2005).

Consistent with published guidelines including NCCN, appropriate medically necessary treatments are:

A. Preoperative Stage II with gross disease:
   1. External beam photon radiation therapy and intrauterine brachytherapy
   2. Up to a total dose of 75 to 80 Gy Low Dose Rate (LDR) equivalent

B. Postoperative:
   1. Brachytherapy should be initiated as soon as the vaginal cuff has healed or no later than 12 weeks following surgery
      a. Following the performance of a hysterectomy, brachytherapy using a vaginal cylinder is generally limited to the upper vagina with the dose prescribed at the vaginal surface or to a depth of 0.5 cm
      b. HDR vaginal cylinder regimens of 4 to 6 Gy for 2 to 3 fractions to the vaginal mucosa are common in conjunction with external beam photon radiation treatment
   2. As definitive treatment alone without external beam photon radiation therapy
      a. HDR regimens using a vaginal cylinder include 7 Gy for 3 fractions prescribed to a depth of 0.5 cm from the vaginal surface or 6 Gy for 5 fractions prescribed to the vaginal surface

II. External beam photon radiation therapy doses to the pelvis and tumor volume for microscopic disease

A. Doses range from 45 to 50 Gy usually in 1.8 Gy daily fractions
B. Computed tomography (CT)-planned 3D techniques are generally used
C. For treatment of the postoperative pelvis with planned external beam photon radiation therapy boosts to positive lymph nodes or positive surgical margins, IMRT may be considered medically necessary to reduce doses to critical organs
D. IMRT may also be considered for postoperative pelvic radiation as part of a sequential or concurrent treatment plan incorporating the para-aortic lymph node treatment. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/NCCN

III. External beam photon radiation therapy doses to the para-aortic region

A. When treatment of the para-aortic nodes is indicated, treatment may be concurrent or sequential. Both regimens are considered medically appropriate
B. For concurrent treatment, up to 6 gantry angles are approved, and a conedown (additional phase) may be appropriate

C. For sequential treatment, up to 6 gantry angles, one conedown, and up to 28 additional fractions may be appropriate
D. If judged clinically necessary by the radiation oncologist and supported by dosimetry analysis, IMRT may be used in lieu of 3DCRT to reduce doses to critical organs including the kidneys, small bowel, liver and spinal cord. IMRT may also be considered for postoperative para-aortic radiation as part of a sequential or concurrent treatment plan in which IMRT is being administered to the postoperative pelvis with planned external beam photon radiation therapy boosts to positive lymph nodes or positive surgical margins

IV. IMRT

A. The use of IMRT is not routinely appropriate for the treatment of cancer of the uterus as studies have demonstrated difficulty in daily reproducibility and dosimetry
B. IMRT is medically necessary in the postoperative setting when doses to critical organs can be meaningfully reduced compared to 3DCRT
C. There is solid evidence that the risk of severe small bowel injury after conventional radiotherapy for postoperative patients with gynecologic cancer is 5 to 15% (Corn et al., 1994; Gallagher et al., 1986). RTOG 0418 showed that postoperative pelvic IMRT for endometrial cancer is feasible across multiple institutions with use of a detailed protocol and centralized quality assurance. Multiple dosimetric studies and smaller clinical studies have demonstrated that dose to the small bowel can be decreased using IMRT and should impact on the risk of small bowel injury. The major concern at RTOG was the ability of multiple institutions to safely implement IMRT programs for pelvic RT in gynecologic patients. The conclusion of RTOG 0418 is that this can be done. More mature data on the use of postoperative IMRT in endometrial cancer has now been reported. With a median follow up of 52 months, Shih et al. (2013) at Memorial Sloan-Kettering Cancer Center (MSKCC), reported on 46 high risk patients. Thirty also received concurrent chemotherapy. There were only 2% grade III gastrointestinal and 11% hematologic toxicities. The 5-year disease-free survival (DFS) and overall OS rates were 87% and 97%. There was only 1 vaginal failure (2%) and no pelvic failures. IVRT was not used.
D. It is recommended that all IMRT treatments be accomplished with photon beams not exceeding 10 MV to reduce integral neutron dose in this highly curable population of individuals

V. Chemotherapy

A. The use of chemotherapy and radiation treatment in the management of endometrial cancer either concurrently or sequentially remains for the most part the object of clinical study and investigation
B. Combined modality treatment may be considered for an individual with high risk of recurrence, recurrent, or metastatic disease
C. For a completely surgically staged individual, current disease presentations considered for chemotherapy and radiation include but are not limited to Stage IB G3; Stage II G3; Stages III A, B, and C; Stages IVA and IVB

An incompletely surgically staged individual with no risk factors and a tumor less than 2 cm with Stage IA G1-G2 disease may be observed. All other individuals with Stage IA, IB, and II incompletely staged disease should undergo either imaging or surgical restaging. If imaging results are negative, they should be treated according to their assigned stage. If positive or suspicious, however, an attempt should be made to either restage surgically or document the presence of metastatic disease. Individuals who have been surgically restaged should be treated according to their appropriate new Stage and findings. It should be noted that immediate surgical restaging without the benefit of imaging is a Category 3 NCCN recommendation.

D. An individual with Stage IB or Stage II with G3 cancer should be considered for chemotherapy as well

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Radiation Therapy for Esophageal Cancer

POLICY

I. Neoadjuvant treatment

A. For an individual with stage T1b node-positive or T2-T4a disease, the use of 23 to 28 fractions of three-dimensional conformal radiation (3DCRT) is considered medically necessary. The use of intensity-modulated radiation therapy (IMRT) will be considered on a case-by-case basis

II. Adjuvant treatment (if no preoperative or prior irradiation given)

A. For an individual with squamous cell carcinoma when there are positive margins or adenocarcinoma with at least pT2 or node-positive disease, the use of 25 to 28 fractions of 3DCRT is considered medically necessary. The use of IMRT will be considered on a case-by-case basis

III. Definitive treatment

A. For an individual with T1b node-positive or T2-T4a disease, the use of 25 to 28 fractions of 3DCRT is considered medically necessary. The use of IMRT will be considered on a case-by-case basis.

B. For tumors located in the cervical esophagus, up to 39 fractions of 3DCRT or IMRT is considered medically necessary

IV. Palliation

A. The use of 15 fractions of 3DCRT is considered medically necessary

Key Clinical Points

I. Neoadjuvant chemoradiotherapy (CRT)

Historically, surgery alone has been associated with relatively high rates of recurrence and dismal rates of survival. Among the treatments investigated to improve upon these results is the use of preoperative chemoradiotherapy.

One of the largest randomized controlled trials to investigate preoperative CRT was the CROSS trial. In this trial, 368 patients with resectable clinical stage T1N1 or T2-3N0-1M0 squamous cell carcinoma, adenocarcinoma or large-cell undifferentiated carcinoma of the esophagus and gastroesophageal junction (GEJ) were randomized to preoperative CRT (carbo/taxol with 41.4 Gy) followed by surgery or to surgery alone. At a median follow up of 45.4 months, the median overall survival (OS) was 24.0 months (CRT) vs. 4.94 months (surgery alone). The OS at 1, 2, 3, and 5 years was 82% vs. 70%, 67% vs. 50%, 58% vs. 44% and 47% vs. 34%, respectively for preoperative CRT vs. surgery alone. Other benefits to preoperative CRT included a significantly higher R0 resection (92% vs. 69%), higher incidence of a pathological complete response (pCR) (29% vs. 23%), a

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lower incidence of node positivity (31% vs. 75%) and no difference in occurrence of postoperative complications.

A recent analysis of CROSS I and II trials revealed a reduced rate of local-regional recurrence (LRR) with preoperative CRT (34.7% vs. 57.1%). Furthermore, the majority of these recurrences had a component of distant recurrence whereas the rate of an isolated LRR was (3.3% vs. 9.3%).

Finally, a large meta-analysis revealed a significant reduction in all-cause mortality with preoperative CRT (hazard ratio [HR] 0.78) compared with surgery alone, translating into an absolute survival benefit of 8.7% at 2 years (Sjoquist et al., 2011).

II. Adjuvant chemoradiotherapy (CRT)

A. Squamous cell carcinoma
There is no definitive evidence of a benefit with postoperative CRT. For example, a randomized control trial of 45 patients found no significant improvement with postoperative CRT vs. postoperative chemotherapy (Tachibana et al., 2003). It is also noted that NCCN recommends adjuvant treatment only in the setting of a R1 or R2 resection.

B. Adenocarcinoma
Postoperative CRT is indicated for an individual with stage IB-IV (M0) based on the INT 0116 study. In INT 0116, 559 patients with stage IB-IV adenocarcinoma of the stomach or GEJ (20% of patients) following R0 resection were randomized to CRT (5-FU/leucovorin before, during and concurrent with radiation to 45 Gy) or to no further treatment. In the most recent update with a 10-year median follow up, CRT continues to show a significant improvement in OS (HR 1.32) and for relapse-free survival (RFS) (HR 1.51). This benefit extended to all T stages, N stages as well as location in the GEJ.

III. Definitive chemoradiotherapy (CRT)

In an individual who is not medically operable or who refuses surgery, definitive CRT remains the standard treatment. This is primarily based on data from RTOG 8501 (Herskovic et al., 1992). In this randomized stratified phase III trial, patients with T1-3, N0-1, M0 squamous cell carcinoma or adenocarcinoma (90% were squamous cell carcinoma) of the esophagus, including GEJ, were randomized to radiation alone (to 64 Gy) or CRT (50 Gy + 5-FU/cisplatin). In the most recent update, 5-year survival was 26% vs. 0% and persistence of disease was 37% vs. 25%.

In an attempt to improve upon these results, INT 0123 evaluated radiation dose escalation in combination with chemotherapy (Minsky et al., 2002). Two hundred and thirty-six (236) patients with T1-4, N0-1 squamous cell carcinoma or adenocarcinoma were randomized to 50.4 Gy + 5-FU/cisplatin or 64.8 Gy + 5-FU/cisplatin. It is noted "…because of the concern that the stomach could not safely tolerate 64.8 Gy, eligibility was limited to patients whose tumors did not

extend to within 2 cm of the GEJ." This trial was stopped early due to an increase in death in the high-dose arm.

Specifically, 11 deaths occurred in the high-dose arm vs. 2 in the standard-dose arm. Of these 11 deaths, 7 occurred at or below a dose of 50.4 Gy. As such, the standard-dose arm was associated with a non-significant improvement in median survival (18.1 months vs. 13 months) and 2-year survival (40% vs. 31%). On the other hand, the high-dose arm was associated with a non-significant reduction in local-regional persistence or failure (50% vs. 55%) and in distant failure (9% vs. 16%). As a result of these findings, the authors conclude, "…the standard radiation dose is 50.4 Gy."

In a quality of life (QOL) analysis (Kachnic et al., 2011), the high-dose arm had a significantly lower total QOL at the end of CRT (p=0.02). At 8 and 12 months, the high-dose arm had a lower total QOL as compared to the standard arm, though this was not statistically significant. These results support that the high-dose arm does not improve patient QOL. The authors state, "…these results lend further weight to our previous conclusion that radiotherapy to 50.4 Gy should remain the standard of care in patients treated with definitive CRT for esophageal cancer."

IV. Treatment technique

Recently published data from RTOG 0617 suggests that, on multivariate analysis cardiac volume (V), V5 and V30 predict patient survival. Though there is no indication that similar findings will be borne out of INT 0123, it underscores the importance of cardiac dose. For example, in the treatment of esophageal carcinoma, several studies have confirmed an association between cardiac dose and toxicity.

Konski et al. (2012) found that symptomatic cardiac toxicity correlated with the whole heart V20, V30 and V40. Symptomatic toxicity was not observed if the whole heart V20, V30 and V40 was kept below 70%, 65% or 60%, respectively. In addition, Tait et al. (2013) also found a correlation of cardiac V20, V30 and V40 with toxicity whereby patients with a V20 above 71%, a V30 above 64.5% and V40 above 57% had increased odds of developing cardiac toxicity.

In attempt to reduce dose to nearby critical structures, several studies have evaluated the use of IMRT.

For example, Kole et al. (2012) revealed that in the treatment of 19 patients with carcinoma of the distal esophagus, IMRT significantly reduced heart dose, spared more of right coronary artery and improved target conformity.

Using a fitted multivariate inverse probability weighted-adjusted Cox model, Lin et al. (2012) found that patients treated with 3DCRT had significantly greater risk of dying (72.6% vs. 52.9%) and of local regional recurrence. In addition, and increased cumulative incidence of cardiac death was also seen.

IMRT should be considered with caution, however, due to the integral dose within the lungs.
For example, Kumar et al. (2012) found that IMRT, compared to 3DCRT, increased the lung V20 and that a V20 of > 15% increased the risk of chronic pneumonitis.

Other studies have also shown the effect of low-dose radiation within the lung. For example, Gergel et al. (2002) found that, in the 3D treatment of esophageal cancer in 20 patients, the percent of absolute lung volume that received a total dose between 7 and 10 Gy may be significantly correlated with the percent decline of carbon monoxide diffusing capacity, total lung capacity and vital capacity.

Lee et al. (2003) also found an increase in postoperative pulmonary complications when the pulmonary V10 was greater than 40% and when the V15 was greater than 30%. In an update of this study, Wang et al. (2006) revealed that the pulmonary V5 correlated with postoperative pulmonary complications.

NCCN Guidelines® indicate that IMRT "…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." Given this and the available data, the use of IMRT will be considered on a case-by-casis.

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Radiation Therapy for Gastric Cancer

POLICY

I. Neoadjuvant treatment

A. For an individual with stage T2-T4 or node-positive disease, the use of up to 28 fractions of 3D conformal radiation (3DCRT) is considered medically necessary. The use of intensity modulated radiation therapy (IMRT) will be considered on a case-by-case basis.

II. Adjuvant treatment (if no preoperative or prior irradiation given)

A. For an individual with at least pT2 or node-positive disease, microscopic or macroscopic residual diasease or high risk features such poor differentiation, lymphovascular invasion, neural invasion, and age less than 50, the use of up to 28 fractions of 3DCRT is considered medically necessary. The use of IMRT will be considered on a case-by-case basis.

III. Definitive treatment

A. For an individual who is inoperable (i.e. due to co-morbidity), the use of up to 28 fractions of 3DCRT is considered medically necessary.

IV. Palliation

A. The use of 15 fractions of 3DCRT is considered medically necessary

Key Clinical Points

According to Eighth Edition of the AJCC Cancer Staging Manual, "…if a tumor involves the esophagogastric junction (EGJ) and its epicenter is ≤2 cm into the proximal stomach (i.e., ≤2 cm distal to the EGJ)…" it is classified as esophageal cancer. "Tumors involving the EGJ with their epicenter >2 cm into the proximal stomach (i.e., > 2 cm distal to the EGJ)…" are classified as gastric cancer.

In the postoperative treatment of gastric carcinoma, chemoradiation is indicated for an individual with stage IB-IV (M0) based on the INT 0116 study. In INT 0116, 559 patients with stage IB-IV adenocarcinoma of the stomach or GEJ (20% of patients) following R0 resection were randomized to chemoradiotherapy (CRT) (5-FU/leucovorin before, during and concurrent with radiation to 45 Gy) or to no further treatment. In the most recent update with a 10-year median follow up, CRT continues to show a significant improvement in overall survival (OS) (HR 1.32) and for relapse-free survival (RFS) (HR 1.51). This benefit extended to all T stages, N stages as well as location in the GEJ.

In terms of historical progression of treatment planning techniques; after the Intergroup 0116 trial, which used AP-PA field arrangement, Soyfer et al. (2007) published data

concluding that non-coplanar 3D conformal approach yielded better results than AP-PA plans. In 2008 this same group compared IMRT to 3D conformal techniques for adjuvant management of gastric cancer, concluded that IMRT confers only marginal benefit, and should be used "…only in the small subset of patients with risk factors for kidney disease or those with preexisting nephropathy."

In 2010, the group at Stanford (Minn et al.) published on sequential groups of patients treated in the adjuvant setting, initially 3DCRT (26 patients), and after 2002 with IMRT (33 patients). The 2-year OS for the 3DCRT and IMRT groups was 51% and 65%, respectively (p = 0.5). The 2-year disease-free survival (DFS) for the 3DCRT and IMRT groups was 60% and 54%, respectively (p = 0.8). The two-year local control rate for the 3DCRT and IMRT groups was 83% and 81%, respectively (p = 0.9). The Stanford group interpreted this data to show that IMRT could be delivered effectively without compromising outcome. In terms of toxicity, 3 patients required a treatment break of a median duration of 7 days due to toxicity in the 3DCRT group (range, 4 to 10 days), whereas no patient in the IMRT group required a treatment break. Grade 2 or higher acute GI toxicity was noted in 61.5% and 61.2% of patients in the 3DCRT and IMRT groups, respectively. Regarding late toxicity, among the 3DCRT patients, 1 patient died of small bowel perforation requiring surgical intervention (grade 5). Grade 3 late toxicity was experienced by 3 patients who developed small bowel obstruction. Two patients developed grade 2 late toxicity (jaundice and esophagitis). In the IMRT group, grade 3 late toxicity was experienced by 1 patient who had a stricture requiring surgery. Grade 2 late toxicity was experienced by 3 patients: 1 with gastritis, 1 with esophagitis, and 1 with an ulcer. The conclusion of this paper was "…although locoregional control is good with adjuvant chemoradiotherapy, overall outcomes for gastric cancer remain poor. Improvements in both local and systemic therapy are required. Adjuvant chemoradiotherapy was well tolerated with either 3DCRT or IMRT, with similar acute and late toxicities reported. Despite higher doses used, IMRT provides sparing to the liver and possibly the kidneys."

Additional publications have failed to show a definitive benefit to IMRT. Further, NCCN Guidelines® state that IMRT "…may be used in clinical settings where reduction in dose to organs at risk (eg, heart, lungs, liver, kidneys, small bowel) is required, which cannot be achieve by 3-D techniques." Further, variations in gastric filling and respiratory motion should be accounted for when delivering IMRT. Given this and as data remains mixed with respect to the benefit of IMRT, the use of IMRT will be considered on a case-by-case basis.

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Radiation Therapy for Head and Neck Cancer

POLICY

I. Radiation therapy techniques

A. Three-dimensional conformal radiation therapy (3DCRT) and Intensity-Modulated Radiation Therapy (IMRT) techniques are medically necessary when the extent of disease allows preferential sparing of organs not needing radiation without compromising the dose delivered to tumor. In certain situations in which the extent of disease precludes better sparing of organs at risk by IMRT, an IMRT technique may not be medically necessary. In certain situations of limited disease, IMRT is not medically necessary

B. Adaptive therapy is medically necessary with re-planning, upon significant alteration of tumor status or neck contour due to weight change

C. The use of photon beam and electron beam radiation therapy is medically necessary

D. The use of neutron beam therapy is medically necessary in select cases of salivary gland tumors (See Neutron BeamTherapy guideline)

E. Preoperative radiation therapy is medically necessary in select cases
   1. May be given in up to 35 fractions in 3 phases
   2. May use Complex, 3DCRT, or IMRT techniques

II. Radiation therapy treatment intent/timing

A. Definitive radiation therapy
   1. Is medically necessary for selected T1-2, N0 cases as monotherapy
   2. May employ up to 42 fractions in a maximum of 2 phases
   3. Depending on the simplicity or complexity of the case, Complex, 3DCRT, or IMRT techniques may be necessary

B. Definitive radiation therapy as monotherapy
   1. Is medically necessary for selected T1N1 and T2N0-1 cases
   2. Radiation may be given utilizing any of several schedules including conventional daily fractionation, concomitant boost accelerated fractionation, and hyperfractionation (twice-daily radiation)
   3. Up to 68 fractions may be medically necessary, in 2 phases

C. Definitive concurrent chemoradiation
   1. Is medically necessary in unresected T2-4a, N0-3 cases utilizing up to 42 fractions with conventional schedule
   2. 3DCRT or IMRT techniques are medically necessary, in up to 4 phases
   3. Concurrent chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

D. Postoperative radiation therapy
   1. Is medically necessary for cases that have any of the following high risk factors:
      a. PT3 or pT4 primary tumors
      b. N2 or N3 nodal disease
      c. Positive nodes in levels IV or V
      d. Perineural invasion
      e. Vascular tumor embolism
      f. Positive surgical margins or residual gross disease
   2. 35 fractions are medically necessary
   3. 3DCRT or IMRT techniques are medically necessary, in up to 3 phases
   4. Chemotherapy may be added concurrently with postoperative radiation and is medically necessary in cases with positive margins or extracapsular nodal extension
   5. Concurrent chemotherapy also may be considered in cases with the other high risk factors mentioned above, in which up to 40 fractions in 2 phases are medically necessary
   6. Concurrent chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

III. Radiation therapy, brachytherapy

A. Low Dose Rate (LDR) or High Dose Rate (HDR) brachytherapy is medically necessary in select cases of epithelial tumors of the head and neck region. In appropriate early cases, it is medically necessary as monotherapy. In more advanced cases, it may be substituted for one phase of 3DCRT or IMRT
B. Brachytherapy for head and neck malignancies should be performed only by those radiation oncologists specifically trained in its use

IV. Radiation therapy, palliative

A. In a previously un-irradiated individual with symptomatic local disease, Complex, 3DCRT or IMRT techniques are indicated for symptom control
B. Up to 20fractions are medically necessary, in 1 phase

V. Re-treatment for salvage after prior radiation

A. Re-irradiation may be indicated in cases of recurrent or persistent disease, or for in-field new primary tumors, in cases in which there are no known distant metastases.
B. Reirradiation carries increased risk. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Head and Neck Cancers Version 2.2017 – May 8, 2017, “In general, the reirradiated population of head and neck cancer patients as described in the current literature represents a diverse but highly selected group of patients treated in centers where there is a high level of expertise and systems in place for managing acute and long-term toxicities. When the goal of treatment is curativeand surgery is not an option, reirradiation strategies can be considered

for patients who: develop locoregional failures or second primaries at ≥ 6 months after the initial radiotherapy; can receive additional doses of radiotherapy of at least 60 Gy; and can tolerate concurrent chemotherapy. Organs at risk for toxicity should be carefully and analyzed through review of dose volume histograms, and consideration for acceptable doses should be made on the basis of time interval since original radiotherapy, anticipated volumes to be included, and patient's life expectancy."

C. Enrollment in a clinical trial is preferred
D. Stereotactic Body Radiation Therapy (SBRT) may be medically necessary for retreatment in patients who have no evidence of metastatic disease

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society for Radiation Oncology [ASTRO], NCCN), radiation therapy is considered an integral component in the multidisciplinary management of malignancies of the head and neck region. Primary anatomic sites included in this category include paranasal sinuses (ethmoid and maxillary), salivary glands, the lip, oral cavity, oropharynx, hypopharynx, glottic larynx, supraglottic larynx, nasopharynx, and occult/unknown head and neck primary sites. The preponderance of literature addresses tumors of epithelial origin. Non-epithelial malignancies of the head and neck region (e.g. tumors arising in bone, cartilage, soft tissues, and lymphomas) are not covered by this policy.

Utilization of radiation therapy should be preceded by workup and staging and planned in conjunction with the appropriate members of a multi-disciplinary team that also includes: diagnostic imaging, pathology, medical oncology; otorhinological, oral, plastic and reconstructive, neuro- and ophthalmologic surgeons; psychiatry; addiction services; audiology and speech therapy; rehabilitation and nutritional medicine; pain management, dentists, prosthodontists, xerostomia management, smoking and alcohol cessation, tracheostomy and wound management, social workers and case management. Participation in a national clinical trial is encouraged.

Initial management may require surgery, chemotherapy, and radiation therapy in various combinations and sequences.

I. Radiation treatment schedules

Radiation therapy treatment schedules published in peer-reviewed consensus documents such as NCCN Guidelines® include the following regimens that encompass a broad range of doses that must be customized to an individual's circumstance. These schedules are based on the extent of the primary and nodal disease as well as the treatment intent, such as definitive, preoperative or postoperative. The use of additional therapeutic strategies such as concurrent chemotherapy or brachytherapy is described in the NCCN Guidelines®.

A. Primary site and lymph nodes
   1. Conventional schedule, high risk
      a. 50 to 74 Gy at 2 Gy/daily fraction, with or without brachytherapy
      b. For doses greater than 70 Gy, the use of daily doses less than 2 Gy may be considered for all or a portion of the radiation therapy to minimize toxicity
   2. Conventional schedule, low to intermediate risk (possible sub-clinical spread)
      a. 44 to 50 Gy at 2 Gy per fraction to 54 to 63 Gy at 1.6 to 1.8 Gy per fraction
   3. Accelerated fractionation schedule
      a. 66 to 74 Gy in 30 fractions, 6 fractions per week
   4. Concomitant boost accelerated schedule
      a. 72 Gy in six 6 weeks, with twice-daily treatments on each of the final 12 treatment days
   5. Hyperfractionation schedule
      a. 81.6 Gy in 68 fractions at 1.2 Gy twice daily

B. Postoperative
   1. High risk adverse features such as positive margins
      a. 60 to 66 Gy at 2 Gy/daily fraction
   2. Low to intermediate risk sites with suspected sub-clinical spread
      a. 44 to 50 Gy at 2 Gy per fraction to 54 to 63 Gy at 1.6 to 1.8 Gy per fraction

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Radiation Therapy for Hepatobiliary Cancer

For treatment using Proton Beam Therapy, please refer to the Proton Beam Therapy guideline.

For treatment using Selective Internal Radiation Therapy (SIRT), please see Selective Internal Radiation Therapy (SIRT) guideline.

POLICY

I. Primary hepatocellular carcinoma (HCC)

A. Definitive treatment
   1. In the treatment of medically or technically unresectable localized HCC in an individual with adequate hepatic reserve
      a. The use of 25 to 39 fractions of 3DCRT or IMRT is considered medically necessary
      b. The use of 3 to 5 fractions of SBRT is considered medically necessary to treat concurrently one or more tumors when there is evidence of the ability to protect an adequate volume of uninvolved liver.

B. Palliative treatment
   1. In an individual with localized disease or local disease with minimal extrahepatic disease, up to 20 fractions of 3DCRT is considered medically necessary

II. Intrahepatic bile duct cancer (cholangiocarcinoma)

A. Definitive treatment
   1. In the management of unresectable localized intrahepatic bile duct cancer
      a. The use of 25 to 33 fractions of 3DCRT or IMRT is considered medically necessary
      b. The use of up to 5 fractions of SBRT is considered medically necessary

B. Adjuvant (postoperative) treatment
   1. In the management of resected intrahepatic bile duct cancer with positive margins and/or positive regional lymph nodes
      a. The use of 25 to 33 fractions of 3DCRT or IMRT is considered medically necessary

C. Palliative treatment
   1. In an individual with unresectable localized intrahepatic bile duct cancer, up to 20 fractions of 3DCRT is considered medically necessary

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III. Extrahepatic Bile Duct Cancer (cholangiocarcinoma)

A. Definitive treatment
   1. In the management of unresectable localized extrahepatic bile duct cancer
      a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
      b. The use of IMRT will be considered on a case-by-case basis
      c. The use of SBRT is considered not medically necessary

B. Adjuvant (postoperative) treatment
   1. In the management of resected extrahepatic bile duct cancer
      a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
      b. The use of IMRT will be considered on a case-by-case basis
      c. The use of SBRT is considered not medically necessary

C. Palliative treatment
   1. In an individual with unresectable localized extrahepatic bile duct cancer, up to 20 fractions of 3DCRT is considered medically necessary

IV. Gallbladder Cancer

A. Definitive treatment
   1. In the management of unresectable localized gallbladder cancer
      a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
      b. The use of IMRT will be considered on a case-by-case basis
      c. The use of SBRT is considered not medically necessary

B. Adjuvant (postoperative) treatment
   1. In the management of resected gallbladder cancer with positive margins and/or positive regional lymph nodes
      a. The use of 25 to 33 fractions of 3DCRT is considered medically necessary
      b. The use of IMRT will be considered on a case-by-case basis
      c. The use of SBRT is considered not medically necessary

C. Palliative treatment
   1. In an individual with unresectable localized gallbladder cancer, up to 20 fractions of 3DCRT is considered medically necessary

Key Clinical Points

I. Primary liver cancer (HCC)

The incidence of HCC is increasing in the United States, most notably in the population infected with hepatitis C virus that have developed cirrhosis. Cirrhosis from other causes, such as genetic hemochromatosis, also carries a high risk of developing HCC. Because of the underlying cirrhosis, the healthy liver reserve is often decreased. Screening of populations known to be at high risk for HCC has led to an increased rate of detection of HCC and often at an earlier stage amenable to local treatment.

Prior to treatment, an assessment of liver health is necessary and is traditionally quantitated using the Child-Pugh classification system.The Child-Pugh score is based on laboratory and clinical measures and assigns a patient with cirrhosis into compensated (class A) or uncompensated (class B or C) status. Additional measures of liver health include factors of portal hypertension and the presence of varices. The Model for End-stage Liver Disease (MELD) includes a numerical scale that often is applied when there is consideration of liver transplantation.

There are three types of HCC based on morphology: nodular (most commonly associated with cirrhosis), massive (most commonly in a non-cirrhotic liver), and diffuse (numerous nodules throughout the liver).

Numerous staging systems have been devised for HCC; each often having its own specific applicability, such as prognosis, suitability for a given intervention, or based on HCC etiology. National Comprehensive Cancer Network (NCCN) categories include potentially resectable or transplantable based on performance status or comorbidities, unresectable, inoperable based on performance status or comorbidities with local disease only, and metastatic disease.

Management of HCC depends on etiology and the underlying health of uninvolved liver. Partial hepatectomy, liver transplantation, bridge therapy while awaiting transplantation, downstaging strategies, and locoregional therapies are potentially available. Locoregional therapies include ablation (chemical, thermal, cryo) with criteria regarding tumor number, size, location, and general liver health often dictating the ideal approach. Locoregional therapy may be performed by laparoscopic, percutaneous, or open approach. Arterially directed therapy involves the selective catheter-based infusion of material that causes embolization of tumors using bland, chemotherapy-impregnated, or radioactive products.

EBRT is a treatment optionfor certain cases of HCC not amenable to resection fortechnical or medical reasons, and can be delivered using one of several available highly-conformal techniques such as 3DCRT, IMRT and SBRT. Proton Beam Radiation Therapy (PBT) generally is not medically necessary but may be considered in unique clinical settings. (See Proton Beam Radiation Therapy guideline) For each technique, there must be sufficient uninvolved liver such that the technique is capable of respecting the tolerance of normal liver tissue. Several radiation schedules are available, including hypofractionation, SBRT (1 to 5 fractions), and conventional fractionation. Safety data are limited for treating other than Child-Pughclass A cases. A dose modification is needed when treating Child-Pugh class B. Radiation therapy is generally not given for class C cases. Combinations of several locoregional therapies may be required. Locoregional

management may serve as a bridge to liver transplant.
For the many cases of HCC that are advanced at the time of presentation and not amenable to locoregional therapies with intent to cure, systemic therapy has been employed. Systemic therapies include cytotoxic chemotherapy drugs and the multikinase angiogenesis inhibitor sorafenib. These are most commonly utilized in Child-Pugh class A patients, where data demonstrating a benefit in overall survival and better tolerance have been reported.While the intent of locoregional therapy is local control, EBRT may also play a role of palliation of symptoms in the liver, or distantly in cases of metastatic disease.

II. Intrahepatic bile duct cancer (cholangiocarcinoma)

The junction of the right and left hepatic ducts serves as the dividing location. Cholangiocarcinomas that occur on the hepatic side of the junction of the right and left hepatic ducts within the hepatic parenchyma are also known as intrahepatic bile duct cancers, or "peripheral cholangiocarcinomas". Those cancers that occur at or near the junction of the right and left hepatic ducts are known as Klatskin tumors and are considered extrahepatic. Early stage cancers in this location are less likely to present with biliary obstruction than their extrahepatic counterparts. Symptoms may be nonspecific, and detection may be incidental. They are typically adenocarcinomas. Surgical resection has the highest potential for cure, though surgery is often not possible due to local extent of disease or metastases. Highest surgical cure rates are seen if there is only one lesion, vascular invasion is not present, and lymph nodes are not involved.

The role of adjuvant radiation therapy after resection is not firmly established, but is considered an option for adjuvant management in the post-resection R1 and R2 situations, and/or when nodes are positive, for definitive management of unresectable tumors, and for palliation. Numerous other methods of locoregional treatment, such as radiofrequency ablation, transarterial chemoembolization and photodynamic therapy are available. The use of intraluminal brachytherapy (low dose rate [LDR] or high dose rate [HDR]) has been described and may be useful in unique situations. Data are limited; the optimal approach is not established.

The selection of radiation technique and the use of concurrent chemotherapy are best made in the context of a multidisciplinary approach. When radiation therapy is used, the preservation of normal liver function and respect for constraints of nearby other normal organs must be maintained. When SBRT has been employed for larger lesions, doses >= 80.5 Gy biologically equivalent dose (BED) have been found to be effective. When SBRT type technique is used for more than 5 fractions, it is to be reported as 3D or IMRT.

III. Extrahepatic bile duct cancer (cholangiocarcinoma)

The junction of the right and left hepatic ducts serves as the dividing location of intra-and extrahepatic bile duct cancers. Those extrahepatic cholangiocarcinomas that arise near the right and left hepatic duct junction are known as hilar or Klatskin tumors. Those more distal may occur anywhere along the common bile duct down to near the ampulla of Vater. They are typically adenocarcinomas, and are more likely to present with bile duct obstruction than their intrahepatic counterpart. Surgical resection is the only potentially

curative treatment.
As the incidence is low, there is no firmly established role of radiation therapy, though its use is an accepted option in postoperative cases of R0, R1, R2 margins and/or positive nodes. When radiation therapy is used, the preservation of normal liver function and respect for constraints of nearby other normal organs must be maintained, especially the small bowel, stomach, and kidneys. Data to support specific regimens are limited.
The selection of radiation technique and the use of concurrent chemotherapy are best made in the context of a multidisciplinary approach. Because of the proximity to hollow viscus structures, daily doses in excess of 2.2 Gy are avoided.

IV. Gallbladder cancer

Gallbladder cancers are the most common of the biliary tract cancers, tend to be very aggressive, and most commonly are adenocarcinomas. They tend to invade locally and cause both nodal and distant metastases. A common presentation ofgallbladder cancer is to be diagnosed at the time of cholecystectomy for what was preoperatively thought to be cholecystitis. Complete resection provides the only realistic chance for cure, the likelihood of which decreases as the extent of surgery needs to increase to achieve clear margins.

The use of adjuvant radiation therapy after resection appears to be most beneficial in patients with T2 and higher primary tumor status, or if nodes are positive, and is most commonly given concurrent with capecitabine or gemcitabine. T1a and T1b, N0 cases have not been shown to benefit from adjuvant radiation, which may be omitted. Because of the proximity to hollow viscus structures, daily doses in excess of 2.2 Gy are avoided, unless the target is within the hepatic parenchyma.

Definitive radiation therapy along with fluoropyrimidine-based chemotherapy is an option for patients with unresectable gallbladder cancer that has not spread beyond a locoregional state. Such an approach often becomes a palliative exercise, and should be weighed against other means of palliation that includes biliary decompression followed by chemotherapy.

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Radiation Therapy for Hodgkin's Lymphoma

POLICY

I. Definitive radiation therapy

A. Definitive radiation therapy as sole therapy is medically necessary for selected cases of stage I-IIA lymphocyte predominant Hodgkin's lymphoma
   1. Doses ranging from 30 to 36 Gy in a single phase may be required
   2. Complex, three dimensional (3D) Conformal Radiation Therapy (3DCRT) or Intensity-Modulated Radiation Therapy (IMRT) techniques may be used

II. Adjuvant radiation therapy (combined modality treatment) after chemotherapy

A. Radiation treatment regimens following chemotherapy depend on clinical stage, presence or absence of bulky disease, the chemotherapy regimen used (ABVD or Stanford V), as well as the response to treatment (Positron Emission Tomography [PET] scan Deauville 3-4)
   1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
   2. Complex, 3DCRT, or IMRT techniques are medically necessary

B. Combined modality treatment after chemotherapy is medically necessary in some cases of individuals with stage III-IV disease to areas of initial bulky involvement or to areas of less than a complete response (CR)
   1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
   2. Complex, 3DCRT, or IMRT techniques are medically necessary, directed at up to 4 separate sites in up to 2 phases apiece

C. Concurrent chemotherapy carries a high toxicity burden, requires substantial supportive care, and the expertise of an experienced multidisciplinary team

III. Salvage radiation therapy

A. Salvage radiation therapy is medically necessary after chemotherapy to areas of relapsed bulky involvement
   1. Doses ranging from 20 to 45 Gy with conventional fractionation may be required
   2. Complex, 3DCRT, or IMRT techniques are medically necessary, directed at up to 4 separate sites in up to 2 phases apiece

B. Salvage radiation therapy may be medically necessary in an individual who relapses after solo chemotherapy for initial stage I/IIA disease
   1. Definitive radiation doses ranging from 30 to 45 Gy using conventional fractionation may be required
   2. Depending on the extent of the disease, Complex, 3DCRT or IMRT techniques may be necessary

a. Treatment of up to 3 sites may be required with up to 2 phases per site
b. Complex, 3DCRT, or IMRT techniques may be used

IV. Palliative radiation therapy

A. In an individual with advanced or recurrent disease that is felt not to be curative and who has symptomatic local disease, photon and/or electron techniques are indicated for symptom control
   1. Up to 10 fractions are medically necessary in 1 phase
   2. Complex, 3DCRT, or IMRT techniques may be used

V. Radiation therapy, photon and/or electron techniques

A. Complex, 3DCRT, and IMRT techniques are medically necessary
B. Respiratory gating techniques and image guidance techniques may be appropriate to minimize the amount of critical tissue (such as lung) that is exposed to the full dose of radiation. IGRT may be approved for 3D treatment in the thorax or for small volume fields elsewhere
C. The use of photon beam and/or electron beam radiation therapy may be medically necessary

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society for Radiation Oncology [ASTRO], National Comprehensive Cancer Network [NCCN]), radiation therapy is considered an integral component in the multidisciplinary management of Hodgkin's lymphoma (HD). Proper management of the disease requires the cooperation of a complex multi-disciplinary team that includes experts in diagnostic imaging, pathology, radiation oncology and medical oncology. HD treatment is based on initial stage of disease as well as the medical condition of the individual, and treatment is dynamically modified based on the speed and extent of response to initial therapy. At diagnosis, areas of involvement may be supra-diaphragmatic only, sub-diaphragmatic only, or a combination of the two in the more advanced stages. The stage determines decisions made about the proper extent of radiation. The varied pathologic subtypes, for the most part at present, do not materially affect the dose or field decisions to be made in this disease.

Treatment decisions are preceded by workup and staging and planned in conjunction with the appropriate members of the multi-disciplinary team. Participation in a national clinical trial is encouraged.

Initial management will usually require chemotherapy (in a variety of different acceptable regimens), followed by assessment of response, leading to an appropriate choice of doses and fields of radiation therapy. Chemotherapy alone may be appropriate for early stage non-bulky disease, with radiation therapy reserved for relapse. As mentioned in the Policy section, treatment is individualized depending on the initial clinical stage, presence or absence of bulky disease, chemotherapy regimen

used, and response to chemotherapy as evaluated by repeat staging including a PET scan with results incorporating the Deauville criteria.

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Radiation Therapy for Kidney and Adrenal Cancer

POLICY

External beam photon radiation therapy is medically necessary for the following:

I. **In the adjuvant setting for a high risk individual with adrenal cancer**

II. **Palliation**

III. **Radiation is not medically necessary in the definitive or adjuvant treatment of renal cell cancer**

Fractionation

I. **In the adjuvant setting for adrenal cancer, up to 30 fractions is medically necessary**

II. **In the palliative setting, up to 20 fractions is medically necessary**

Techniques

I. **3D conformal technique is medically necessary in the adjuvant or palliative setting**

II. **In the adjuvant setting, intensity modulated radiation therapy (IMRT) may be indicated when dose to critical organs is of concern. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the acceptable normal tissue constraints using standard radiation therapy criteria from the Radiation Therapy Oncology Group (RTOG) or National Comprehensive Cancer Network (NCCN).**

Key Clinical Points

Standard of care for localized renal cell cancer is surgical resection. A partial nephrectomy can be used in the treatment of early stage renal cell cancer while an open radical nephrectomy is used with locally advanced disease. There is no benefit with radiotherapy in the adjuvant or neo-adjuvant setting in the treatment of renal cell cancer (Escudier, 2014). In an individual with unresectable disease or recurrent disease, radiation can be utilized to improve local control (Mourad, 2014). There are

preliminary reports examining the use of stereotactic body radiotherapy (SBRT) in the treatment of early stage inoperable renal cancer. However, there are no prospective studies examining this issue, and current standard of care for patients with inoperable localized renal cell cancer include radio frequency or cryo-ablative therapies (Mourad, 2014).

Adrenal cancers include adrenocortical carcinoma and malignant pheochromocytoma. Surgical resection of adrenal tumors remains the standard of care. For nonmetastatic adrenocortical cancer, adjuvant radiation can be considered for an individual with high risk of recurrence including one with positive margins, ruptured capsule, large size (> 7 cm), or high grade (Sabolch, 2015). Adjuvant mitotane can also be considered in this setting (Terzolo, 2007).

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Radiation Therapy for Lung Cancer

I. Non-small cell lung cancer (NSCLC)

POLICY

A. Definitive external beam photon radiation therapy is medically necessary for an individual with either:
   1. Stage III
   2. Stage I or Stage II (node negative)
      a. Surgery refused or
      b. Medically inoperable
      c. A non-biopsied pulmonary nodule with evidence of progressive growth on xrays, Computed Tomography (CT) scans and a positive Positron Emission Tomography (PET)/CT with written documentation from a Tumor Board recommending proceeding with Radiation Therapy (RT).

B. Preoperative (neoadjuvant) external beam photon radiation therapy is medically necessary for an individual with either:
   1. N2 disease clinically or by mediastinoscopy with planned lobectomy
   2. T3 or T4 primary lesion
   3. Superior sulcus tumors

C. Postoperative external beam photon radiation therapy is medically necessary for an individual with one or more of the following:
   1. Any mediastinal nodes positive for tumor
   2. No surgical sampling of mediastinal nodes
   3. Margins of the resected specimen are positive or close

D. Palliative external beam photon radiation therapy is medically necessary in an individual with:
   1. Stage IV disease and at least one of the following symptoms:
      a. Airway obstruction
      b. Hemoptysis
      c. Pain
      d. Cough
      e. Endobronchial obstruction
      f. Superior vena cava obstruction or syndrome

II. Small cell lung cancer (SCLC)

POLICY

A. Definitive external beam photon radiation therapy is medically necessary for an individual with:
   1. Limited stage disease, defined as disease which is limited to the thorax and that can be entirely encompassed in a radiation field
   2. Extensive stage disease in which all systemic disease (metastases) has complete or near-complete resolution with chemotherapy

B. Prophylactic cranial irradiation (PCI) is medically necessary in a responding individual (local disease and extensive disease) with good performance status.
C. Palliative radiation therapy is medically necessary for an individual with:
   1. Extensive stage SCLC
   2. Airway obstruction
   3. Hemoptysis
   4. Pain
   5. Cough
   6. Endobronchial obstruction
   7. Superior vena cava obstruction or syndrome

III. Technique

A. Three-dimensional Conformal Radiation Therapy (3DCRT) is medically necessary
B. Intensity-Modulated Radiation Therapy (IMRT) is not medically necessary
   1. Exceptions to the IMRT rule will be made on a case-by-case basis, especially in situations:
      a. Where there is disease in the bilateral mediastinum or bilateral hilar regions
      b. Where there is disease in the para-spinal region
      c. For superior sulcus tumors
      d. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
C. Stereotactic Body Radiation Therapy (SBRT) (with 3D or IMRT planning) is medically necessary for an individual with medically inoperable Stage I or II NCSLC
D. In the palliative treatment of lung cancer, the use of 3DCRT or radiation planned using a complex isodose technique is medically necessary
E. Image-Guided Radiation Therapy (IGRT). Please refer to separate IGRT policy

Key Clinical Points

I. Treatment of stage III non-small cell lung carcinoma

Approximately one-third of individuals with non-small cell lung carcinoma present with locally advanced disease that is considered unresectable due to clinically apparent involvement of mediastinal lymph nodes or T4 disease. Until the mid-1990s, such individuals were treated with radiation therapy alone. RTOG 73-01 (Perez et al., 1987) was designed to assess the optimal dose of radiotherapy for patients with locally advanced disease, including those with poor performance status and/or significant weight loss. Local control and 2-year survival were better with 60 Gy in 6 weeks compared with lower doses. The seminal study of Dillman et al. from the Cancer and Leukemia Group B (CALGB) was published in 1996 and was the first study to demonstrate a survival benefit with the use of induction

chemotherapy followed by external beam photon radiation therapy for patients with good performance status and weight loss of less than 5%. Cisplatin-vinblastine for two cycles followed by thoracic external beam photon radiation therapy to a dose of 60 Gy in 6 weeks was compared with the same external beam photon radiation therapy alone in 155 randomized patients. Induction chemotherapy improved median survival, and 3- and 7-year overall survival (OS). These results were confirmed in RTOG 88-08 (Sause et al., 2000), a study of 458 patients with Stage III NSCLC randomized to the positive arm of the CALGB trial (induction vinblastine-cisplatin followed by external beam photon radiation therapy) versus hyperfractionated external beam photon radiation therapy to 69.6 Gy versus standard fractionation external beam photon radiation therapy of 60 Gy in 6 weeks. These and other trials established the use of induction chemotherapy followed by standard fractionation of external beam photon radiation therapy as superior to external beam photon radiation therapy alone, and such therapy became the standard of care in the early 1990's for inoperable patients with Stage III disease and good performance status. Use of concurrent chemo-radiotherapy was also evaluated. RTOG 9410 is the largest trial assessing the value of concurrent versus sequential chemo-radiotherapy. In this trial, 610 patients with Stage III disease were randomized to three arms: the positive arm of the CALBG trial reported by Dillman et al. (induction cisplatin-vinblastine for two cycles followed by external beam photon radiation therapy to 63 Gy) versus the same chemotherapy given concurrently versus a third arm of oral etoposide and weekly cisplatin given concurrently with 69.6 Gy hyperfractionated external beam photon radiation therapy (HART). Local control was better with concurrent HART, however, the best survival was seen with concurrent cisplatin-vinblastine and standard fractionated external beam photon radiation therapy. The use of concurrent external beam photon radiation therapy was associated with a significantly increased acute esophagitis as compared to sequential therapy, and concurrent HART was associated with even more frequent severe esophagitis.

The use of 3DCRT techniques, which are now standard, has made possible a decrease in normal tissues receiving high doses. 3DCRT techniques allow the development of complex multiple field radiotherapy plans that decrease the amount of normal tissue exposed to high doses. Better delineation of the target volume can be achieved with F-fluorodeoxyglucose-Positive Emission Tomography (FDG-PET). If FDG-PET has not been done for prior staging purposes, use of FDG-PET for staging and radiation planning is appropriate. Incorporating the information from PET/Computed Tomography (CT) can change the target volume in a significant proportion of patients as compared with CT alone. The radiotherapy target volume can decrease (due to the ability of PET to differentiate atelectatic lung from tumor) or increase (due to FDG uptake at mediastinal lymph nodes that were not positive by CT size criteria alone). In the

increasingly common situation today when elective nodal irradiation is avoided, more accurate definition of involved sites of disease with PET decreases the likelihood that tumor-bearing nodes will not be encompassed in the target volume.

The use of techniques that account for mobility of the tumor with respiration takes on greater importance when 3DCRT treatment planning is utilized. By accounting for tumor motion on an individualized basis, smaller margins can be utilized thereby decreasing exposure to normal lung tissue. One approach to this problem is the use of respiratory gating or breath-hold technique. Gating the treatment with the respiratory cycle or treating with breath hold can help to reduce the planning target volume or avoid marginal miss. Another method incorporates so-called four-dimensional (4D) imaging. Use of rapid spiral CT scanning and acquisition of multiple images during breathing allows for better definition of the target volume, so that changes in the shape and location of the tumor during the breathing cycle can be taken into account in radiation delivery. With this technique temporal changes in tumor position and anatomy are incorporated into the treatment planning process. External beam photon radiation therapy delivery that adjusts in real-time to changes in tumor and normal anatomy holds further promise to decrease the necessary tumor margin and exposure to uninvolved lung.

Use of IMRT is also being studied. With this technique, the intensity of the beam is spatially varied in real time and delivery is accomplished using multiple fields at different angles or with rotational arc therapy. The primary disadvantage is that a greater volume of normal tissue gets low doses. Since the normal lung has low tolerance to even small doses, this technique is not appropriate in the majority of cases of locally advanced non-small cell carcinoma. IMRT may offer advantages in the treatment of an individual with bilateral mediastinal nodal involvement or in the treatment of an individual with definitive radiotherapy (without surgery) for superior sulcus tumors or para-spinal tumors. Recent attempts (Harris et al., 2014) to support the use of IMRT concluded that IMRT is “as effective as” but is “not better than” 3D. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the RTOG/NCCN.

Dose and fractionation regimens are evolving in the definitive treatment of locally advanced NSCLC, but no randomized trial has shown a benefit to doses higher than 60 Gy. The results of RTOG 0617, in which patients with stage IIIA or IIIB non-small-cell-lung cancer were randomized to standard-dose external beam chemoradiation (60 Gy) or high-dose chemoradiation (74 Gy) revealed that OS was 28.7 months in the standard-dose population vs. 20.3 months in those receiving high-dose radiation therapy. There was a trend towards increased treatment-related deaths in the high-dose population (8 vs. 3), and severe

esophagitis was significantly increased in the high dose population 21% (43/207) vs. the standard-dose population (7% (16/217). The authors concluded that high-dose radiation for individuals with stage IIIA or stage IIIB non-small-cell-lung cancer was not better and might actually be harmful. Following publication of the official results of 0617, several additional analyses of the data emerged which have provoked controversy in the literature.

The study does not include in its primary or secondary objectives a comparison of randomized IMRT and 3DCRT treatment techniques. Indeed in the Treatment Planning section, the study states: “IMRT is allowed as long as the participating institution is credentialed by the RTOG for intra-thoracic IMRT Treatments.” Hence, there is no formal randomization.

Chun, Hu, Choy et al. (2015) published a secondary analysis of 0617 in which they compared IMRT to 3DCRT. With a follow-up time period of two years, they noted no difference in overall survival (OS), progression free survival (PFS), local failure, and distant metastasis-free survival between the two techniques. They did conclude however that IMRT produced statistically significant lower heart doses than 3DCRT and that the volume of the heart receiving 40 Gy was also statistically significant in affecting OS. They recommended continued follow-up of the IMRT cardiac effects as the time period might be too short to measure them accurately. In their evaluation of pulmonary toxicity, the authors stated no difference in survival. They noted however that IMRT patients generally had larger tumor volumes, more advanced stage, and worse socio-economic status. IMRT was associated with statistically significant fewer cases of grade 3 pneumonitis .Grade 3 esophagitis, dysphagia, weight loss and cardiovascular toxicity were not different. The lung V5 was significantly larger in the IMRT cases but was not associated with grade 3 toxicity. The article concluded that IMRT should be used routinely to treat locally advanced NSCLC.

Eaton, Pugh, Bradley et al. (2016) published a review of 0617 based on institutional accrual. They noted that patients treated at High Volume Centers (HVCs) were more often treated with IMRT than 3DCRT (54.0% vs. 39.5%) with lower mean esophageal and cardiac doses. HVCs had a more statistically significant acceptability rating on Protocol review than Low Volume Centers (LVCs) as well. In acknowledging the importance of reduced cardiac dose with IMRT, the authors noted that the volume of heart receiving 50 Gy or more was an independent predictor of adverse events. In summarizing their review the authors stated: “The differences in treatment technique, however, cannot solely account for the statistically significant longer OS demonstrated at HVCs as IMRT itself was not found to be associated with clinical outcome. Although a greater proportion of patients treated at HVCs were randomly assigned to the 60 Gy dose level, treatment at an HVC was associated with longer OS even among the subsets of patients randomly assigned to 60 Gy.” They concluded that

institutional accrual volume should be considered in future clinical trials.

In correspondence to the Journal of Clinical Oncology, Ball, Manus, Siva et al. (2017) pointed out that there were only two grade 5 toxicities due to pneumonitis in 0617. In their editorial, they questioned whether the 0617 analysis was a true planned secondary evaluation and noted that interstitial lung disease, as well as other risk factors, were not taken into account. They noted institutional settings might have played a role in the determinations. For some patients and in less experienced centers the authors felt that 3DCRT might actually result better and safer treatment. Their editorial concluded that it was premature to recommend IMRT routinely for all patients based on the 0617 paper. In their reply to Ball et al, Chan, Hu and Bradley (2017) agreed that the secondary analysis did not provide the same level of evidence as a properly randomized Phase III study intentioned to address the different techniques. They stated that RTOG 0617 "…used stratified blocked randomization, with radiation technique as one of the stratification factors…"and that it has "…long been the intent to perform a secondary analysis." They pointed out that IMRT has been adopted for other cancers without randomized studies and that the evidence provided in 0617 was sufficient to recommend the routine use of IMRT in locally advanced NSCLC.

The described literature does indeed raise important questions. In the formally-stated objectives of 0617, the stratification and endpoints to not necessarily support the concept of a sub-analysis, especially since IMRT was "permitted." Given the difference in plan acceptability between HVCs and LVCs and the better survival of patients regardless of technique at an HVC, there may indeed be an overall difference and possible unintentional bias not only in treatment but also in the supportive care and treatment of side effects. Kong and Wang (2015) reviewed the non-dosimetric risk factors for radiation induced pulmonary toxicity. Age, sex, smoking status, pre-existing lung disease, pulmonary function, tumor location, volume stage, biologic and genetic factors, may also play a strong role in radiation treatment toxicity and possible outcomes. The 0617 study does not include all of these risk factors. Similarly, in assessing cardiac effects, current cardiac status and potential cardiac risk factors should be taken into account in trial design. As such, until additional evidence is available from properly designed studies, 3DCRT remains the usual and customary treatment for locally advanced lung cancer. It is recognized, however that in individual cases, IMRT may be medically necessary. Requests for IMRT will be reviewed on a case-by-case basis by eviCore Medical Directors.

II. Preoperative and postoperative therapy

An individual with Stage IIIA disease based on ipsilateral mediastinal nodal involvement has traditionally been considered unresectable, as outcome with surgery has generally been poor when there has been clinically apparent mediastinal involvement, particularly when multiple station N2 disease is present.

However, with improvements in modern staging and more generalized use of multimodality therapy, there may be subsets of individuals with clinical N2 disease who might benefit from surgery. Attempts have been made to "downstage" individuals with preoperative chemoradiotherapy. The dose of radiation in the preoperative setting is generally 45 Gy in25 fractions of external beam photon radiation therapy. 3DCRT techniques may be helpful, even at these lower doses, to reduce the dose to normal lung. Similarly, respiratory gating techniques may also be helpful, particularly for lower lobe primary tumors.

Postoperative radiotherapy (PORT) with external beam photon radiation therapy improves locoregional control as demonstrated by an early trial conducted by the Lung Cancer Study Group; however, this did not translate into an overall survival benefit. Enthusiasm for postoperative external beam photon radiation therapy diminished after the publication of the PORT meta-analysis, which included 2,128 patients with stage I to III non-small cell lung carcinoma enrolled on 9 randomized trials from 1966 to 1994. In the entire group of patients, there was a 7% absolute reduction in survival for patients who received external beam photon radiation therapy. The trials included in the meta-analysis have a variety of serious pitfalls, including the inclusion of ineligible patients, inadequate staging work-up, inclusion of node-negative patients, and techniques that today would be expected to produce deleterious outcomes. Most of the trials used higher total dose (> 50 Gy) or high dose per fraction (e.g. 2.5 Gy per fraction). In many of the trials, opposed off-cord lateral fields were used, which exposes a significant volume of normal lung to intolerable radiation volume, dose per fraction and total doses. Additionally, systemic therapy was not used, and improved local control is more likely to translate into a survival benefit if effective systemic therapy is available. An individual with N2 disease is likely to achieve a significant local control benefit from postoperative external beam photon radiation therapy, and with modern techniques the individual may accrue a survival benefit. An American Intergroup trial and a European Organisation for Research and Treatment of Cancer (EORTC) trial are presently underway to re-evaluate the role of external beam photon radiation therapy for patients with N2 disease.

III. PCI for NSCLC

Twenty to 50% of individuals with clinical Stage III non-small cell lung carcinoma will develop brain metastases during the course of the disease and in individuals who have responded to prior multimodality therapy; a significant proportion experience relapse in the brain as the first or isolated site of failure. Early trials of PCI (Russell et al., 1991) showed greater than 50% relative risk reduction in the incidence of brain metastases with PCI, however, this did not translate into a survival benefit in any of the trials. Concerns of neurocognitive morbidity from PCI are largely related to the early experience with the use of PCI for small cell carcinoma, which is associated with a significant proportion of patients having

neurocognitive dysfunction prior to radiation. More modern trials (Gregor et al., 1997) that employ lower dose per fraction and avoid concurrent chemotherapy have not found any impact of PCI on neurocognitive function. The RTOG conducted a study (Gore et al., 2009) of patients with Stage III non-small cell carcinoma who did not have progressive disease to evaluate the potential benefit of PCI. Patients were randomized to 30 Gy in 15 fractions versus observation after definitive local therapy. The primary endpoint was survival, and secondary endpoints were the rate of CNS metastasis, quality of life, and neurocognitive effects. The trial was negative for survival, but decreased local failure. Results of effects on neuropsychological function and quality of life are not yet available. Outside of a clinical trial, PCI for NSCLC is not appropriate.

IV. Early stage NSCLC

External beam photon radiation therapy is appropriate for curative intent treatment of an individual with Stage I and II NSCLC who is medically inoperable. An individual with hilar nodal involvement should be treated with standard fractionation (e.g. 60 Gy in 6 weeks) and 3DCRT techniques are preferred. For node negative Stage I and Stage II non-small cell lung cancer in an individual who is medically inoperable or who refuse surgery, SBRT is an appropriate option. SBRT is a technique that uses multiple intersecting beams of radiation to deliver a very high radiation dose to a precisely defined area, while minimizing radiation to surrounding areas. Precise immobilization techniques are required to deliver SBRT. Treatment is generally delivered in 3 to 5 fractions. A linear accelerator can be used to deliver SBRT. The CyberKnife™ is a robotic version that can be used to treat any part of the body. SBRT is an appropriate technique for patients with node negative peripheral lung cancers less than 5 cm in maximum dimension. Patients with central tumors can experience excessive toxicity when higher fraction sizes and fewer fractions (e.g. 3) are utilized Use of mediastinoscopy is appropriate for staging of clinical stage T2N0 patients prior to definitive SBRT. IGRT may also improve the therapeutic ratio. Accurate set-up of the individual with the use of radiopaque markers placed in the tumor or use of daily CT scan imaging can essentially eliminate any additional margin that might otherwise be needed for daily individual set-up variability.

V. Oligometastatic presentations/genetic variants

Lung cancer may present in an intermediate phase where cancer may be limited to the primary region with three or fewer metastatic sites that are also amenable to definitive treatment. Requests for definitive radiation treatment to the primary site will be considered on a case-by-case basis. Please see the Oligometastatic Clinical Guideline.

Similarly, a small subset of patients may present with Alk+; ROS1+ or EGFR+ mutations (exon 21, exon19) that have longer durable responses to targeted agents despite a significant metastatic disease burden. Alk+ tumors with CNS

metastases may have survival in excess of 40 months. As such, circumstances may present where a more protracted radiation therapy regimen may benefit these patients rather than a short-term palliative regimen when substantial benefit has been gained from systemic therapy. These requests will also be reviewed individually. In the case of EGFR+ mutations it should be noted that exon 20 mutations are not associated with this benefit.

Additionally, the use of anti-PD-1 and PDL-1 agents such as Pembrolizumab are now being used as first line therapy in both metastatic squamous and adenocarcinomas which have a positive test of 50% or greater for PDL-1. The use of radiation therapy in this setting will also be reviewed on a case-by-case basis.

Please see the NCCN Non-Small Cell Lung Cancer Guidelines® (Version 8.2017 – July 14, 2017) for additional discussion.

VI. Palliative treatment

An individual with localized disease but with significant co-morbidities, poor performance status, or significant weight loss may be appropriate for external beam photon radiation therapy as definitive treatment with a hypofractionated schedule, use of split-course treatment, or use of more conventional fractionation alone (e.g. 60 Gy in 6 weeks). In addition, external beam photon radiation therapy is effective in the palliation of symptoms due to local tumor, such as hemoptysis, cough, or imminent endobronchial obstruction. Approximately 40% of individuals with NSCLC present with Stage IV disease. One multi-institutional phase III randomized study (Simpson et al., 1985) examined a variety of fractionation schemes including 40 Gy split course, 30 Gy in 10 fractions, and 40 Gy in 20 fractions. There was no difference between arms, and 60% of patients achieved symptom relief. Bezjak et al. (2002) reported a phase III trial of 231 patients randomized to 20 Gy in 5 fractions versus 10 Gy in 1 fraction. Similar palliation was seen in both arms, although patients in the 20 Gy arm had longer median survival. The Medical Research Council compared 17 Gy in 2 fractions (one per week) with 30 Gy in 10 fractions over 2 weeks. There was no difference in survival or palliation of symptoms. Hemoptysis was relieved in 86% of patients, cough in approximately 60% of patients, and pain in approximately 50% of patients. Therefore, data supports the use of short hypofractionated regimens, and there is generally no general role for more protracted schemes beyond 10 or 15 fractions. Endobronchial (EBB) radiation has also been found in retrospective studies to be effective in the palliation of symptoms due to intraluminal tumor, including obstruction, dyspnea, and cough. The procedure requires bronchoscopic guidance of the brachytherapy catheter. There is no proven role for more than 3 applications. EBB will be considered medically necessary after a failed course of external beam photon radiation therapy. American Society for Radiation Oncology (ASTRO) has published an evidence-based guideline for

palliative lung cancer that reviews the various dose and fractionation regimens and the role of EBB. The ASTRO guideline specifically states that there is no benefit to adding concurrent chemotherapy to external beam photon radiation therapy in the palliative setting.

VII. Small cell carcinoma

There is little role for surgery in the management of an individual with SCLC. In the few cases of clinical stage T1-T2N0 disease, surgery establishes the diagnosis and effectively removes the primary tumor. Such individuals should also be staged with mediastinoscopy, and if mediastinal lymph nodes are negative, chemotherapy alone can be entertained. External beam photon radiation therapy improves survival of an individual with limited stage SCLC. Concurrent chemo-radiotherapy leads to improved survival as compared with sequential therapy. Standard external beam photon radiation therapy fractionation consists of either 45 Gy given at 1.5 Gy bid (hyper-fractionation/accelerated) or at 1.8 to 2 Gy per day to 54 to 70 Gy. Local thoracic external beam photon radiation therapy for individuals with extensive stage disease is not an established approach, however, in selected individuals it may be considered, such as those with clinically apparent disease only at the primary site and complete response elsewhere.

More than 50% of individuals with SCLC will experience brain metastases during the course of disease. Prophylactic cranial radiotherapy reduces this risk by approximately 50% in relative terms, and improves overall survival in an individual with chemo-responsive limited stage SCLC and extensive stage SCLC. Concerns regarding neurocognitive defects are obviated by avoiding high dose per fraction treatment and concurrent chemotherapy. PCI is not appropriate for an individual with severe co-morbidities, one who is bedridden most of the time, or one with severely impaired cognitive functioning. The recommended doses/fractionation for PCI are 25 Gy in 10 daily fractions, 30 Gy in 10 to 15 daily fractions, or 24 Gy in 8 daily fractions. In selected individuals with extensive disease, a shorter course, such as 20 Gy in 5 fractions may be appropriate. Higher doses have not proved beneficial and are associated with more neurocognitive deficits.

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Radiation Therapy for Non-Hodgkin's Lymphoma

POLICY

I. Photon and/or electron techniques for the treatment of non-Hodgkin's lymphoma (NHL) are medically necessary, generally using involved-site radiation therapy (ISRT)

A. Complex and three-dimensional conformal radiation therapy (3DCRT) techniques
B. Intensity-Modulated Radiation Therapy (IMRT) for an individual with disease located above the diaphragm. Respiratory gating techniques and image guidance techniques may be appropriate to minimize the amount of critical tissue (such as lung) that is exposed to the full doses of radiation
C. In sub-diaphragmatic presentations, IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
D. Photon and/or electron beam radiation therapy
E. The treatment of lymphomas with radiation is generally done using relatively low doses in the range of 15 to 36 Gy at standard fractionation, sometimes with doses as low as 4 Gy in 2 fractions
F. IMRT is not medically necessary for the treatment of an individual with low dose radiation, i.e., 2 Gy in 2 fractions

II. Definitive radiation therapy

A. As sole therapy is medically necessary for an individual with stage I-IIA low grade NHL
   1. Doses up to 36 Gy, directed at a single site in a single phase
   2. Using Complex or 3D techniques with image guidance
   3. IMRT for an individual with supra-diaphragmatic presentation. A request for IMRT for an individual with sub-diaphragmatic presentation will require a case-by-case discussion to document that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by RTOG/NCCN
B. Mucosa-associated lymphoid tissue (MALT) lymphomas of gastric or non-gastric origin, that are confined to the organs of involvement
   1. Doses of 36 Gy directed at a single site in a single phase
   2. Complex or 3D techniques with image guidance
   3. IMRT will be considered on a case-by-case basis for gastric involvement, as it is a sub-diaphragmatic presentation

C. Extranodal NK/T-cell lymphoma, nasal lymphoma
   1. Doses of 54 Gy
   2. 3D or IMRT techniques
   3. 30 fractions in 2 phases
D. Consolidative radiotherapy after initial chemotherapy
   1. Doses of 36 Gy to the original extent of disease for the following histologies:
      a. Mantle cell lymphoma
      b. Diffuse large cell B-cell lymphoma (DLBCL)
      c. Burkitt's lymphoma
      d. Lymphoblastic lymphoma
      e. Primary cutaneous B-cell lymphoma
      f. Peripheral T-cell lymphoma

III. Radioimmunotherapy

A. Please refer to the separate Radioimmunotherapy with Zevalin® guideline

IV. Adjuvant radiation after chemotherapy

A. Areas of initial involvement
   1. Adjuvant radiation therapy after chemotherapy in an individual with stage I-IIB disease to areas of initial involvement
      a. Doses of up to 36 Gy
      b. Up to 20 fractions with a conventional schedule
   2. Supra-diaphragmatic presentations
      a. Complex, 3DCRT, or IMRT techniques, with image guidance, directed at a single site in 1 phase
   3. Sub-diaphragmatic presentations
      a. Complex or 3DCRT techniques
      b. IMRT will be considered on a case-by-case basis
B. Areas of less than a complete response (CR)
   1. Adjuvant radiation after chemotherapy in an individual with stage III-IV disease, to areas of less than a CR
      a. Doses of up to 36 Gy
      b. Up to 20 fractions with conventional schedule
   2. Supra-diaphragmatic presentations
      a. Complex, 3DCRT, or IMRT techniques, with image guidance, directed at up to 4 separate sites in 1 phase apiece
   3. Sub-diaphragmatic presentations
      a. Complex or 3DCRT techniques
      b. IMRT will be considered on a case-by-case basis
C. Sequential chemotherapy carries a high toxicity burden and requires substantial supportive care and the expertise of an experienced multidisciplinary team

V. Radiation therapy, palliative

A. In an individual with advanced or recurrent disease that is felt not to be curative and who is experiencing symptomatic local disease, photon and/or electron techniques are indicated for symptom control
   1. Supra-diaphragmatic presentations
      a. Complex, 3D, or IMRT techniques
      b. Up to 10 fractions in 1 phase
   2. Sub-diaphragmatic presentations
      a. Complex or 3D techniques
      b. IMRT will be considered on a case-by-case basis
      c. Up to 10 fractions in 1 phase

Key Clinical Points

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines (American College of Radiology [ACR]/American Society of Radiation Oncologists [ASTRO], NCCN), radiation therapy is considered an integral component in the multidisciplinary management of NHL. Proper management of the disease requires the cooperation of a complex multi-disciplinary team that includes experts in diagnostic imaging, pathology, radiation oncology and medical oncology. NHL treatment is based on the pathologic subtype of the disease, initial stage of disease as well as the medical condition of the individual. Pathology and stage have a critical role in the planning process.

Treatment decisions are preceded by workup and staging and planned in conjunction with the appropriate members of the multi-disciplinary team. Participation in a national clinical trial is encouraged.

Initial management requires chemotherapy as the cornerstone of therapy (in a variety of different acceptable regimens), followed by assessment of response leading to an appropriate choice of radiation therapy technique, dose, and use of radioimmunotherapy as clinically indicated.

I. Radiation treatment schedules

A. Radiation therapy treatment schedules published in peer-reviewed consensus documents such as NCCN Practice Guidelines in Oncology include regimens that encompass a relatively limited range of doses and fields that may be influenced by the histology, initial stage, bulk of the disease at each site, the choice of chemotherapy regimens, and the response to initial chemotherapy. Using current combined modality approaches, the fields covered are usually confined to the initial areas of documented involvement, ISRT.

B. Histology specific recommendations
   1. Chronic lymphocytic leukemia (CLL)
      a. Will not require radiation routinely
   2. Follicular low-grade lymphoma, stage I-II
      a. Radiation alone may be considered adequate therapy, or

   b. Radiation treatment may be given after initial chemotherapy to the original extent of disease
      i. Omitting sites that had no clear involvement in an effort to minimize toxicity
      ii. To doses that range from 20 to 36 Gy
      iii. Generally encompassable in a single site setup, requiring the use of Complex or 3D techniques, with image guidance
      iv. Under some circumstances, IMRT may be appropriate
      v. Radioimmunotherapy may be appropriate
3. Follicular lymphoma, stage III-IV
   a. Systemic chemotherapy is the standard of care
   b. Radiation may be considered for an individual with a sub-optimal response to therapy
4. Transformed lymphoma, i.e., an individual with an original diagnosis of follicular lymphoma that has transformed to a more malignant subtype
   a. Systemic chemotherapy is the mainstay of therapy
   b. Radiation may be considered as an adjunct for locally uncontrolled disease
   c. Radioimmunotherapy may be considered for the management of this disease
5. MALT-lymphoma (gastric or non-gastric)
   a. Radiation may be appropriate as curative therapy
   b. Doses of up to 36 Gy
6. Extranodal natural killer (NK)/T-cell lymphoma, nasal lymphoma
   a. Definitive radiation therapy to a dose of 54 Gy
7. Consolidative radiation therapy after initial chemotherapy, to a dose of 36 Gy, to the original extent of disease for the following histologies:
   a. Mantle cell lymphoma
   b. DLBCL
   c. Burkitt's lymphoma
   d. Lymphoblastic lymphoma
   e. Primary cutaneous B-cell lymphoma
   f. Peripheral T-cell lymphoma

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Radiation Therapy for Non-malignant Disease

POLICY

I. Non-malignant disorders for which radiation therapy is medically necessary when criteria are met:

A. Angiomatosis retinae (von Hippel Lindau syndrome)
   1. Conventional photon external beam radiation therapy (EBRT) in those cases in which a simpler approach is contraindicated.

B. Arteriovenous malformation (AVM)
   1. Stereotactic radiosurgery (SRS) for
      a. deep or eloquently-located AVMs less than 3 cm in size, for which surgery poses a greater risk
      b. lesions elsewhere in the brain that require treatment and surgical excision is not an option

C. Basalioma (see separate Guideline, Radiation Therapy of the Skin: Basal Cell, Squamous Cell, and Malignant Melanoma Cancers of the Skin)
D. Carotid body tumor (see chemodectoma)
E. Cavernous malformation (see AVM)
F. Chemodectoma (carotid, glomus jugulare, aortic body, glomus vagale, glomus tympanicum [chromaffin negative])
G. Chordoma (also see separate Guideline, Proton Beam Radiation Therapy)
H. Choroidal hemangioma (also see separate Guideline, Proton Beam Radiation Therapy)
I. Craniophayngioma (also see separate Guideline, Proton Beam Radiation Therapy)
J. Desmoid tumor
K. Dupuytren's contracture (fibromatosis)
L. Eosinophilic granuloma (see Langerhans cell histiocytosis)
M. Exophthalmos (refer to specific etiology)
N. Extramammary Paget's disease (adenocarcinoma of the skin)
O. Extramedullary hematopoiesis (hypersplenism)
P. Giant cell tumor of bone (osteoclastoma)
Q. Glomus jugulare (see chemodectoma)
R. Glomus tympanicum (see chemodectoma)
S. Glomus vagale (see chemodectoma)
T. Gorham-Stout syndrome (disappearing bone syndrome)
U. Graves' ophthalmopathy
V. Gynecomastia
W. Hemangiomas
X. Heterotopic ossification
Y. Histiocytosis (see Langerhans cell histiocytosis)

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Z. Hypersalivation of amyotropic lateral sclerosis (ALS)
AA. Hypersplenism (see Splenomegaly)
BB. Hyperthyroidism
CC. Keloid scar
DD. Langerhans cell histiocytosis
EE. Lethal midline granuloma
FF. Meningioma
GG. Morbus Ledderhose
HH. Optic pathway glioma
II. Osteoarthritis
JJ. Paraganglioma (chromaffin positive)
KK. Parotid adenoma
LL. Peyronie's disease (morbus peronie, induratio penis plastica)
MM. Pigmented villonodular synovitis (tenosynovial giant cell tumor)
NN. Pinealoma (pineal parenchymal tumors)
OO. Pituitary adenoma
PP. Plantar fasciitis
QQ. Polymorphic reticulosis (see lethal midline granuloma)
RR. Precancerous melanosis
SS. Psoriasis
TT. Pterygium
UU. Splenomegaly
VV. Stent placement
WW. Steward's disease (see lethal midline granuloma)
XX. Vertebral hemangioma (hemangioma)

II. Non-malignant disorders for which radiation therapy may be medically necessary when criteria are met (Note that all requests require review by an eviCore radiation oncologist):

A. Acoustic neuroma (vestibular schwannoma)
B. Adamantinoma (ameloblastoma)
C. Aneurysmal bone cyst
D. Angofibroma of nasopharynx (juvenile nasopharyngeal angiofibroma)
E. Bowen's disease (squamous cell carcinoma *in situ*)
F. Bronchial adenoma
G. Bursitis, synovitis, tendonitis
H. Carcinoid tumor
I. Castleman's disease (giant lymph node hyperplasia)
J. Castration
K. Choroid plexus papilloma
L. Cystic hygroma (lymphangioma) (see Lymphangioma)
M. Dermatitis
N. Epilepsy
O. Erythroplasia of Queyrat
P. Immunosuppression
Q. Infections (viral)

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R. Inverted papilloma
S. Lymphangiomas (capillary, cavernous, cystic hydromas, lymphangeal hemangiomas)
T. Lymphoma “benign”
U. Mikulicz syndrome (salivary lymphoepithelial lesion)
V. Myasthenia gravis (see Thymoma)
W. Neurofibroma (benign, von Recklinhausen)
X. Orbital myositis
Y. Orbital pseudotumor
Z. Parkinson’s disease
AA. Persistent lymphatic fistula
BB. Pseudotumor (orbit)
CC. Rosai-Dorfman disease
DD. Rotator cuff syndrome (see tendonitis)
EE. Sarcoidosis
FF. Sterilization (see castration)
GG. Synovitis
HH. Tendonitis
II. Tennis elbow (see tendonitis)
JJ. Thymoma
KK. Tolosa-Hunt syndrome (episodic orbital pain)
LL. Total body irradiation
MM. Total lymphoid irradiation
NN. Trigeminal neuralgia (tic douloureux)
OO. Warts

III. Non-malignant disorders for which radiation therapy is not indicated and not medically necessary:

A. Abortion
B. Acne
C. Amyloidosis
D. Ankylosing spondylitis
E. Anovulation
F. Arachnoiditis
G. Arthritis (also see Total Lymphoid Irradiation for radioimmunosuppression)
H. Corneal vascularization
I. Corneal xanthogranuloma
J. Eczema
K. Fibrosclerosis (sclerosing disorders)
L. Fungal infections
M. Gas gangrene
N. Herpes zoster
O. Infections (bacterial)
P. Infections (fungal and parasitic)
Q. Inflammatory (acute/chronic) disorders not responsive to antibiotics (furuncles, carbuncles, sweat gland abscesses)

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R. Juvenile xanthogranuloma
S. Keratitis (bullous and filamentary)
T. Macular degeneration
U. Orbital myositis
V. Ocular trichiasis (epilation)
W. Orbital pseudotumor (lymphoid hyperplasia)
X. Osteoid osteoma (osteoblastoma, giant osteoid osteoma)
Y. Otitis media
Z. Pancreatitis
AA. Parotitis
BB. Peptic ulcer disease
CC. Perifolliculitis (scalp)
DD. Plasma cell granuloma (benign)
EE. Pregnancy
FF. Pseudotumors (orbit) (see orbital pseudotumor)
GG. Psychiatric disorders
HH. Pyogenic granuloma
II. Rheumatoid arthritis
JJ. Sclerosing disorders (see fibrosclerosis)
KK. Sinusitis
LL. Thyroiditis
MM. Tinea (see infections [fungal])
NN. Tonsillitis
OO. Tuberculosis lymphadenitis
PP. Vernal catarrh

For specific details, including criteria needed to meet medical necessity and typical treatment regimen(s), please refer to the comprehensive list in the Key Clinical Points section of this Guideline.

Key Clinical Points

It was not long after the discovery of xrays in 1895 that radiation was used for therapeutic purposes. Since benign disorders do not always follow a benign course, radiation was employed for many conditions for which there was no suitable therapeutic alternative. As improvements in competing therapies have been developed, such as antibiotics, antifungals, antivirals, chemotherapies, improved surgical techniques, and immunological therapy, radiation therapy is no longer appropriate for many disorders, yet has become the preferred therapy for others. New indications have evolved over time. Where applicable, comments regarding changed indications are included in the brief discussion that follows of disorders for which radiation may have been used in the past or is presently in use. Each of the disorders listed is addressed in at least one of the references and, therefore, included in this policy.

Disorders treatable with radiation fall into the general categories of inflammatory, degenerative, hyperproliferative, functional, or "other" in nature.

Acceptance of the appropriateness of using radiation has developed using several means. Historically a trial and error approach prevailed, not different from the empiric use of pharmacological agents and surgical procedures that satisfied logic but lacked validation by now-customary rigor of prospective trials. Current indications may be based on experience-based consensus or on higher-level evidence that has resulted from formal study. Over the past five decades, consensus has been measured by polling practitioners on what is considered the appropriate uses of radiation. Such surveys in the United States, Germany and the United Kingdom supplement peer-reviewed journal publications and chapters in major radiation oncology texts, the latter reporting more evidence-based guidance that is the result of clinical studies. Both necessarily serve as the foundation for this policy.

As should be the case with all therapies, a decision whether to use radiation to treat a non-cancerous disorder should be based on safety, efficacy, and availability as measured against competing modalities, including the natural history of the disorder if left untreated, and must be subjected to informed consent. Consistent with that end, disorders have been grouped into categories for which radiation is considered: generally accepted; accepted if more customary therapy is unavailable, refused or has failed, or appropriate only as a last resort; or inappropriate under any circumstance. When utilized, radiation should be delivered using a technique that is not unnecessarily complex, and to the lowest dose that is sufficiently likely to achieve the desired result.

The earlier (more than 50 years ago) history of the use of radiation therapy to treat non-cancerous conditions is also very rich, but precedes the overview below. For a review of pre-1965 thoughts, the review by Dr. Stephen Dewing is recommended. Additional information regarding specific disorders may also be obtained from subscription services such as the Cochrane Review and UpToDate.

I. Condition

A. Abortion

It is known that radiation at sufficient dose can cause an abortion. There is no support for its use in any of the references cited. **Policy: Not indicated and not medically necessary.**

B. Acne

Historically, superficial xray therapy was used to treat acne by 41.8% of dermatologists in the U.S. Department of Health, Education, and Welfare survey report of 1977. No subsequent modern era radiation oncology review supports the use of ionizing radiation in the treatment of acne. Improved alternative treatments and the risk of radiation-induced cancer render its use obsolete for the treatment of acne. **Policy: Not indicated and not medically necessary.**

C. Acoustic neuroma (vestibular schwannoma)

These benign tumors of Schwann cell origin are relatively common and vary in presentation. Management may be initial observation, surgery, or highly conformal radiation. Bulky, fast-growing tumors, especially those causing brainstem compression, most commonly are approached surgically. Single fraction stereotactic radiosurgery (SRS) has a high local control rate with low risk of sequelae when performed with modern techniques. Fractionated SRS, most commonly employed for larger tumors may have the potential for lower risk of hearing loss, but randomized controlled study comparison has not been done. Factors that influence patient selection include symptoms such as hearing loss, status of hearing in the contralateral ear, age and life expectancy, tumor size and rate of growth, patient preference, comorbidities, and availability of therapeutic options. Typical radiation treatment is with stereotactic radiosurgery (SRS) or intensity modulated radiation therapy (IMRT). **Policy: Surgery remains the standard treatment. However, the use of single-fraction SRS and fractionated SRS is medically necessary for those cases in which surgery is declined or not indicated.**

D. Adamantinoma (ameloblastoma)

These rare, locally aggressive but usually histologically benign tumors are of epithelial origin and are most commonly of jaw or tibial location. The etiology of epithelial tissue in an unusual location is the subject of debate. These tumors tend to recur and require aggressive surgery. Being rare, experience is very limited. Most references agree surgery is the treatment of choice. The use of radiation is reported historically as beneficial, but with little evidence. The 2002 text by Order and Donaldson supplies several references, each with few cases to report, and mainly of mandible or maxillary origin. **Policy: Radiation therapy is not indicated as primary modality. Requests for use in conjunction with surgery require physician review.**

E. Amyloidosis

There is only an occasional case report of the use of ionizing radiation therapy in the treatment of amyloidosis. There is no support for its use in the modern era. **Policy: Not indicated and not medically necessary.**

F. Aneurysmal bone cyst

These are relatively rare and benign osteolytic lesions of bone usually occurring in children or young adults. They are not true neoplasms, rather are a hyperplasia filled with blood-filled channels. Initial management is surgical. Interventional radiology procedures are also available. Because of the availability of alternative therapy and the typically young age of patients, the use of ionizing radiation is a last resort. **Policy: All cases require medical review. Radiation therapy is medically necessary only if accompanied by documentation that its use is considered essential by a multi-disciplinary team.**

G. Angiofibroma of nasopharynx (juvenile nasopharyngeal angiofibroma)
While optimum management is controversial, there is general agreement that surgery is preferred if considered safe, as in cases when there is no extension into the orbital apex or base of skull. Since the typical patient is young, regard for the long-term hazard of radiation is important. When radiation is used, the radiation dose is lower than in malignant tumors of the same location. Response to treatment tends to be slow and may take several years to be evident. **Policy: Radiation therapy is medically necessary in those cases with extension into the orbital apex or base of skull.**

H. Angiomatosis retinae (von Hippel Lindau syndrome)
Capillary hemangiomas associated with von Hippel Lindau syndrome may be single or multiple, and can severely affect vision. They may be associated with hemangiomas in the cerebellum and brainstem. Multiple therapies exist including thermal and laser photocoagulation, cryotherapy, vitreoretinal surgery, beta plaque radiation therapy, and external beam radiation therapy (EBRT). Reports have described the successful use of EBRT for salvage. **Policy: Conventional photon EBRT is medically necessary in those cases in which a simpler approach is contraindicated.**

I. Ankylosing spondylitis
The use of radiation therapy in the treatment of ankylosing spondylitis is of historical interest. The risk of radiation-induced cancer and other morbidity contraindicates its use and is often cited as a common example of radiation carcinogenesis in radiobiological studies. **Policy: Radiation therapy is not indicated and not medically necessary.**

J. Anovulation
The use of radiation therapy in the treatment of anovulation is of historical interest only and is occasionally discussed in the treatment of functional pituitary adenomas. **Policy: Not indicated and not medically necessary.**

K. Arachnoiditis
In the pre-antibiotic era the beneficial use of radiation for the treatment of arachnoiditis was described. This is obsolete in the modern era. **Policy: Not indicated and not medically necessary.**

L. Arteriovenous Malformation (AVM)
Typical treatment is with stereotactic radiosurgery (SRS), which is most suitable for deep or eloquently-located AVMs less than 3 cm. in size, for which surgery poses greater risk. Resolution is slow and may take years, during which the risk of hemorrhage is not eliminated. Prior downsizing of the nidus using embolization may be helpful. **Policy: SRS is medically necessary for deep or eloquently-located AVMs less than 3 cm. in size, for which surgery poses greater risk, and for lesions elsewhere in the brain that require treatment and surgical excision is not an option.**

M. Arthritis (see total lymphoid irradiation for radioimmunosuppression) (see rheumatoid arthritis) (see osteoarthritis)

N. Basalioma

This synonym for basal cell carcinoma of the skin is sometimes included in lists of "benign" disorders of skin suitable for treatment with radiation therapy. **Policy: See separate guideline on skin cancer.**

O. Bowen's disease (squamous cell carcinoma *in situ*) (see also erythroplasia of queyrat)

This entity is considered pre-malignant and may progress into invasive cancer. The term "Bowen's disease" refers to the specific anatomic locations of the shaft of the penis or the hairy skin of the inguinal or suprapubic regions. It can be mistaken for other disorders because of the features it shares with psoriasis and eczema. Earlier references include superficial radiation as a means of treatment. Evidence consists only of case reports and modest consensus in older literature. The use of superficial radiation should be limited to situations in which typical alternatives (surgery, electrodessication and curettage, topical 5FU), are not possible. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

P. Bronchial adenoma

This term in the past has lumped together a variety of tumors arising from the mucous glands of the tracheobronchial tree including carcinoid, cylindroma, and mucoepidermoid carcinoma. The presentation and behavior ranges from truly benign to aggressive with metastatic potential. Surgical resection has historically been the treatment of choice with radiation reserved for technically or medically inoperable cases. Precise histologic classification may help discriminate those truly benign lesions that would not be expected to benefit from radiation therapy from lesions that would be best treated as invasive carcinomas. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

Q. Bursitis, synovitis, and tendinitis

Randomized studies in 1952, 1970, and 1975 cited in the Order and Donaldson review claimed "no benefit" to the use of radiation therapy for any of these, and the authors of the review recommend against its use. The U.S. Department of Health, Education, and Welfare survey report of 1977 reporting the results of a survey of American radiation oncologists included these diagnoses as acceptable for treatment, as did the German survey of 2008. There is support in modern era texts, concluding that the use of radiation "may provide an alternative to conventional conservative treatment for patients who are not surgical candidates" (Perez-Brady). When used, radiation should be to a low dose. Typical treatment is with photon beam therapy using, at most, complex treatment planning in five or fewer

fractions. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

R. Carcinoid tumors

These may be secretory or non-secretory. Surgical resection is the indicated initial treatment if removal is possible. For those unresectable non-secretory lesions causing symptoms such as pain, radiation may be beneficial. For secreting tumors, radiation therapy is limited to those causing symptoms that are not controllable by medical means. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

S. Carotid Body Tumor (see chemodectoma)

T. Castleman Disease (giant lymph node hyperplasia)

This disorder is characterized by angiofollicular lymphoid hyperplasia and can occur in any location in the body, commonly in the orbit (orbital pseudotumor) and Waldeyer's ring. The relationship to subsequent malignant lymphoma is unclear, with malignant lymphoma reported in as many as 30% of cases. Synonyms include giant follicular lymph node hyperplasia, follicular lymphoreticuloma, angiomatous lymphoid hamartoma, and giant benign lymphoma. As described by Castleman, it is a benign condition. True lymphoma should be ruled out by biopsy to prove a polyclonal nature. Steroids are indicated as initial management. Low dose radiation therapy has been reported as effective in refractory or relapsed cases if further use of steroids is contraindicated. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

U. Castration

There is evidence that with sufficient dose radiation can effectively and permanently cease gamete production and hormone production in the testes and ovaries. The indications for doing so are very limited. Surveys reported by Order and Donaldson (1998) indicated 75% of surveyed radiation oncologists would use radiation for this purpose with the appropriate indication. The U.S. Department of Health, Education, and Welfare survey report of 1977 included castration as an acceptable indication. The availability of drugs which achieve the same result has largely rendered this as obsolete. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

V. Cavernous Malformation (see AVM)

W. Chemodectoma (carotid body, glomus jugulare, aortic body, glomus vagale, glomus tympanicum) (chromaffin negative)

Chemodectoma is a general term that includes many specific types based on the location of the body in which they arise. These are chromaffin-negative, benign tumors that can arise in the chemoreceptor system, such as the aortic body; carotid body; glomus jugulare; and tympanic body. Synonyms also include paragranuloma

and nonchromaffin paragranuloma. It is generally accepted that radiation therapy, with or without surgical resection, is medically necessary, with a significant probability of control. Typical treatment is with three dimensional conformal radiation therapy (3DCRT), stereotactic radiosurgery (SRS), or intensity modulated radiation therapy (IMRT). **Policy: Radiation therapy is medically necessary.**

X. Chordoma

Radiation therapy is known to be useful in the management of chordomas. These tumors of notochord origin can be benign or malignant, but all tend to be locally invasive and tend to recur locally, some with the potential to metastasize. Surgery is the primary approach, but is often inadequate to control the primary tumor. Postoperative radiation therapy, and radiation therapy for inoperable lesions, is considered medically necessary. Typical treatment is with three dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT). See separate Guideline, Proton Beam Radiation Therapy. **Policy: Radiation therapy is medically necessary.**

Y. Choroid plexus papilloma

Choroid plexus papillomas range from the very benign (WHO grade 1) to the invasive carcinomas (WHO grade III). They are more common in very young children. Surgery is the treatment of choice. Adjuvant radiation is not indicated unless there is progression that cannot be dealt with surgically. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

Z. Choroidal Hemangioma

These are rare vascular tumors and may be circumscribed or diffuse, the latter associated with Sturge-Weber syndrome. Non-radiation treatments are available (photodynamic, laser, thermotherapy.) Radiation therapy is preferable for diffuse lesions, especially if near the macula or papilla, and for those not responding to other therapeutic maneuvers. Typically, radiation therapy is given using complex or three dimensional conformal external photon beam technique, or using low dose rate brachytherapy plaque. See separate Guideline, Proton Beam Radiation Therapy. **Policy: Radiation therapy is medically necessary.**

AA. Corneal Vascularization

Radiation therapy is not indicated in the treatment of corneal neovascularization. The entity is not to be confused with pterygium (see below). **Policy: Not indicated and not medically necessary.**

BB. Corneal xanthogranuloma

Corneal xanthogranulomas may develop in association with generalized juvenile xanthogranuloma and generalized histiocytosis. Reports in old literature of the treatment by contact radiation or photons do not establish any definite benefit. They commonly regress spontaneously. First line therapy, when observation is

not selected, is steroid therapy or surgery. **Policy: Not indicated and not medically necessary.**

CC. Craniophayngioma
Radiation therapy most oftenly is used as an adjuvant after maximal safe resection. Local control rates are similar whether radiation is given at time of first relapse or immediately after surgery. Highly conformal techniques are recommended using external beam technique. Craniophayngioma cysts may recur and grow during a course of radiation therapy, and repeat imaging (CT or MRI) is recommended at least every two weeks after treatment begins so that replanning may be done. The daily use of Image Guided Radiation Therapy (IGRT) may be done in lieu of this if image quality is adequate to detect recurrent cysts. Typical treatment is with three dimensional conformal radiation therapy (3DCRT), stereotactic radiosurgery (SRS), or intensity modulated radiation therapy (IMRT). See separate Guideline, Proton Beam Radiation Therapy. **Policy: Radiation therapy is medically necessary.**

DD. Cystic hygroma (lymphangioma) (see lymphangiomas)

EE. Dermatitis
Skin inflammation from a variety of etiologies (both known and unknown) has been treated in the past by using low dose, very superficial radiation or Grenz rays. The use of radiation for this purpose is reserved for cases refractory to non-radiation measures. **Policy: Cases require medical review to confirm alternative approaches have been exhausted.**

FF. Desmoid Tumor
Also known as aggressive fibromatosis or deep musculoapeuronotic fibromatosis, a desmoid tumor is a histologically benign connective tissue tumor with a high recurrence rate after resection. Most common sites are trunk, extremity, abdominal wall, and intra-abdominal sites, including bowel and mesentery. If stable, observation is appropriate. Surgical resection with negative surgical microscopic margins in the treatment of choice for most. Radiation therapy is indicated for inoperable cases, and may be used in conjunction with surgery and chemotherapy. Typical treatment is with three dimensional conformal radiation therapy (3DCRT) in twenty-eight or fewer fractions. Fractionated radiation therapy in excess of 50 Gy is needed for control, which may preclude its use in those of intra-abdominal location. **Policy: Radiation therapy is medically necessary.**

GG. Dupuytren's Contracture (fibromatosis)
This may develop in the hand (Morbus Dupuytren) or foot (Morbus Ledderhose) and is a connective tissue disorder of the palmar or plantar fascia. Radiation therapy is useful, especially in the earlier stages of development, and has been demonstrated in prospective clinical trials. Typical treatment is with photon beam therapy using, at most, complex treatment planning, or with electron beam

therapy in ten or fewer fractions. **Policy: Radiation therapy is medically necessary.**

HH. Eczema
There is little support in the recent American literature for the use of ionizing radiation in the treatment of eczema. The 2002 German survey supported its use, whereas the 2015 U.K. survey reported there is very little indication in the modern era, stating that only if there is no alternative would low doses of suitable energy orthovoltage or superficial radiation be appropriate. **Policy: Not indicated and not medically necessary.**

II. Eosinophilic granuloma (see Langerhans cell histiocytosis)

JJ. Epilepsy
Stereotactic radiosurgery (SRS) may be an alternative to surgery in medically refractory cases of patients who are not surgical candidates. The use of SRS is not routine for this condition. The follow-up of treated patients has been shorter than necessary to establish fully long-term efficacy and safety. Short-term responses may be slow to develop, but results have been encouraging. **Policy: Cases will require medical review, including documentation that medical management has been exhausted and unsatisfactory.**

KK. Erythroplasia of Queyrat
This *in situ* form of epidermoid carcinoma involves the mucosal or mucoepidermoid areas of the prepuce or glans penis. An invasive component is not infrequent. Sometimes it is referred to as Bowen's disease of the penis. Erythroplasia of Queyrat involves the mucosal or mucoepidermoid areas of the prepuce or glans penis, whereas the term Bowen's disease refers to squamous cell carcinoma *in situ* involving the shaft of the penis or the hairy skin of the inguinal or suprapubic region. While radiation treatments were used in the past, as Erythroplasia of Queyrat is non-invasive, its treatment can be managed with a non-radiotherapeutic approach using topical agents. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

LL. Exophthalmos
Refer to specific etiology section (Graves's ophthalmopathy, Langerhans cell histiocytosis, etc.)

MM. Extramammary Paget's disease (adenocarcinoma of the skin)
When it occurs, adenocarcinoma of the skin usually arises in areas of abundant apocrine glands. Treatment is most commonly surgical. Radiation therapy is indicated when resection is inappropriate or incomplete. The entity is discussed in the non-cancer policy due to historical references to its being a benign condition. See the section on skin cancer for policy.

NN. Extramedullary hematopoiesis (hypersplenism)
This is a myeloproliferative syndrome that most commonly involves the spleen, but can occur in the liver, lymph nodes, lungs, kidneys, GI tract, and central nervous system. Chemotherapeutic management is the initial treatment of choice. Radiation therapy is necessary in those cases in which medical management is ineffective or otherwise contraindicated. **Policy: Radiation therapy is medically necessary.**

OO. Fibrosclerosis (sclerosing disorders)
Unifocal and multifocal episodes of sclerosis have been treated in the past using radiation therapy. Sites reported include retroperitoneum, mediastinum, bile ducts, thyroid, meninges, orbits and others. While anecdotal reports of improvement have been reported, radiation therapy is generally regarded as ineffective and should not be used. **Policy: Radiation therapy is not medically necessary.**

PP. Fungal infections (see Infections, fungal)
In the 1940s and 1950s xrays were not infrequently used to treat tinea capitis and other skin fungal infections. In the modern era of available pharmacologic agents for the treatment of fungal infections, the benefit of use of radiation therapy is outweighed by the risk of carcinogenesis. **Policy: Radiation therapy is not medically necessary.**

QQ. Gas gangrene
Before the discovery of antibiotics, radiation therapy was used to treat open wounds to prevent infections, and reports exist that this was of benefit. There is no benefit of the use of radiation in the era of antibiotics. **Policy: Radiation therapy is not medically necessary.**

RR. Giant cell tumor of bone (osteoclastoma)
Once thought to be a benign disorder, these tumors are best regarded as malignant with a potential for metastasis. Surgery is the initial treatment of choice, but many osteoclastomas arise in bones (spine and pelvis) in which surgical resection would be unnecessarily debilitating. Local control with radiation is reported in the 75% to 85% range and can be administered safely using modern era equipment. **Policy: Radiation therapy is medically necessary.**

SS. Glomus Jugulare (see chemodectoma)

TT. Glomus tympanicum (see chemodectoma)

UU. Glomus Vagale (see chemodectoma)

VV. Gorham-Stout Syndrome (disappearing bone syndrome)
Also known as phantom bone, this entity is characterized by a destructive proliferation of endothelial-lined sinusoidal or capillary proliferation that may or may

not be progressive, causing bone destruction most commonly in the pelvis or shoulder girdle that results in a functional deformity. Surgery is an alternative to radiation. Typical treatment is with three dimensional conformal radiation therapy (3DCRT) in twenty-five or fewer fractions. **Policy: Radiation therapy is medically necessary.**

WW. Graves' Ophthalmopathy

This is an autoimmune disorder associated with hyperthyroidism that affects the eye musculature and retrobulbar tissues causing proptosis and visual impairment. It may be unilateral or bilateral. Carefully selected cases that do not respond to medical measures may be improved with the use of carefully administered conformal radiation. Typical treatment is with complex or three dimensional conformal radiation therapy (3DCRT) in ten fractions. **Policy: Radiation therapy is medically necessary.**

XX. Gynecomastia

In the older era of orchiectomy or the use of diethylstilbestrol for the treatment of metastatic or locally advanced prostate cancer, it was commonplace to irradiate the breasts on a prophylactic basis to prevent uncomfortable gynecomastia. In the modern era of chemical androgen deprivation for the treatment of prostate cancer, the use of modest doses of radiation to the breasts may arrest or prevent the resultant gynecomastia and is medically appropriate**.** Typically the radiation is given with electron beam therapy in five or fewer fractions. **Policy: Radiation therapy is medically necessary.**

YY. Hemangiomas

Though benign by histology, these vascular tumors that may arise in the brain, spinal cord, subglottis, glottis, liver, GI tract, urinary tract, joints and orbit may be disastrous. The use of radiation therapy is a suitable alternative to surgical or medical management. It is especially important to explore alternative therapy in pediatric cases. Depending on circumstances, the technique employed may range from simple to intensity modulated, and is usually delivered in thirty or fewer sessions. **Policy: Radiation therapy is medically necessary.**

ZZ. Herpes Zoster

Presented here only for historical perspective, the use of radiation to treat the nerve roots associated with cutaneous eruption of zoster was once employed, and even said to be sometimes acceptable in the 1977 survey of the U.S. Department of Health, Education and Welfare. More recent surveys and study have shown no benefit. The subsequent development and use of antiviral drugs is appropriate. **Policy: Radiation therapy is not medically necessary.**

AAA. Heterotopic Ossification (before or after surgery)

Radiation is known to prevent the heterotopic bone formation often seen in association with trauma or joint replacement in high risk patients. The radiation is

most effective if given shortly (within four hours) prior to surgery, or within three or four days after surgery. A radiation dose of 7 Gy to 8 Gy in a single fraction of complex planned therapy is typical. **Policy: Radiation therapy is medically necessary.**

BBB. Histiocytosis (see Langerhans cell histiocytosis)

CCC. Hypersalivation (of amyotrophic lateral sclerosis)
It is well known that radiation will decrease saliva production as a consequence of treating head and neck cancer. This phenomenon has occasionally been exploited in cases of excess saliva production in patients with ALS. While literature is scant, surveys indicate general acceptance of the use of radiation in this situation when other means of management are ineffective or impractical. **Policy: Radiation therapy is medically necessary.**

DDD. Hypersplenism (see splenomegaly) (see extramedullary hematopoiesis)

EEE. Hyperthyroidism
The use of systemic 131-I is an accepted alternative to surgery and/or medical management. **Policy: Radiation therapy is medically necessary.**

FFF. Immunosuppression
Total lymphatic irradiation as an immunosuppressive agent has been used to suppress the immune system for a variety of conditions. Its use to treat autoimmune or immune-mediated diseases (lupus, rheumatoid arthritis, multiple sclerosis) is considered investigational. Similarly, its use for immunosuppression in conjunction with organ transplants is also investigational. *Ex vivo* treatment of organs or blood products to eliminate lymphocytes is recognized and accepted as medically appropriate prior to transfusion. The use of total body radiation as part of a conditioning regimen prior to stem cell or marrow transplant is considered medically necessary. **Policy: Because of the wide variation of circumstances, requests for the use of radiation for the purpose of immunosuppression require medical review.**

GGG. Infections (bacterial)
In the antibiotic era, there is no recognized indication for the use of radiation therapy in the treatment of bacterial infections. **Policy: Radiation therapy is not medically necessary.**

HHH. Infections (fungal and parasitic)
The experimental use of radiation to treat a unusual and rare fungal and parasitic disorders, such as ocular histoplasmosis and cerebral cisticercosis has been reported in the literature. This is regarded as investigational. **Policy: Radiation therapy is not medically necessary.**

lll. Infections (viral)
Past treatment of viral conditions such as condyloma, herpes zoster, and warts is mentioned for historical perspective and completeness. Only in rare instances would radiation be appropriate as a means of last resort. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

JJJ. Inflammatory (Acute/chronic) disorders not responsive to antibiotics (furuncles, carbuncles, sweat gland abscesses).
Variations exist worldwide as to the appropriateness of using ionizing radiation for these disorders. The German review of 2002 lists them as potential indications, however elsewhere this opinion is not supported. The U.K. policy states that for a refractory case with no other alternative, low dose radiation therapy "might be worth considering". **Policy: Not indicated and not medically necessary.**

KKK. Inverted papilloma
The treatment of choice is surgical resection of these usually benign lesions of the nasal cavity and paranasal sinuses. However, a malignant component is found in a small percentage of cases, and radiation therapy is then indicated. In cases of incomplete resection or suspected malignant component, radiation therapy is considered medically necessary. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

LLL. Juvenile Xanthogranuloma (see corneal xanthogranuloma)

MMM. Keloid Scar
Data is abundant that a few fractions of a relatively small amount of radiation will reduce the chance of recurrence after a keloid is resected. This is medically necessary when other means are less appropriate or have proven ineffective. Typical radiation treatment utilizes superficial x-ray, electron beam, or complex photon beam therapy in four or fewer fractions. **Policy: Radiation therapy is medically necessary.**

NNN. Keratitis (bullous and filamentary)
Bullous and filamentary keratitis were listed in the 1977 U.S. Department of Health, Education and Welfare as entities for which radiation therapy was sometimes appropriate. They are not included in the more recent German and U. K. reviews. Current literature does not support the use of radiation for either form of keratitis. **Policy: Radiation therapy is not medically necessary.**

OOO. Langerhans cell histiocytosis
The literature has consistently supported the use of radiation therapy for treatment of this disorder over the time period studied. Involvement can be focal or systemic, and behavior variable. The etiology is unknown, and it may prove to be a non-benign entity. Chemotherapy is commonly utilized when treatment is necessary, with radiation more commonly used to treat localized growths. Typical treatment is

with three dimensional conformal radiation therapy (3DCRT) in twenty-eight or fewer fractions. **Policy: Radiation therapy is medically necessary.**

PPP. Lymphangiomas
There are four types: capillary; cavernous; cystic hygromas; and lymphangeal hemangiomas. Surgery is the treatment of choice. In rare instances, radiation therapy may be appropriate for refractory lesions with repeated recurrence after resection. These may cause a chylous effusion if there is pleural involvement, in which case radiation therapy may be useful in managing chylothorax. A specific presentation of lymphangioma may be Gorham-Stout syndrome (see above). **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

QQQ. Lethal Midline Granuloma
This is a progressive, destructive process which involves the mid-facial structures. It has many synonyms depending on its anatomic presentation. It has been considered a benign entity, may mimic other lymphoproliferative processes, requires caution in diagnosis, and may be a malignant T-cell disorder. Alternative therapy may be more appropriate, but radiation therapy is considered appropriate for management of localized presentations or in conjunction with systemic therapy. **Policy: Radiation therapy is medically necessary.**

RRR. Lymphoma "Benign"
Benign lymphoma was listed in the 1977 U.S. Department of Health, Education and Welfare as an entity for which radiation therapy was sometimes appropriate. This generic term is not included in subsequent reviews. Collections of benign lymphocytes in specific sites (e.g. pseudotumor of the orbit) may be appropriately treated with radiation in some circumstances. **Policy: Radiation therapy requests require medical review.**

SSS. Macular degeneration
There was great optimism that age related wet macular degeneration could be controlled by the use of radiation therapy to arrest the progression of choroidal neovascularization. Radiation was a preferred method of treatment in the USA in the 1990s and early 2000s. Subsequent multi-centered randomized trials have not proven benefit. The use of intraocular injections of anti-VEGF drugs has emerged as the first line of management. Newer approaches to the use of radiation therapy, such as epimacular brachytherapy and stereotactic radiosurgery are being investigated as alternatives or as complementary methods so as to reduce the frequency of intraocular injections. Until the results of these studies are known, the appropriateness of using radiation is unproven. **Policy: Radiation therapy is not medically necessary.**

TTT. Meningioma
The mainstay of management of meningiomas remains surgery. However, when surgery is technically not possible or is medically contraindicated, radiation therapy

is regarded as an appropriate treatment for primary or recurrent lesions. Other indications include postoperative treatment of high grade lesions and for incompletely resected ones. Typical treatment is with three dimensional conformal radiation therapy (3DCRT), stereotactic radiosurgery (SRS), or intensity modulated radiation therapy (IMRT). **Policy: Radiation therapy is medically necessary.**

UUU. Mikulicz Syndrome (salivary lymphoepithelial lesion)
Once other etiologies are ruled out, such as malignant lymphoma and infection, the use of low doses of radiation to treat this lymphoepithelial growth in salivary tissue has been reported as effective in older literature. Competing approaches include steroids, surgery, and chlorambucil. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

VVV. Morbus Ledderhose (see also Dupuytren's contracture)
This may develop in the hand (Morbus Dupuytren) or foot (morbus Ledderhose) and is a connective tissue disorder of the palmar or plantar fascia. Radiation therapy is useful, especially in the earlier stages of development, and has been demonstrated in prospective clinical trials. **Policy: Radiation therapy is considered medically necessary.**

WWW. Myasthenia gravis (see thymoma)

XXX. Neurofibroma (benign, von Recklinghausen)
Benign neurofibromas most commonly develop in association with von Recklinhausen disease, and may occur in central nervous system (CNS) and non-CNS locations. Symptomatic lesions may benefit from treatment with relatively high doses of radiation if not amenable to resection. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

YYY. Ocular trichiasis (epilation)
Of historical interest, on occasion, to cause epilation of eyelashes, radiation has been used in dermatology or ophthalmology practices to aid in the clearance of trachoma or ocular pemphigoid. Radiation is not medically necessary for this in the modern era. **Policy: Radiation therapy is not medically necessary.**

ZZZ. Optic pathway glioma
Gliomas can occur anywhere along the optic pathway from optic nerve to optic chiasm to more posteriorly-situated lesions adjacent to or involving the hypothalamus. As most occur in the pediatric age group, prudence must be exercised in the use of radiation, which is usually reserved for older children. **Policy: Radiation therapy is medically necessary.**

AAAA. Orbital Myositis
This entity is an idiopathic inflammatory condition of the extraocular muscles and may be of autoimmune etiology. It can mimic other similar-appearing orbital inflammatory disorders. Management without radiation, usually with steroids, is first line. Failing conservative measures, radiation is given typically using 3DCRT or complex planning in fifteen or fewer fractions. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

BBBB. Orbital Pseudotumor (lymphoid hyperplasia)
The indications for the use of radiation therapy are for those lesions which recur after surgery, or become refractory to steroids, and not amenable to other management. Typical treatment is with complex or three dimensional conformal radiation therapy (3DCRT) in ten fractions. **Policy: Cases will require medical review and documentation that no other reasonable alternative exists.**

CCCC. Osteoarthritis
Osteoarthritis falls into the category of painful acute and chronic degenerative diseases for which radiation therapy is more commonly used in Europe, and is supported in the German Consensus Guidelines for the treatment of benign disease. Its use is also supported in American texts, as several single institution studies have reported long-term pain relief and functional gain in a majority of patients. Because osteoarthritis occurs later in life and the dose required is low, radiation is considered safe. A second course of treatment is often needed after three months. The typical course of radiation uses complex planning and is delivered in five or fewer sessions. **Policy: Radiation therapy is medically necessary.**

DDDD. Osteoid osteoma (osteoblastoma, giant osteoid osteoma)
Osteoid osteoma, osteoblastoma, giant osteoid osteoma are synonyms. Old literature reports included anecdotes of the use of radiation to treat this entity, for which surgery is the treatment of choice. **Policy: Radiation therapy is not medically necessary.**

EEEE. Otitis media
Bilateral otitis media caused by swollen lymphoid tissue in the nasopharynx was in the past sometimes treated by placement of radioactive material in the nasopharynx to reopen the eustachian tubes. The carcinogenic effect of this makes this treatment inappropriate. **Policy: Radiation therapy is not medically necessary.**

FFFF. Pancreatitis
Radiation therapy has been used in the past for its anti-inflammatory effect in the treatment of pancreatitis. There is no role for its use for this purpose in the modern era. **Policy: Radiation therapy is not medically necessary.**

GGGG. Paraganglioma (chromaffin positive)
As with their chromaffin negative counterparts, radiation therapy is indicated in those cases which are inaccessible by surgery, for salvage if recurrent, or as adjuvant therapy if incompletely removed. Typical treatment is with three dimensional conformal radiation therapy (3DCRT), stereotactic radiosurgery (SRS), or intensity modulated radiation therapy (IMRT). **Policy: Radiation therapy is medically necessary.**

HHHH. Parkinson's disease
SRS is an acceptable treatment of last resort after medical management has failed. Documentation of such is required. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

IIII. Parotid adenoma
Pleomorphic adenomas of the parotid gland more commonly occur in younger persons and the use of radiation must be approached judiciously. There are indications for radiation therapy such as size > 4 cm. positive margin status, and multinodularity. **Policy: Radiation therapy is medically necessary.**

JJJJ. Parotitis
Although historically appropriate in the pre-antibiotic era because of a high mortality rate for post-operative suppurative parotitis, radiation is not indicated in the present era. **Policy: Radiation therapy is not medically necessary.**

KKKK. Peptic ulcer disease
Subsequent to the availability of H2 blockers, radiation therapy is not indicated in the management of peptic ulcer disease despite prior evidence of its efficacy. The increased risk of carcinogenesis of the pancreas, colon, and stomach is a strong contraindication. **Policy: Radiation therapy is not medically necessary.**

LLLL. Perifolliculitis (scalp)
The use of radiation to cause hair loss and allow the infection of this disease to then clear has been described in older literature. The availability of topical agents and of laser treatment has rendered obsolete the use of radiation for this purpose. **Policy: Radiation therapy is not medically necessary.**

MMMM. Persistent lymphatic fistula
Lymphatic leaking, most commonly after arterial reconstruction surgery in the groin, is usually treated with additional surgery (ligation, flap construction), direct pressure, application of hemostatic healing agents, and the use of negative pressure. It is listed in the German literature as an indication for the use of radiation therapy, without reference. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

NNNN. Peyronie's Disease (Morbus Peronie, Induratio penis plastica)
There is sufficient (older and current) literature support to justify the use of low doses of radiation in the treatment of this disease of the penis. Simple, complex-planned photon beam radiation, orthovoltage, or electron beam radiation in five or fewer fractions is typical. **Policy: Radiation therapy is medically necessary.**

OOOO. Pigmented Villonodular Synovitis (tenosynovial giant cell tumor)
Surgical resection and synovectomy or joint replacement is the treatment of choice. However if recurrent after resection, or diffuse or bulky disease causing bone destruction is present, the use of radiation is justified. Radiation treatment with photon beam therapy using complex treatment planning or three dimensional conformal radiation therapy (3DCRT) planning in twenty-eight or fewer sessions is typical. **Policy: Radiation therapy is medically necessary.**

PPPP. Pinealoma (Pineal parenchymal tumors)
Pinealoma refers to tumors that arise in the pineal gland. For the tumors at the benign end of the spectrum of such tumors, surgical resection is preferred. Postoperative radiation is appropriate for those that cannot be removed completely. For higher grades of tumor, refer to the separate Guideline, Radiation Treatment of Primary Cranial and Spinal Tumors and Neurologic Conditions. **Policy: Radiation therapy is medically necessary.**

QQQQ. Pituitary Adenoma
Surgical removal is the treatment of choice, with radiation therapy indicated for medically inoperable cases, recurrence after surgery, incomplete resection, or persistence of elevated hormones after resection of functional adenomas. Typical treatment is with three dimensional conformal radiation therapy (3DCRT), stereotactic radiosurgery (SRS), or intensity modulated radiation therapy (IMRT). **Policy: Radiation therapy is medically necessary.**

RRRR. Plantar fasciitis
Recent publications, mainly originating in Europe, support the use of radiation therapy to treat plantar fasciitis if conservative measures fail. The typical dose of 1 Gy per week for six weeks was associated with a response rate approaching 80% and durable at 48 weeks. Using complex radiation planning, up to eight sessions is considered appropriate. Occasionally an individual requires repeat treatment. **Policy: Radiation therapy is medically necessary.**

SSSS. Plasma cell granuloma (benign)
Treatment of a true benign plasma cell granuloma is surgical resection. **Policy: Radiation therapy is not medically necessary.**

TTTT. Polymorphic reticulosis (see lethal midline granuloma)

UUUU. Precancerous melanosis
Precancerous melanosis may also be called Lentigo Maligna, Hutchinson's melanotic freckle, or circumscribed precancerous melanosis of Dubreuilh, and has lentigo maligna melanoma as an invasive counterpart. About one third of these will transform into the malignant version if left untreated. Radiation therapy is indicated for those which recur or for more extensive lesions. **Policy: Radiation therapy is medically necessary**

VVVV. Pregnancy
Radiation therapy has been used in the past for both an attempt at improving fertility (see anovulation) and for the termination of intrauterine or tubal pregnancy (see abortion). Presently, neither indication is medically appropriate. **Policy: Radiation therapy is not medically necessary.**

WWWW. Pseudotumors (orbit) (see orbital pseudotumor)

XXXX. Psoriasis
Both the German and the U.K. reviews include psoriasis as an indication for the use of low dose radiation in the treatment of some cases. Generally radiation is a treatment of last resort and is reserved for inaccessible locations such as the nail beds. Typical radiation treatment utilizes superficial x-ray, electron beam, or complex photon beam therapy in four or fewer fractions. **Policy: Radiation therapy is medically necessary.**

YYYY. Psychiatric Disorders
Radiation therapy has been used to treat some psychiatric disorders in mimicry of surgical procedures with the same intent, such as SRS to achieve a ventral capsulotomy in the treatment of obsessive compulsive disorder. The use of radiation for this purpose is considered investigational and unproven. **Policy: Radiation therapy is not medically necessary.**

ZZZZ. Pterygium
The use of radiation to treat a pterygium is supported in the clinical references reviewed. It is usually performed with contact beta brachytherapy in three sessions. **Policy: Radiation therapy is medically necessary**

AAAAA. Pyogenic granuloma
Despite one case report in the literature of successful treatment of a pyogenic granuloma of the middle ear with radiation, treatment of a pyogenic granuloma is surgical. There is no current support in the American or European literature. **Policy: Radiation therapy is not medically necessary.**

BBBBB. Rheumatoid arthritis
Attempts at treating rheumatoid arthritis with radiation have included single joint external beam radiation, intra-articular infusions of radioactive isotopes, and total

lymphoid irradiation for immunosuppression. None is standard of care. **Policy: Radiation therapy is not medically necessary.**

CCCCC. Rosai-Dorfman Disease
Rosai-Dorfman Disease is a rare disorder characterized by a benign histiocyte proliferation. It can produce massive adenopathy. Treatments used have included surgery, chemotherapy, and steroids. In lesions involving the airway not responding to more conservative measures, radiation therapy has been used with success. When utilized, radiation planning using complex or three-dimensional technique and delivered in up to twenty-two sessions is typical. **Policy: cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

DDDDD. Rotator Cuff Syndrome (see tendonitis)

EEEEE. Sarcoidosis
If primary medical management fails to control those lesions in need of treatment, the use of radiation therapy is appropriate. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

FFFFF. Sclerosing disorders (see Fibrosclerosis)

GGGGG. Sinusitis
Sinusitis caused by infection does not have literature support for treatment by radiation therapy. **Policy: Radiation therapy is not medically necessary.**

HHHHH. Splenomegaly
Splenomegaly treated by radiation therapy is most commonly caused by leukemic or myeloproliferative diseases, and to a lesser extent by metastases from solid tumors. The policy for the use of radiation therapy in these malignant conditions is not covered in this Guideline for the treatment of non-malignant disorders. However, the use of radiation therapy for the treatment of hypersplenism or splenomegaly caused by a "benign" or pre-malignant myelodysplastic syndrome also has a basis in the literature. Very low doses of radiation on a less than daily schedule are usually advised. Typically radiation is delivered in ten or fewer sessions, planned using complex or three-dimensional technique. **Policy: Radiation therapy is medically necessary**

IIIII. Stent placement
Brachytherapy is an accepted procedure when used as an adjunct to percutaneous coronary intervention (PCI) for treatment of in-stent restenosis in a native coronary artery bare-metal stent or saphenous vein graft. While once common, this procedure has been less frequently performed with the availability of drug eluting stents. **Policy: Radiation therapy is medically necessary**

JJJJJ. Sterilization (see castration)

KKKKK. Stewards Disease (see lethal midline granuloma)

LLLLL. Synovitis
The use of intra-articular radioisotopes has been described in older literature to treat hemophilia, recurrent hemarthrosis, synovitis, and Baker's cyst. Support for this has not continued into newer references other than Pigmented Villonodular Synovitis**. Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

MMMMM. Tendonitis
There is ample world literature that describes the successful use of radiation to treat insertion tendonitis, a practice that is more common in Europe than the Americas. It is described in modern radiation oncology texts. The mainstay of treatment is conservative using a pharmacologic or physical therapy approach. Typical treatment is with photon beam therapy using, at most, complex treatment planning, and delivered in up to five sessions. **Policy: Radiation therapy is medically necessary for those cases not responding to conservative measures and case will require medical review.**

NNNNN. Tennis elbow (see tendonitis)

OOOOO. Thymoma
Surgery is the mainstay of treatment for tumors of the thymus. There are several types of thymoma ranging from the benign medullary thymoma to true invasive thymic carcinomas. There is general agreement that thymomas respond to radiation therapy, but controversy exists on the value of using radiation in low and intermediate stages and grades, especially if encapsulated and fully resected. This policy only pertains to those thymomas considered to be benign. Radiation therapy is appropriate if unresectable or incompletely resected, particularly if causing a paraneoplastic syndrome. Depending on circumstances, the technique employed may range from simple to intensity modulated, and is usually delivered in thirty or fewer sessions. **Policy: Cases will require medical review.**

PPPPP. Thyroiditis
Presently there is no indication for the use of radiation therapy for the treatment of thyroiditis**. Policy: Radiation therapy is not medically necessary.**

QQQQQ. Tinea [see Infections (fungal and parasitic)]

RRRRR. Tolosa-hunt syndrome (episodic orbital pain)
This is caused by nonspecific inflammation of the cavernous sinus or superior orbital fissure. Steroids commonly are used first. For refractory cases, drugs such as methotrexate may be used. The successful use of low dose radiation has been

reported and may be used as a last resort. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

SSSSS.Tonsillitis
In the modern era of antibiotics, the use of radiation to treat inflamed or infected tonsils is obsolete. **Policy: Radiation therapy is not medically necessary.**

TTTTT. Total body irradiation
For the preparation of patients for bone marrow or stem cell transplant for malignant disorders, see the Guideline for the primary disease. For non-malignant, pre-malignant and quasi-benign marrow disorders such as aplastic anemia or myelodysplastic disorders, total body irradiation prior to transplant may be appropriate if chemotherapeutic preparation is not possible. The use of total body irradiation for immunosuppression as treatment of totally non-malignant disorders, such as auto-immune diseases is not medically appropriate. **Policy: Cases will require medical review.**

UUUUU. Total lymphoid irradiation
Total lymphoid irradiation has been used for the purpose of immunosuppression in the treatment of immune-mediated disorders (e.g. autoimmune disorders) and for the purpose of prevention of rejection of transplanted organs, where it has been found useful in the short term, but with decreased subsequent efficacy and the development of myelodysplasia. Further research is needed to establish its role, but it remains an option in situations of chronic rejection in which conventional anti-rejection treatment is no longer viable. **Policy: Requests require medical review and confirmation that alternatives have been exhausted.**

VVVV. Trigeminal neuralgia (tic douloureux)
Radiation therapy is considered appropriate for cases not responding to conservative management if a surgical approach is not possible for technical or medical reasons. Typical treatment is with stereotactic radiosurgery (SRS). **Policy: Cases will require medical review.**

WWWW. Tuberculosis lymphadenitis
Prior to the availability of antibiotics for tuberculosis, lymphadenitis caused by this disease responded to therapeutic radiation. Available antibiotics obviates this disorder as an indication for radiation. **Policy: Radiation therapy is not medically necessary.**

XXXXX.Vernal catarrh
This disorder is characterized by inflammation of the conjunctiva associated with infiltration by eosinophils, lymphocytes, plasma cells and histiocytes. The resultant hyperplasia of the conjunctival epithelium may respond to ionizing radiation, but alternative therapy is readily available and the use of radiation is no longer

supported in any literature. **Policy: Radiation therapy is not medically necessary.**

YYYYY.Vertebral Hemangioma (see hemangioma)

ZZZZZ. Warts
Older literature describes an 80% response rate in treating warts with a relatively low dose of radiation and it is described in at least one modern text (Gunderson). With the availability of alternative therapy, the use of radiation should be reserved for those cases requiring treatment for which alternative, simpler therapy has been unsuccessful. **Policy: Cases will require medical review and documentation that non-radiation alternatives have been exhausted.**

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Radiation Therapy for Oligometastases

POLICY

I. Stereotactic Body Radiotherapy (SBRT) for extra-cranial oligometastases is medically necessary in the following clinical situations:

A. For an individual with non-small cell lung cancer who:
   1. Has had or who will undergo curative treatment of the primary tumor (based on T and N stage) and
   2. Has 1 to 3 metastases in the synchronous setting

B. For an individual with colorectal cancer who:
   1. Has had or who will undergo curative treatment of the primary tumor and
   2. Presents with 1 to 3 metastases in the lung or liver in the synchronous setting and
   3. For whom surgical resection is not possible

C. For an individual with:
   1. A clinical presentation of one 1 to 3 adrenal gland, lung, liver or bone metastases in the metachronous setting when all the following criteria are met:
      a. Histology is non-small cell lung, colon, breast, sarcoma, renal cell, or melanoma
      b. Disease free interval of > 1 year from the initial diagnosis
      c. Primary tumor received curative therapy and is controlled
      d. No prior evidence of metastatic disease (cranial or extracranial)

All cases will require review by an eviCore radiation oncologist of the consultation note and the most recent positron emission tomography (PET) scan (demonstrating no evidence of widespread metastatic disease).

Key Clinical Points

I. Definitions

A. Oligometastatic
   1. A malignancy that has progressed to 1 to 3 hematogenous metastatic sites

B. Synchronous Oligometastasis
   1. Oligometastatic disease found at the time of the diagnosis of the primary tumor

C. Metachronous Oligometastasis
   1. Oligometastatic disease found after treatment of the primary tumor

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D. Oligoprogression
   1. Progression of a limited number of metastatic sites while other metastatic disease sites remain controlled. SBRT is not routinely medically necessary in an individual witholigoprogressive disease.

II. Discussion

Oligometastases is described as an intermediate state in the spread of cancer between early-stage localized disease and widespread metastases. Specifically, it is a malignancy that has progressed to a limited number of hematogenous metastatic sites, defined in most studies as 1 to 3 sites. Chemotherapy remains the standard of care for patients with metastatic cancer, however this is rarely curative. The concept of oligometastasis has important implications for cancer treatment because it is believed that patients with limited numbers of metastasis previously thought by some clinicians to be incurable may be cured with local treatments such as radiotherapy.

The data supporting the treatment of extracranial oligometastases is limited to single institution or registry studies demonstrating improved survival outcomes compared to historical controls. There is no level one phase III evidence demonstrating a clear benefit. The data with the longest follow-up is the surgical literature examining the resection of non-small cell lung and hepatic metastases. The International Registry of Lung Metastases examined 5,206 patients between 1945 and 1995 at 18 institutions and found 36% survival at 5 years (Pastorino et al., 1997). Patients with the best prognosis were those with a single resectable metastases with a disease free interval > 3 years. In metastatic colorectal cancer to the liver, hepatic resection has resulted in a 5-year survival of 28% in a well-selected population (Nordlinger et al., 1996). Similar outcomes have been demonstrated in adrenal metastectomy for non-small cell lung cancer and pulmonary metastatectomy for osteosarcoma in children (Kager et al., 2003; Tanvetyanon, et al., 2008).

Recently, SBRT or Stereotactic Ablative Radiotherapy (SABR) has been investigated as an alternative to surgical resection in the treatment of oligometastatic disease. SBRT offers greater precision to a limited target volume than previous radiation delivery technologies. There have been several phase I/II studies which have demonstrated the technical feasibility of delivering SBRT for patients with non-small cell lung, liver and spine metastases (Lee et al., 2009; Milano et al., 2012; Rusthoven, et al., 2009; Salama et al., 2012; Wang et al., 2012). Furthermore, there have been several reports documenting the efficacy of SBRT or hypofractionated radiation in various different histologies including non-small cell lung, breast, colon, renal, melanoma, and sarcoma (Hasselle, et al., 2012; Hoyer, et al., 2006; Milano, et al., 2009; Ranck et al., 2013). These studies have used anywhere from 3 to 10 fractions across a range of total doses. All have demonstrated local control of the treated lesions from 70 to 90%.

The major limitation of these studies is that they are single arm, non-controlled, with small patient numbers and often limited to single institutions. Furthermore, they are subject to “immortal” time bias that artificially inflates the survival of patients who underwent metastatectomy compared to those who did not. Therefore, none of these reports offers definitive clinical evidence that overall outcomes are improved with metastases directed SBRT compared to best standard therapies. Selection of an appropriate individual is imperative when deciding who is eligible to receive SBRT in the oligometastatic setting. One study revealed a 40% progression rate within 3 months of SBRT for 1 to 5 metastases and 80% progression at 2 years, which emphasizes the fact that the vast majority of patients have micro-metastatic disease at time of treatment (Milano, et al., 2012). Furthermore, disease free survival (DFS) after SBRT is associated with time to recurrence. One analysis found 3-year survival after SBRT was 53% for patients with a disease free interval of more than 12 months vs. 19% for patients with a disease free interval of less than 12 months (Inoue, et al., 2010). Another analysis found a disease free interval of more than 12 months was also associated with improved outcomes following treatment with SBRT for oligometastatic disease (Zhang, et al., 2011).

A. Non-small cell lung

There is a population of individuals with non-small cell lung cancer presenting with oligometastatic disease that will benefit from metastases-directed ablative procedures. A recent retrospective analysis of patients with oligometastatic non-small cell lung cancer who underwent metastasis directed treatment (intra and extra cranial) found a 2-year survival of 38% (Griffioen, et al., 2013). A recent review of the literature found that while the majority of patient’s progress within 12 months, there is a subset of long-term survivors (Ashworth et al., 2013).

SBRT is considered medically necessary in an individual with non-small cell lung cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease, and good performance status, assuming SBRT can be delivered safely to the involved sites.

Recent evidence has suggested that patient with actionable mutations in non-small cell lung cancer may derive a greater benefit from receiving SBRT or hypofractionated radiotherapy for oligoprogressive disease (Gan, et al., 2014; Iyengar, et al., 2014). Due to the limited number of patients included in these analyses, it is difficult to make definitive conclusions regarding the benefit of SBRT for oligoprogressive disease for patients with actionable mutations. Therefore, SBRT is not considered medically necessary for an individual with oligoprogressive non-small cell lung disease.

B. Colon
Surgical series have shown that selected patients with colorectal cancer undergoing resection of hepatic and/or pulmonary metastases results in a cure for a proportion of patients with a 5-year survival of 38% (Kanas et al., 2012). The European Organisation for Research and Treatment of Cancer (EORTC) conducted the only randomized phase II study in the oligometastatic setting where patients with liver metastases from colon cancer were randomized to radiofrequency ablation plus chemotherapy or chemotherapy alone (Ruers et al., 2012). The 30 month survival was 61% in the radiofrequency ablation arm and 56% in the control arm ($p = 0.22$), demonstrating the excellent survival of patients with oligometastatic disease who do not receive local therapy.

SBRT is considered medically necessary in an individual with colorectal cancer who presents in the synchronous or metachronous setting, has 1 to 3 sites of disease limited to the lung or liver, and good performance status, assuming surgical resection is not feasible.

C. Breast
An analysis of breast cancer patients who underwent treatment with SBRT for oligometastatic disease compared outcomes to other histologies. Patients who underwent SBRT for oligometastatic breast cancer had a progression free survival (PFS) at 2 years of 36% vs. 13% for non-breast histology, and overall survival (OS) at 6 years was 47% vs. 9% for non-breast histology.

SBRT is considered medically necessary in an individual with breast cancer who presents in the metachronous setting; has 1 to 3 sites of disease limited to the lung, liver, or bone, has a disease free interval of > 1 year; and received curative therapy to the primary tumor.

D. Sarcoma, renal, melanoma
A retrospective analysis examining pulmonary metastases from sarcoma found those who received local ablative treatment to have improved and improved median survival of 45 months vs. 12 months for those who had no local therapy to the metastases (Falk, et al., 2015). Previous retrospective literature has demonstrated a survival benefit for patients with metastatic sarcoma who underwent a pulmonary metastasectomy (van Geel, et al., 1996). Pulmonary resection for renal cell cancer is associated with a 5-year survival of 20% (Murthy, et al., 2006). In the setting of melanoma there have also been retrospective studies demonstrating a benefit to lung resection of metastases. An analysis of melanoma in the international registry of lung metastasis found a 5-year survival of 22% after complete metastasectomy.

Based on this data, SBRT is considered medically necessary in an individual with sarcoma, renal, or melanoma metastases who meets the following

criteria: disease free interval of > 1 year from the initial diagnosis, primary tumor received curative therapy and is controlled, and no prior evidence of metastatic disease.

E. Treatment of > 3 sites or nonhematogenous sites
The toxicity of using SBRT for treating multiple metastases (> 3 metastases) can be potentially significant. In light of this, the Radiation Therapy Oncology Group (RTOG) is currently conducting a phase I study examining the safety of SBRT for the treatment of multiple metastases. Furthermore, there is an ongoing international randomized phase II study examining SBRT for up to 5 metastases vs. standard of care without SBRT. Based on these ongoing studies, SBRT to > 3 sites is considered experimental/investigational. Furthermore, the current medical literature has primarily only examined the use of SBRT in patients with hematogenous spread (lung, liver, bone). Therefore, the use of SBRT to non-hematogenous sites of spread such as lymphatic regions is considered experimental/investigational.

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Radiation Therapy for Other Cancers

POLICY

Though the majority of requests for radiation therapy are addressed by individual eviCore clinical guidelines, it is recognized that there may be requests that are not. For such requests, adjudication will be conducted on a case-by-case basis utilizing, as appropriate and applicable:

I. Evidence-based guidelines including, but not limited to:

A. National Comprehensive Cancer Network (NCCN) Guidelines™
B. American Society for Radiation Oncology (ASTRO) (i.e. Evidence-Based Guidelines; Evidence-Based Consensus Statement)
C. American College of Radiology (ACR) (i.e. ACR Appropriateness Criteria®)
D. American Society of Clinical Oncology (ASCO)
E. Radiation Oncology Coding Resource

II. Peer-reviewed literature

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2. American Society for Radiation Oncology (ASTRO) Clinical Practice Guidelines. Accessed July 20, 2017. https://www.astro.org/Clinical-Practice-Statements.aspx
3. American College of Radiology (ACR) ACR Appropriateness Criteria®. Accessed July 20, 2017. https://www.acr.org/quality-safety/appropriateness-criteria
4. American Society of Clinical Oncology (ASCO) Guidelines, Tools & Resources. Accessed July 20, 2017. https://www.asco.org/practice-guidelines/quality-guidelines/guidelines

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Radiation Therapy for Pancreatic Cancer

POLICY

I. Indications for radiation therapy

A. Preoperatively (neoadjuvant) resectable
B. Preoperatively (neoadjuvant) borderline resectable
C. Locally advanced/unresectable
D. Postoperatively (adjuvant) resectable
E. Palliation

II. Radiation treatment techniques

A. Three-Dimensional Conformal Radiation Therapy (3DCRT) is medically necessary for most presentations of pancreatic cancer
B. Intensity-Modulated Radiation Therapy (IMRT) may be considered medically necessary on a case-by-case basis when acceptable doses to critical organs, such as the kidney, spinal cord, small bowel, stomach, or liver cannot be achieved with 3D planning. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the “Acceptable” normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN)
C. Motion management techniques should be employed when respiration significantly impacts on stability of the target volume
D. Stereotactic Body Radiation Therapy (SBRT) using up to 5 radiation treatment fractions will be considered on a case-by-case basis for:
    1. Preoperative (neoadjuvant resectable or borderline resectable) cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression
    2. Definitive treatment for medically inoperable or locally advanced cases following a minimum of 2 cycles of chemotherapy and restaging in which there is no evidence of tumor progression and the disease volume can be entirely encompassed in the radiation treatment volume
    3. Postoperative (adjuvant) cases in which there is residual gross disease or positive microscopic margins that can be entirely encompassed in the radiation treatment volume
E. For palliative situations, up to 15 fractions in 1 phase of Complex or 3D external beam photon radiation therapy is considered medically necessary. IMRT and SBRT are not considered medically necessary

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Key Clinical Points

Pancreatic cancer is the fourth leading cause of cancer mortality in the United States. Surgical resection is integral to the curative management of pancreatic cancer. Unfortunately only twenty percent of individuals present with resectable disease. Resectability is typically defined by a lack of encasement of the superior mesenteric vein and portal veins and clear fat planes around the celiac artery, superior mesenteric artery and hepatic artery. Borderline resectability generally includes involvement of superior mesenteric vein or portal vein, but lack of encasement of the adjacent arteries. Patel et al. (2011) have reported on the use of neoadjuvant chemotherapy and IMRT to improve the likelihood of successful complete resection. In their study, 8 of 17 borderline resectable patients achieved negative margin resection after neoadjuvant therapy.

The underpowered but landmark Gastrointestinal Tumor Study Group (GITSG) study established the role of postoperative chemoradiation by demonstrating a survival benefit with this treatment strategy. The GITSG study included 43 patients, randomized to surgery alone or surgery followed by chemoradiation. This trial used a 40 Gy split course regimen that is rarely used today. Though underpowered, there was a 5-year improvement in overall survival (OS). Studies from the Mayo Clinic and Johns Hopkins have supported the use of chemoradiation following resection. The Mayo Clinic study retrospectively reviewed 472 patients. The Johns Hopkins study included 616 patients. Both studies demonstrated improved 5-year overall survivals in the cohorts receiving chemoradiation. A Johns Hopkins-Mayo Clinic Collaborative Study analyzed patients receiving adjuvant chemoradiation compared with surgery alone. In a retrospective review of 1,045 patients with resected pancreatic cancer, 530 patients received chemoradiation. Median and overall survivals were significantly improved in the chemoradiation group. In contrast, the heavily criticized European Organization for Research and Treatment of Cancer (EORTC) and European Study Group for Pancreatic Cancer (ESPAC) studies have not supported the use of adjuvant chemoradiation. These studies were heavily criticized for trial design, inclusion of more favorable histologies, lack of quality assurance, and use of split course radiation.

Following surgical resection, chemotherapy alone or chemoradiation may be the appropriate course of action. In an individual with borderline resectable pancreatic cancer, radiation is often utilized in the neoadjuvant setting in conjunction with chemotherapy. In an individual with unresectable pancreatic cancer, external beam photon radiation therapy is generally used as definitive treatment usually in conjunction with chemotherapy. A GITSG study of 194 patients with unresectable pancreatic cancer, randomized patients to 60 Gy of radiation alone, split course 40 Gy with concurrent fluorouracil (5-FU), and split course 60 Gy with concurrent 5-FU. Survival was improved in the chemoradiation arms with 1-year survival rates of 38% and 36%.

3D techniques are critical to respect the radiation tolerance of the surrounding critical structures, notably the kidneys, liver, small bowel and spinal cord. Dose prescription is typically 50.4 to 60 Gy and generally involves a conedown following 45 Gy. Dose escalation studies are under investigation. IMRT has increasingly been employed to decrease radiation dose to surrounding critical structures, in particular, the kidneys,

liver, small bowel and spinal cord, and dosimetric studies have confirmed significantly lower doses to these structures with IMRT compared to 3D techniques. IMRT is associated with a statistically significant decrease in acute upper and lower GI toxicity among individuals treated with chemoradiotherapy for pancreatic/ampullary cancers. Based on these studies, IMRT is considered medically necessary in the treatment of pancreatic cancer in the definitive and adjuvant settings, when dose constraints to organs at risk cannot be met with 3DCRT techniques. When using IMRT in the upper abdominal region, the uncertainty inherent due to organ motion underscores the utility of image guidance. Respiratory gating techniques are often used with both 3DCRT and IMRT.

The benefits of dose escalation with both 3DCRT and IMRT techniques are under investigation and thus far inconclusive. The aforementioned landmark GITSG study did not demonstrate a meaningful improvement in survival for the cohort receiving 60 Gy split-course with concurrent 5-FU compared with 40 Gy split-course with concurrent 5-FU. A phase III trial of locally advanced unresectable pancreatic cancer, compared intensive induction chemoradiotherapy consisting of 60 Gy, 5-FU and cisplatin followed by maintenance gemcitabine, to gemcitabine alone. Survival was improved in the gemcitabine alone arm. One year OS was 32% in the chemoradiotherapy cohort vs. 53% in the gemcitabine alone arm. There was greater grade 3 and 4 toxicity in the chemoradiotherapy arm. A phase II study from the Netherlands analyzed the feasibility of dose escalation in locally advanced unresectable pancreatic cancer, treated with radiation alone. Forty-one patients were treated with 3DCRT in doses of 70 to 72 Gy. The median survival was 11 months with acceptable toxicity. RTOG 8801 was a phase I/II trial of localized unresectable pancreatic cancer. Treatment consisted of 61.2 Gy with continuous infusion (CI) 5-FU, prophylactic hepatic irradiation, followed by 6 months of 5-FU. Seventy-nine patients were evaluable with a minimum follow up of 8.2 months. Thirty-one patients had severe grade 3 toxicity. Persistent or progressive pancreatic cancer was noted in 73%. Median survival was 8.4 months.

There is no clear consensus regarding the appropriate maximum dose when utilizing IMRT. Fuss et al. (2007) retrospectively reviewed 41 patients undergoing ultrasound-based image guided IMRT for pancreatic cancer. The mean total dose was 55 Gy (range 45 to 64 Gy). Grade 3 toxicity was 7.3%. Actuarial one- and two-year survival were 38% and 25%, respectively, comparable to published survival data. Brown et al. (2006) reviewed dose escalation in unresectable pancreatic cancer comparing 3DCRT, sequential IMRT boost and integrated IMRT boosts techniques. In 15 patients, treatment plans were generated and dosimetric analysis performed at doses of 54 Gy, 59.4 Gy and 64.8 Gy. Doses to the kidney, small bowel, liver and spinal cord were analyzed as well as target coverage. The authors concluded that the integrated boost IMRT technique allowed dose escalation to 64.8 Gy with acceptable normal tissue doses. Cost, as well as increased effectiveness of IMRT, has been questioned. Continued investigation of radiation dose escalation in the setting of clinical trials is warranted.

While data on the use of SBRT in cancer of the pancreas continues to emerge, there is a growing consensus on its use following 2 to 3 cycles of chemotherapy. Mellon EA et

al. (2015) reported on 159 patients with borderline resectable and locally advanced disease. Patients received chemotherapy for 2 to 3 months followed by a total of 30 Gy to tumor and 40 Gy dose painted to tumor-vessel interfaces administered with 5 SBRT daily treatments. The resection and negative margin rate for borderline resectable patients who completed treatment was 51% and 96% respectively. Median survival was 34.2 months for surgically resected patients and 14.0 months for unresected patients. Locally advanced pancreas cases that received FOLFIRINOX (leucovorin calcium [folinic acid], fluorouracil, irinotecan hydrochloride, oxaliplatin) and SBRT underwent a negative margin (R0) resection with a trend towards improved survival. Grade 3 or higher possible radiation toxicity was 7%. A phase II multi-institution trial evaluating gemcitabine and SBRT in locally advanced unresectable patients by Herman JM et al. (2015) reported a median survival of 13.9 months and freedom from disease progression at one year of 78%. Of the 49 patients entered, 4 patients (8%) underwent negative margin and negative lymph node resections. Both early and late gastrointestinal toxicity was reported as minimal. A single institution review of 88 patients by Moningi S et al. (2015) had similar findings. Of the 19 patients who underwent surgery, 79% had locally advanced disease and 84% had margin negative resections. SBRT in resected pancreatic adenocarcinoma with close or positive margins combined with post-radiation chemotherapy (Rwigema JC et al., 2012) achieved freedom from local progression at 6 months, 1, and 2 years of 94.7%, 66% and 44% in a series of 24 patients. Overall median survival was 26.7 months and the 1- and 2-year statistics were 80.4% and 57.2% respectively. Gastrointestinal toxicities were minor with no patients having a grade 3 or 4 toxicity. Given these encouraging findings, requests for the use of SBRT will be considered on a case-by-case basis as described above in section II, which outlines treatment techniques and indications.

Dose escalation studies investigating intraoperative radiation therapy (IORT), SBRT, brachytherapy as well as IMRT are ongoing in an attempt to improve the therapeutic ratio and disease outcome.

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Radiation Therapy for Primary Craniospinal Tumors and Neurologic Conditions

POLICY

I. Complex, three-dimensional conformal radiation therapy (3DCRT), or Intensity-Modulated Radiation Therapy (IMRT) techniques are medically necessary for:

A. The treatment of primary malignant gliomas of the brain in any of the following cases:
   1. Diagnosed by biopsy or resection
      a. Low grade tumors (WHO grade I-II)
         i. Up to 30 fractions
         ii. 3DCRT/IMRT
         iii. Procarbazine, lomustine (CCNU) and vincristine (PCV) should be considered upon the completion of radiation therapy
      b. High grade tumors (WHO grade III-IV)
         i. Up to 33 fractions
         ii. 3DCRT/IMRT
         iii. Radiation therapy combined with temozolomide is the current standard of care
      c. In a poorly performing or elderly individual, a hypofractionated-accelerated course may be effective. Typical fraction schedules are 34 Gy/10, 40.05 Gy/15 or 50 Gy/20

B. Recurrent disease with good prognostic factors including an Eastern Cooperative Oncology Group (ECOG) status of 0, 1, or 2

C. Proton beam therapy – please refer to the policy on Proton Beam

D. Craniospinal irradiation (CSI) in ependymoma, adult medulloblastoma and primitive neuroectodermal tumors (PNET)
   1. Up to 20 fractions depending on risk of recurrence and use of concurrent chemotherapy and a boost – up to a combined total of 33 fractions including CSI

II. Recurrent inoperable malignant gliomas that have received prior radiation treatment will be considered for stereotactic radiosurgery (SRS) on a case-by-case basis

III. Brachytherapy is considered experimental, investigational, or unproven (EIU) for the treatment of a malignant glioma brain tumor

IV. Complex, 3DCRT, or IMRT techniques are medically necessary for the treatment of a primary central nervous system (PCNS) lymphoma for any of the following:

A. A young adult with good performance status and good response to chemotherapy
B. Poor response to chemotherapy
C. Without chemotherapy in an individual with a poor performance status, or who is severely immunocompromised
D. Presence of ocular disease
E. Recurrent disease

V. 3DCRT, IMRT, or SRS is considered medically necessary for the treatment of the following benign conditions:

A. Arteriovenous (AV) malformations (only SRS)
B. Benign brain tumors including any of the following:
   1. Acoustic neuroma
   2. Craniopharyngioma
   3. Glomus tumor
   4. Hemangioblastoma
   5. Meningioma
   6. Pineocytoma
   7. Pituitary adenoma
   8. Schwannoma
C. Cavernous malformations

Please note that a maximum of 5 fractions is authorized for SRS. For an Individual prescribed more than 5 fractions, 3DCRT or IMRT technique should be specified as appropriate.

VI. SRS is medically necessary for any of the following diseases that are refractory to medical treatment and/or invasive neurosurgical treatment:

A. Epilepsy
B. Parkinson's disease
C. Essential tremor
D. Familial tremor classifications with major systemic disease
E. Trigeminal neuralgia.
F. Authorization for this class of diseases will only be granted once all standard treatments have proven to be ineffective. Discussion with an eviCore radiation oncologist will be required.

VII. 3DCRT, IMRT, or SRS is medically necessary for the treatment of an inoperable primary spinal tumor with compression or intractable pain

Key Clinical Points

Surgical removal is recommended for most types of brain tumors in most locations, and their removal should be as complete as possible within the constraints of preservation of neurologic function. Treatment with photons has a major role in the treatment of patients with most tumor types, as evidenced in the European Organization for Research and Treatment of Cancer EORTC-22845 and Medical Research Council MRC-BR04 trials, and can increase the cure rate or prolong disease-free survival. IMRT may yield better dosimetry with sparing of normal brain tissue, especially in dose-escalated protocols.

I. High-grade gliomas

Since the development of the Radiation Therapy Oncology Group-Recursive Partitioning Analysis (RTOG-RPA) risk classes for high-grade glioma, radiation therapy in combination with temozolomide (TMZ) has become standard care. While this combination has improved survival, the prognosis remains poor in the majority of individuates. In a phase III randomized study (Keime-Guibert, et al., 2007) of glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) in the New England Journal of Medicine (NEJM), post-operative external beam photon radiation therapy in the elderly statistically significantly improved the median survival compared to observation. Another phase III randomized study (Stupp et al., 2005) of high-grade gliomas revealed temozolomide plus external beam photon radiation therapy statistically significantly increased the survival rate compared to external beam photon radiation therapy alone. For high-grade brain tumors (WHO grade III-IV), typically 33 fractions of external beam photon radiation therapy are administered post-operatively with up to five coplanar or non-coplanar beams using 3DCRT or IMRT.

II. Low-grade gliomas (LGG)

For low-grade brain tumors (WHO grade I-II), the role of postoperative radiotherapy (PORT) remains controversial. Cerebral low-grade gliomas (LGG) in adults are mostly composed of astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. An analysis using data from the EORTC 22844/22845 studies concluded that several factors portend a poor prognosis: age ≥ 40 years, astrocytoma histology, tumor size ≥ 6 cm, tumor crossing midline, and preoperative neurologic deficits. PORT may benefit patients with high-risk features. The EORTC trial 22844 did not revealed the presence of radiotherapeutic dose-response for patients with LGG for the two dose levels investigated with this conventional setup. A phase III prospective randomized trial (Shaw et al., 2002) of low- versus high-dose radiation therapy for adults with supratentorial low-grade astrocytoma, oligodendroglioma, and oligoastrocytoma found somewhat lower survival and slightly higher incidence of radiation necrosis in the high-dose RT arm. The most important prognostic factors for survival are histologic subtype, tumor size, and age. Recently updated results of RTOG 9802 showed significant improvement in progression-free survival (PFS) when patients also received chemotherapy with procarbazine/CCNU/vincristine (PCV). Median, 5-year, and 10-year PFS improved dramatically with the combined approach from 4.0 years to 10.4 years, from 44.1% to 61.2%, and from 20.9% to 50.5% respectively. For

those patients who receive PORT, typically 30 fractions of external beam photon radiation therapy are administered with up to 5 coplanar or non-coplanar beams 3DCRT or IMRT.

III. Recurrent disease

Currently the following options for salvage may be considered: re-resection, re-irradiation with either conventionally-fractionated doses, Stereotactic Radiation Therapy (SRT), Stereotactic Radiosurgery (SRS), interstitial brachytherapy, or single/poly-chemotherapy schedules including new dose-intensified or alternative treatment protocols employing targeted drugs. A recent review publication (Niyazi et al., 2011) concluded that these have only modest efficacy. The relative value of each approach compared to other options is unknown as well as it remains open which sequence of modalities should be chosen. Some individuals with recurrent disease may benefit from retreatment with radiotherapy, depending on prognostic factors including grade of tumor, age, and performance status. Other factors such as corticosteroid use may be important. A study (Wong et al., 1999) of several hundred patients retreated for recurrent gliomas at MD Anderson showed that 34 (9%) had complete or partial response, whereas 80 (21%) were alive and progression-free at 6 months (APF6). The median PFS was 10 weeks and median overall survival (OS) was 30 weeks. Histology was a robust prognostic factor across all outcomes. GBM patients had significantly poorer outcomes than AA patients did. The APF6 proportion was 15% for GBM and 31% for AA, whereas the median PFS was 9 weeks for GBM and 13 weeks for AA. Results were also significantly poorer for patients with more than two prior surgeries or chemotherapy regimens.

IV. Primary CNS lymphoma

The incidence of primary CNS lymphoma dramatically increased in the last several decades, in part related to human immunodeficiency virus (HIV) infection. Primary CNS lymphoma (PCNSL) now accounts for 2 to 5% of CNS tumors. PCNSL occurs in the brain, leptomeninges, eye and spinal cord. Untreated PCNSL portends a dismal prognosis. Treatment is dependent on age, performance status, extent of disease, and HIV status. Surgery plays little role in the management of PCNSL. Continued investigation is underway to develop the optimal treatment strategy. Recommendations for individuals with good performance status include a high dose methotrexate regimen. For younger individuals, this is usually followed by radiation (24 to 45 Gy in standard fractionation). The timing of radiation is controversial; despite high response rates with a combination of the two modalities, increased neurotoxicity has been observed. Therefore, the recommendation for older (non-immune-suppressed) individuals is chemotherapy alone. For individuals with poor performance status single modality treatment is used, either radiation therapy or chemotherapy. Radiation is also indicated when there has been an incomplete or limited response to chemotherapy and in the setting of ocular or recurrent disease. For individuals with acquired immunodeficiency syndrome (AIDS) with low CD4 counts, treatment is usually palliative radiotherapy alone, 30 Gy in 10 fractions.

V. SRS

A. Malignant tumors

In 2005, the American Society for Radiation Oncology (ASTRO) published an evidenced-based review on the use of SRS for malignant glioma. ASTRO concluded that for individuals with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam photon radiation therapy and bis-chlorethylnitrosourea (BCNU) does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam photon radiation therapy and BCNU. The use of radiosurgery boost is associated with increased toxicity. For an individual with malignant glioma, there is insufficient evidence regarding the benefits/harms of using SRS at the time progression or recurrence. There is also insufficient evidence regarding the benefits/harms in the use of stereotactic fractionated radiation therapy for individuals with newly diagnosed or progressive/recurrent malignant glioma. More recent publications have not provided evidence that would change these conclusions. While small, well-defined, unresectable low-grade gliomas are attractive targets for stereotactic irradiation, and fractionated stereotactic irradiation of these targets has the theoretical benefit of increased normal tissue sparing beyond that provided by the physical characteristics of SRS, no study has demonstrated its benefit compared to standard techniques. Published results from McGill (Roberge et al., 2006) which includes those of 241 patients treated in nine other institutional series conclude that data regarding the use of SRS is limited and, in their opinion, insufficient to claim a clear therapeutic advantage to SRS in the initial management of low-grade glioma (2006). Several small single institution retrospective studies of higher-grade malignancies have been published between 2007 and 2012, and while they claim efficacy, there is no convincing evidence that these are better than standard therapies (Cuneo et al., 2012; Ernst-Stecken et al., 2007; Fields et al., 2012).

B. Benign conditions

The success and excellent safety margin of SRS in many other clinical situations has led to exploration of its use in benign tumors and neurologic conditions which are refractory to medical treatment and would otherwise require surgical procedures with significant morbidity and possible mortality. The condition to be treated must be causing severe symptoms or pose a serious threat to function or life expectancy and have an expected benefit of stabilizing or improving the clinical state. An individual with limited life expectancy and/or generally poor performance status (ECOG > 2) which are not expected to improve significantly with treatment should not be considered for SRS.

The delivery of SRS may take 1 to 5 treatment sessions. By definition the performance of SRS must include:

1. Patient immobilization with or without a frame
2. Radiographic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) or other radiologic modalities to localize precisely the target area
3. The use of computerized image guidance to insure precise treatment delivery. As per American Medical Association (AMA) coding guidelines, Image-Guided Radiation Therapy (IGRT) is included in the daily treatment delivery code and may not be billed separately.
4. Dedicated treatment planning and precise calculation with verification of setup and accuracy of all treatment parameters including but not limited to multiple isocenters, arcs, angles, number of beams (size and weight), isodose plans and calculations.
5. Accurate simulation and reproducibility of all treatment angles or arcs

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Malignant tumors

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Radiation Therapy for Prostate Cancer

POLICY*

Low-risk prostate cancer is defined as having all of the following:

1. Stage T1 to T2a
2. Gleason score (GS) ≤ 6
3. Prostate specific antigen (PSA) < 10 ng/mL

Intermediate-risk prostate cancer is defined as having any of the following:

1. Stage T2b to T2c
2. Gleason score (GS) is 7
3. PSA 10 to 20 ng/mL

High-risk prostate cancer is defined as having any of the following:

1. Stage ≥ T3a
2. Gleason score (GS) ≥ 8
3. PSA > 20 ng/mL

Bone scans are recommended only for an individual with the following presentations:

1. T1 and PSA > 20
2. T2 and PSA >10
3. GS > 8
4. T3, T4
5. Symptomatic

Radiation therapy for prostate cancer is medically necessary in the following situations:

I. Monotherapy with three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), radioactive seed implant, or high dose rate (HDR) brachytherapy when the individual meets both of the following:

A. Low- and intermediate-risk prostate cancer
B. Negative bone scan within the last 6 months, where applicable

II. External beam photon radiation therapy (3DCRT or IMRT) alone or combined with brachytherapy (HDR or radioactive seed implant)

A. Intermediate-risk and high-risk prostate cancer
B. Negative bone scan within the past 6 months, where applicable

III. Stereotactic body radiation therapy (SBRT) alone

A. Low-, intermediate-, and high-risk prostate cancer
B. Negative bone scan within the last 6 months, where applicable

IV. External beam photon radiation therapy (3DCRT or IMRT) in the postoperative setting for at least one of the following:

A. Positive surgical margins
B. Extracapsular extension
C. Seminal vesicle involvement
D. Positive lymph nodes
E. Detectable or rising postoperative PSA level

*For proton beam treatment of prostate cancer, please see separate Proton Beam Therapy policy.

Key Clinical Points

I. Brachytherapy

Brachytherapy is one type of radiation therapy used to treat prostate cancer. Unlike 3DCRT or IMRT photon techniques, in which high-energy xray beams generated by a machine are directed at the tumor from outside the body, brachytherapy involves placing radioactive material directly inside the prostate. This can be accomplished by performing a permanent seed implant by injecting radioactive seeds directly into the prostate gland, and typically using either Iodine or Palladium seeds. As part of the post-implant evaluation of the adequacy for the implant, a single computed tomography (CT) scan of the prostate is performed approximately one month after the implant to determine the dosimetric quality of the implant, so that decisions about the potential need for additional therapy can be made. HDR brachytherapy, as opposed to permanent low dose seed implants, uses temporary radioactive sources. Needles are placed into the prostate gland. A high activity radioactive seed (Iridium-192) is directed to pre-determined positions in these needles for precalculated dwell times via a remote after-loading system, and after the appropriate dose is delivered the needles are removed, usually within 24 hours.

Brachytherapy, either as monotherapy or combined with external beam photon radiation therapy (3DCRT or IMRT), may be appropriate depending on the clinical situation. The resurgence of interest in prostate brachytherapy is principally due to the evolution of transrectal ultrasonography, the development of a closed transperineal approach, and sophisticated treatment planning software. These imaging and planning advances dramatically improved the accuracy of seed placement. Brachytherapy as monotherapy is well established for low-risk prostate

cancer. Permanent prostate brachytherapy is a highly efficacious treatment for clinically localized prostate cancer with biochemical outcomes and morbidity profiles that compare favorably with those of competing local modalities. HDR monotherapy is also appropriate in cases of low-risk disease, and either form of brachytherapy may be appropriate in selected low and intermediate-risk cases. Both the National Comprehensive Cancer Network (NCCN) Guidelines® and the American Brachytherapy Position Paper on HDR back these approaches despite lack of prospective randomized data. The American College of Radiology (ACR) Appropriateness Criteria® published in Brachytherapy in 2014 is clear that data for HDR monotherapy is still emerging.

A modest amount of data has been published from single institutions and in small prospective studies on the strategy of combining external beam photon radiation therapy (3DCRT or IMRT) with either a low dose rate (LDR) or HDR brachytherapy boost for patients with intermediate- to high-risk prostate cancer, and is considered appropriate. In this scenario, a dose of 40 to 50 Gy using 3DCRT or IMRT is considered medically necessary. Such combination therapy is considered not medically necessary for an individual with low risk disease.

II. Complex

Complex photon technique is a method for delivering a beam of high-energy xrays to the location of the individual's tumor. The beam is generated outside the individual, usually by a linear accelerator and is targeted at the tumor site. With careful planning the tumor cells are destroyed and the surrounding tissue is spared from the harmful effects of the radiation. No sources are placed inside the individual's body. Complex technique refers to a treatment planning method wherein the prostate and other target tissues are identified by surrounding anatomy such as bony landmarks and contrast enhanced viscera. Complex technique (plain films are used) is generally not considered appropriate for the definitive treatment of prostate cancer especially in cases of locally advanced or high-risk prostate cancer where higher doses of radiation are usually delivered.

III. 3DCRT

3DCRT is an advanced form of external beam photon radiation therapy that uses CT and computers to create a 3D picture of the tumor so that multiple radiation beams can be shaped exactly to the contour of the treatment area.

IV. IMRT

IMRT employs a very sophisticated computerized 3D treatment-planning system that accurately delivers a high dose of photon radiation to tumors of varying shapes with even more accurate sparing of surrounding tissue than can be accomplished with 3DCRT. IMRT evolved out of the inability of 3DCRT to irradiate tumors that are concave, surrounded by normal tissue, or in very close proximity to sensitive normal tissue, without causing excessive radiation exposure of adjacent normal

tissue. IMRT incorporates two distinct features over 3DCRT: 1) inverse treatment planning and 2) computer-controlled intensity modulation of the photon radiation beam. IMRT is high precision treatment that utilizes computer-controlled linear accelerators to deliver precise radiation doses with photons to the 3D shape of the tumor. This results in sparing surrounding normal tissue and ultimately limiting side effects.

Radiation therapy directed to the prostate is generally not appropriate in men with distant metastatic (stage M1) disease. IMRT with photons is medically necessary for an individual with non-metastatic prostate cancer when there is a reasonable concern about damage to the surrounding normal tissue with the use of Complex or 3DCRT external beam photon radiation therapy. Guidelines on prostate cancer from the NCCN state that 3DCRT and IMRT techniques using photons should be employed in preference to conventional techniques in the treatment of prostate cancer. Doses of 75.6 to 79.2 Gy to the prostate (+/- seminal vesicles for part of the therapy) typically are appropriate for an individual with low-risk cancer. For an individual with intermediate- or high-risk disease, doses of 81 Gy improved PSA-assessed disease control.

In order to ensure that disease is localized prior to delivering high dose radiotherapy, a bone scan must be obtained within the 6 months leading up to radiotherapy in an individual with advanced disease. This includes an individual with stage T3a, T3b, or T4, GS eight (8) to 10, or PSA > 20 ng/ml. An individual being considered for postoperative radiotherapy must also have a bone scan.

Standard 3DCRT and IMRT courses with photons span up to 9.5 weeks (maximum 48 fractions). There may be radiobiologic benefits to using larger doses per fraction and hypofractionated courses. A phase is defined as a distinct change in the target volume, and phases are delivered sequentially. An individual with low-risk disease is treated with 1 or 2 phases (one directed to the prostate and seminal vesicles and another to the prostate alone). In selected intermediate- or high-risk cases, another phase encompassing the pelvic lymph nodes may be appropriate. When external beam photon radiation therapy (IMRT or 3DCRT) is delivered using multiple gantry angles, use of more than 9 gantry angles per treatment phase/target volume is unlikely to provide clinically meaningful improvements in dose distribution and can create greater inhomogeneity within the target. There is also concern over the longer treatment time.

V. Proton beam therapy (PBT)

PBT has been used in a number of institutions to deliver standard doses of radiation to the prostate either as solo therapy or as a boost after conventional therapy directed at the pelvic lymph nodes, building upon the hypothesis that the unique dose deposition characteristics of the proton beam may allow for a reduction in the acute and late toxicity of definitive radiation for early stage prostate cancer. Prospective randomized studies are underway to determine the risks and benefits of this approach compared to IMRT. In the interim, the reader is directed to the specific Proton Beam Therapy policy section of the eviCore clinical guidelines.

VI. SBRT

The American Society for Radiation Oncology (ASTRO) consensus panel statement from April 2010 on the use of stereotactic body radiotherapy approaches (5 fractions or less) states, "…results, primarily available only in abstract form and consisting of reports of clinical experiences from single institutions, show that SBRT for the prostate is technically feasible, with little reported acute morbidity. Very early results, of limited statistical power, suggest that treatment will induce an initial PSA response of a magnitude equivalent to that seen with conventionally fractionated radiotherapy." Since the publication of the ASTRO consensus panel, there have been many more publications on the outcome and toxicity of SBRT for prostate cancer. The data confirms that PSA relapse-free survival and acute and chronic toxicity are equivalent with those of conventional EBRT or permanent brachytherapy, in publications now with medium follow up beyond 5 years. Although late outcome and toxicity data beyond 10 years are not yet available, SBRT for low- and intermediate-risk prostate cancer, in a selected and well-informed individual, is considered a medically necessary first line of treatment. ASTRO has published an updated model policy on SBRT that now confirms that SBRT is "…an appropriate alternative for select patients with low- to intermediate-risk disease".

The use of SBRT in the treatment of high-risk patients continues to evolve. For example, in a prospective trial of 97 patients with high-risk prostate cancer, the actuarial 6-year biochemical disease-free survival (bDFS) was 69% at a median follow up of 5 years. The incidence of late genitourinary (GU) toxicity was low. The incidence of late grade 2 gastrointestinal (GI) toxicity was found to have been higher (13.3%) in those patients who received SBRT following pelvic radiation vs. 0% in those patients receiving SBRT alone. In a subsequent publication, at a median follow up of 6 years, the actuarial 7-year freedom from biochemical failure was 68.5% for high-risk patients with low rates of late toxicity. In a study of 41 high- or very high-risk patients, whole pelvic radiation followed by SBRT resulted

in an estimated 4-year biochemical failure-free survival of 91.9%. Finally, in a pooled analysis of prospective phase II clinical trials, the biochemical relapse free survival was 81% for high-risk patients. With long-term data emerging to support the efficacy and safety of SBRT for treatment of high-risk prostate cancer, SBRT can be considered medically necessary. It should be noted that SBRT is defined as an entire treatment course consisting of five or fewer fractions. Thus, SBRT cannot be billed as a boost.

VII. Postoperative radiation therapy

In the setting of postoperative prostate cancer, external beam photon radiation therapy may be beneficial in the setting of positive margins, extracapsular extension, seminal vesicle involvement, lymph node involvement, or prostate cut-through. In addition, an individual with a detectable or rising postoperative PSA level may benefit from postoperative radiotherapy. In the postoperative setting, the treatment course generally does not exceed 8 weeks (maximum of 42 fractions).

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Radiation Therapy for Rectal and Anal Canal Cancer

POLICY – Rectum

External beam photon radiation therapy using three-dimensional conformal radiation therapy (3DCRT) is medically necessary for the treatment of rectal cancer in any of the following clinical situations:

I. Surgical candidate
- A. Preoperative (neoadjuvant)
- B. Postoperative (adjuvant)

II. Medically inoperable
- A. As definitive radiation therapy

III. Local recurrence or salvage therapy in an individual with isolated pelvic / anastomotic recurrence when either of the following criteria is met:
- A. Resectable cases for either of the following:
  1. Preoperative chemotherapy and radiation therapy
  2. Postoperative followed by chemotherapy and radiation therapy
- B. Unresectable cases in conjunction with chemotherapy

IV. Palliative treatment in a previously un-irradiated individual who meets both of the following criteria:
- A. Has reasonable life expectancy
- B. Has unresectable metastatic disease and symptomatic local disease or near-obstructing primary tumors

POLICY – Anal Canal

External beam photon radiation therapy using 3DCRT or Intensity-Modulated Radiation Therapy (IMRT) is medically necessary for the definitive treatment of anal canal cancer

Key Clinical Points

Colorectal cancer is the third most commonly diagnosed cancer in the United States. Surgical resection plays a key role in treatment. The surgical approach depends on the extent and stage of disease. Transanal excisions are used for early stage lesions. Other transabdominal approaches include low anterior resections, total mesorectal excisions, and abdominal perineal resections. The Swedish Rectal Cancer Trial demonstrated an overall survival advantage to preoperative radiation. The German Rectal Cancer Study

Group investigated preoperative chemoradiation compared with postoperative therapy. Preoperative chemoradiation showed decreased local recurrence rates and improved sphincter function.

External beam photon radiation therapy is utilized in the neoadjuvant, adjuvant, palliative and medically inoperable settings.

Based upon established criteria, assessment of peer-reviewed literature, and consensus present in established guidelines American College of Radiology/American Society for Radiation Oncologists (ACR/ASTRO), National Comprehensive Cancer Network (NCCN) external beam photon radiation therapy is considered an integral component in the multidisciplinary management of rectal cancer. The rectum extends from the transitional zone of the dentate line to the sigmoid colon. Tumors extending below the peritoneal reflection are considered rectal, while more proximal tumors are considered colonic.

I. Treatment of rectal cancer

A. Treatment of rectal cancer requires interdisciplinary interaction between the radiologist, gastroenterologist, colorectal surgeon, radiation oncologist, and medical oncologist. Surgical treatment can range from polypectomy for selected T1 tumors, transanal local excision for selected individuals with low risk T1/T2 tumors in the absence of positive margins, lymphovascular invasion (LVI), or high grade. For individuals who have T2 primary and negative margins, postoperative chemoradiation is appropriate after transanal excision. For individuals with T3 primary or positive nodes total mesorectal excision (TME) either by low anterior resection (LAR) or abdominoperineal resection (APR), depending on the proximity of the tumor to the anal verge.

   Based on earlier randomized trial data, the National Institutes of Health (NIH) Consensus Conference of 1990 recommended postoperative chemoradiotherapy for individuals with T3 and/or node positive disease. More recent trials of preoperative chemoradiation have established that as the preferred approach. Preoperative therapy affords the opportunity for downstaging of the tumor, improved resectability, greater likelihood of sphincter preservation, and improved local control. Individuals who present with synchronous limited metastatic disease amenable to R0 resection may also be candidates for definitive post-operative chemoradiation. Individuals with isolated pelvic or anastomotic recurrence who have not received prior radiation may be appropriately treated with preoperative or postoperative chemoradiation with or without intraoperative external beam photon radiation therapy or with primary chemoradiation if deemed unresectable.

II. External beam photon radiation therapy treatment techniques and schedules for the treatment of rectal cancer

A. External beam photon radiation therapy, preoperative and postoperative
Treatment technique typically involves the use of multiple fields to encompass the regional lymph nodes and primary tumor site. Customized blocking is utilized. 3DCRT is appropriate. IMRT is not medically necessary (see below). A dose of 45 to 54 Gy in 25 to 30 fractions over 5 to 6 weeks is commonly used.

Various treatment techniques may be used to decrease complications, such as prone positioning, customized immobilization (e.g. belly boards), and the use of multiple fields and incorporation of 3D treatment planning.

IMRT with photons is not medically necessary except in rare extenuating circumstances where higher doses are required (e.g. unresectable cases or those with positive margins) and normal tissues such as small bowel cannot be adequately spared. IMRT with photons in the pre- and postoperative settings should only be used in the setting of an institutional review board (IRB)-approved clinical trial. Consideration may be given to the use of IMRT with photons in select cases of locally and regionally advanced cancer when higher doses of radiation may be necessary.

For unresectable cancers or individuals who are medically inoperable, doses higher than 54 Gy may be appropriate. In the preoperative setting a dose of 50.4 Gy in 28 fractions is appropriate. A dose of 25 Gy in 5 fractions can also be considered in select individuals. In the postoperative setting with negative margins, 54 Gy in 30 fractions may be appropriate. Individuals with positive margins may require doses higher than 54 Gy.

B. External beam photon radiation therapy, palliative
In previously un-irradiated individuals with unresectable metastatic disease and symptomatic local disease or near obstructing primaries who have reasonable life expectancy, external beam photon radiation therapy may be appropriate. Up to 20 fractions in 1 phase using 3DCRT or radiation planned using a complex isodose technique with photons is medically necessary. IMRT with photons is not medically necessary.

III. Treatment of anal canal cancer

A. The role of radiation therapy in the treatment of anal canal cancer continues to evolve and is the subject of ongoing study. The current combination of chemotherapy and external beam photon radiation therapy is being explored, as are the optimal doses and techniques. Dose escalation regimens, beyond

those mentioned below, have not been established firmly as improving either local control or survival rates.

IV. External beam photon radiation therapy treatment techniques and schedules for the treatment of anal canal cancer

A. External beam photon radiation therapy using 3DCRT or IMRT is medically necessary for the definitive treatment of anal canal cancer

B. A dose of 45 Gy to 59.4 Gy in 25 to 33 fractions over 5 to 7 weeks is commonly used

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Radiation Therapy for Skin Cancer

POLICY

I. Basal cell and squamous cell skin cancers

A. Overview

In the United States, the incidence of skin cancers outnumbers all other cancers combined, and basal cell cancers are twice as common as squamous cell skin cancers. While the two types share many characteristics, risk factors for local recurrence and for regional or distant metastases differ somewhat. Both types tend to occur in skin exposed to sunlight, and share the head and neck region as the area having the greatest risk for recurrence. Both occur more frequently and be more aggressive in immunocompromised transplant patients. In general, it is the squamous cell cancers that tend to be more aggressive, with a greater propensity to metastasize or to recur locoregionally. A squamous cell cancer is more likely to possess one or more high risk factors.

Anatomic location plays a role in risk stratification and is broken down into: "L" areas (trunk and extremities, excluding pretibia, hands, feet, nail units, ankles); "M" areas (cheeks, forehead, scalp, neck, pretibial); "H" areas (mask areas of face, including central face, eyelids, eyebrows, periorbital skin, lips, chin, overlying mandible, preauricular and postauricular skin, temple, ears, genitalia, hands, feet). Factors identified as placing the patient at increased risk for recurrence for basal and squamous cell skin cancers are included in Table 1.

Table 1

Basal Cell Skin Cancer High Risk Factors	Squamous Cell Skin Cancer High Risk Factors
• "L" area diameter greater than 20 mm • "M" area diameter greater than 10 mm • Any size lesion in "H" area • Poorly defined border • Recurrent presenation • Presence of immunosuppression • In a site of prior radiation therapy • Aggressive growth pattern (morpheaform, basosquamous, sclerosing, micronodular features) • Presence of perineural involvement	• "L" area diameter greater than 20 mm • "M" area diameter greater than 10 mm • Any size lesion in "H" area • Poorly defined border • Recurrent presenation • Presence of immunosuppression • In a site of prior radiation therapy • Rapidly growing lesion • Neurologic symptoms • Poorly differentiated • Unfavorable histology (adenoid, adenosquamous, desmoplastic, metaplastic) • >= 2mm depth, or Clark level IV or V • Perineural, lymphatic, or vascular involvement

B. Management

Treatment should be customized, taking into account specific factors and also patient preferences. The primary goal is to completely remove the tumor and to maximize functional and cosmetic preservation. Surgery is usually the most efficient and effective means to achieve theses goals. Radiation therapy may be selected when cosmetic or functional outcome with surgery is expected to be inferior. In very low risk, superifial cancers, topical agents may be sufficient and cautiously used. When surgery is utilized, margin assessment using Mohs micrographic technique should include examining vertical sections of the specimen to assess deep margin and stage/depth of invasion.

When radiation therapy is utilized, the following are applicable:

1. Photon and/or electron beam techniques are medically necessary for the treatment of basal cell and squamous cell cancers of the skin for any of the following:
   a. Definitive treatment for a cancer in a cosmetically significant location in which surgery would be disfiguring
   b. Adequate surgical margins have not been achieved and further resection is not possible
   c. Definitive management of large cancers as an alternative to major resection requiring significant plastic repair
   d. Definitive management of large cancers that are considered inoperable
   e. Definitive, preoperative, or postoperative adjuvant therapy for a cancers at risk for local or regional recurrence due to perineural, lymphovascular invasion, and/or metastatic adenopathy
   f. Definitive management for non-surgical candidates
   g. Contraindications to the use of photon and/or electron beam techniques:
   h. Radiation therapy should not be used in genetic conditions which predispose to skin cancer, such as xeroderma pigmentosum or basal cell nevus syndrome.
      Radiation treatments should be avoided or only used with great caution in cases of connective tissue disorders
2. Brachytherapy (low dose rate [LDR], high dose rate [HDR], surface, or interstitial technique) is medically necessary when a and b are contraindicated:
   a. Surgical resection
   b. Photon and/or electron beam techniques
3. Electronic brachytherapy is considered medically necessary for for the treatment of basal cell and squamous cell skin cancers, as recent peer reviewed reports demonstrating sufficient long term safety and efficacy have been published.
4. When brachytherapy is required for treatment of skin cancers, up to ten (10) sessions is considered medically necessary.
5. Superficial or kilovoltage (kV) xray treatments with low energy (up to 250 kV) external beam devices are generally used for thinner lesions. The beam

energy and hardness (filtration) dictate the maximum thickness of a lesion that may be treated with this technique.

Higher-energy external electron beam teletherapy (4 megaelectron volt [MeV] and greater) is most commonly utilized to treat the majority of localized lesions. The use of appropriate energy and thickness of build-up bolus material is required, along with proper sizing of the treatment field to account for the electron beam penumbra. Photon external beam teletherapy is required in circumstances in which other beams of lower energy are inadequate to reach the target depth.

In the great majority of cases, simple appositional Complex technique is required, accompanied by lead, cerrobend, or other beam-shaping cutouts applied in the path of the beam and/or on the skin surface to match the shape of the target lesion. In complicated cases, such as when regional adenopathy or perineural invasion is present, more complicated techniques may be medically necessary. Intensity-Modulated Radiation Therapy (IMRT) will be approved when comparative three-dimensional (3D) and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN). Unless clinically evident, dose comparison plans will be required.

Treatment schedules with photons and/or electrons should be matched to the clinical circumstance, including size and depth of the lesion, histology, cosmetic goal, and risk of damage to underlying structures. These schedules can range from a single fraction to a course of 33 fractions. Radiation doses typically range from 35 Gy in fractions of 7 Gy over 5 days, to 66 Gy in 33 fractions of 2 Gy over six and one-half weeks. The margin around tumor is typically different for basal and squamous histologies and for technique used (electrons, photons, superficial radiation). The radiation prescription is to be made by a qualified radiation oncologist who is familiar with the nuances of the dose deposition that accompany the physical characteristics of the radiation beams and techniques. Dose prescription for electrons is at the 90% isodose line, and for superficial or orthovoltage radiation at the Dmax. When sophisticated Complex photon, 3D, or IMRT treatments are used, attention is to be paid to the skin dose, and may require the use of bolus. When regional nodes are to be treated, the dose range is 54 Gy to 66 Gy at 2 Gy per fraction.

When multiple skin cancers are present and to be treated with radiation therapy, they should be treated concurrently rather than sequentially. Medical review will be required for those cases in which sequential

treatment is requested, or if a new request is received for treatment of additional skin cancers within 90 days of previous requests.

II. Malignant melanoma

A. Overview

Malignant melanoma is increasing in incidence in the United States at a rate more rapidly for men than any other malignancy, and more rapidly for women for all malignancies except lung cancer. There are over 75,000 new cases of melanoma in the USA annually, and it accounts for over 10,000 deaths each year. The incidence may be even higher, skewed by under-reporting of superficial and *in situ* cases. Like the non-melanoma skin cancers, excess sun exposure poses an increased risk of developing it, along with skin type, positive personal or family history, and environmental factors. Yet it can also occur in persons without substantial sun exposure, and in any ethnic group or any color of skin. Survival is strongly inversely correlated with degree/depth of invasion, and decreases 50% with lymph node involvement. Some cases of melanoma take an indolent course while others are biologically much more aggressive.

Melanoma can arise outside of the skin, wherever melanocytes exist. Mucosal melanoma represents a spectrum of clinical entities depending on site of origin, and most commonly arises in the head and neck sinuses, the oral cavity, the anorectum, vagina, and mucosa of the GI and GU tracts. There are specific genetic alterations in distinct clinical subtypes of melanoma, often correlated with degree of sun damage. BRAF mutation is seen in roughly half of the non-CSD (non-chronic sun damaged) skin melanomas, whereas KIT gene aberations are rare in that group. Non-mucosal, non-cutaneous melanomas also occur, such as in the uveal tract, and represent distinct presentations. Non-cutaneous melanoma cases (i.e. mucosal melanomas and those of the eye) are addressed in other sections of this clinical guideline, such as the head and neck clinical guideline for melanomas of the sinuses, or the clinical guideline on proton beam therapy for uveal melanomas.

The natural history of cutaneous melanoma is one of local invasion, lymphatic metastases, and hematologic dissemination. The risk of all three may be greater than that of a non-melanoma skin cancer in the same location. Surgery is the primary therapy for cutaneous melanoma. A pre-operative evaluation should include a careful physical examination of the primary site, the regional lymphatics, and the entire skin surface. Equivocal findings on physical examination of the regional lymphatics may trigger an ultrasound exam of the area. If symptomatic, cross-sectional imaging is indicated, otherwise not routinely to be performed for early stage (0, I, II) cases. Sentinal lymph node evaluation is recommended for thicker lesions, but rarely needed with lesions less than 0.75 mm thick. As stage advances higher, baseline imaging is appropriate, or if there is clinical evidence of adenopathy or symptoms are present that suggest nerve or bone invasion. Clinically positive nodes should be confirmed with fine needle aspiration

(FNA) or core biopsy. If there is clinical or radiographic evidence of distant metastases, confirmation by FNA or core biopsy is recommended, as is imaging of the brain. Patients with minimal signs or symptoms of CNS involvement should undergo a brain magnetic resonance imaging (MRI) scan due to the high risk of brain metastases.

The optimal degree of clear margin necessary to minimize the risk of local is dependent on tumor thickness. For thin (<2 mm) lesions it appears a margin of 1 cm is adequate. For thicker lesions, a 2 cm margin is currently recommended. Lentigo maligna and melanoma *in situ* present unique features because of possible lateral subclinical extension, for which imiquimod is an option. Radiation therapy has been also used in such cases, with complete clearance rates in the 85% to 90% range. For a melanoma that has undergone adequate wide local excision and there is no adenoapthy on clincal and/or sentinal node examination, adjuvant radiation therapy is rarely indicated, the possible exception being desmoplastic neurotropic melanoma. If regional adenopathy is clincally present, a complete therapeutic node dissection should be included with wide exision of the primary tumor. If melanoma is found in sentinal nodes but was not clinically suspicious, current recommendations include offering a complete node dissection, though its impact on disease control and survival is not well established and is the focus of current study. Following wide excision and nodal dissection, radiation therapy to the nodal basin is to be considered in high risk cases, based on location, size, and number of positive nodes, and the presence or absence of extranodal extension of melanoma.

Radiation therapy is one option for the treatment of in-transit disease (metastases within lymphatics or satellite locations without metastatic nodes) for which resection is not feasible. Alternatives include intralesional injections, local ablation therapy, and topical imiquimod.

Radiation therapy for brain metastases has been delivered using either whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS), or both. While most studies have been retrospective and reported on few patients with melanoma, WBRT was generally associated with fewer intracranial recurrences but not necessarily a survival advantage. Because of the benefit of emerging more effective systemic therapies such as the immune checkpoint inhibitor Ipilimumab, there is a trend towards increased use of SRS rather than WBRT because of the increased survival with systemic therapy and the possibility of the cognitive impairment late effect of whole brain radiation.

B. Management
   1. Photon and/or electron beam techniques may be medically necessary in the treatment of malignant melanoma at the primary site of the skin in these situations:

a. Adjuvant treatment after resection of a primary deep desmoplastic melanoma with close margins
b. Adjuvant treatment after resection of the primary tumor and the specimen shows evidence of extensive neurotropism
c. Locally recurrent disease after resection

2. Photon and/or electron beam techniques may be medically necessary in the treatment of regional (i.e. those with nodal involvement) malignant melanoma in these situations:
   a. Upon resection of clinically appreciable lymph nodes when
      i. The lactate dehydrodgenase (LDH) level is less than 1.5 times the upper limit of normal **and**
      ii. Extranodal extension of tumor is present in the resected nodes **and/or one or more of the following:**
         01. One or more involved **parotid** lymph nodes of any size
         02. Two or more involved **cervical** lymph nodes and/or tumor within a node is 3 cm or larger
         03. Two or more involved **axillary** lymph nodes and/or tumor within a node is 4 cm or larger
         04. Three or more involved **inguinal** lymph nodes and/or tumor within a node is 4 cm or larger
3. Photon and/or electron beam techniques may be medically necessary to palliate unresectable nodal, satellite, or in-transit disease
4. Photon and/or electron beam techniques are medically necessary in the treatment of metastatic malignant melanoma in these situations:
   a. Symptomatic or potentially symptomatic soft tissue metastases
   b. Symptomatic or potentially symptomatic bone metastases (also see the section of the criteria entitled, Radiation Treatment of Bone Metastases)
   c. Symptomatic or potentially symptomatic visceral metastases
   d. Metastases to the brain (also see the section of the guideline entitled, Radiation Therapy for Brain Metastases)

C. Technique and dose considerations

1. Superficial or kilovoltage (kV) xray treatments with low energy (up to 250 kV) external beam devices are generally used for thinner lesions. The beam energy and hardness (filtration) dictate the thickness of a lesion that may be treated with this technique.

2. Higher-energy external electron beam teletherapy (4 megaelectron volt [MeV] and greater) is most commonly utilized to treat the majority of localized lesions. The use of appropriate energy and thickness of build-up bolus material is required, along with proper sizing of the treatment field to account for the electron beam penumbra. Photon external beam teletherapy is required in circumstances in which electron beams are inadequate to reach the target depth.

   In the great majority of cases, simple appositional Complex technique is required, accompanied by lead, cerrobend, or other beam-shaping cutouts

applied in the path of the beam and/or on the skin surface to match the shape of the target lesion. In complicated cases, more conformal techniques may be medically necessary. Intensity-Modulated Radiation Therapy (IMRT) will be approved when comparative three-dimensional (3D) and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the NRG Oncology/National Comprehensive Cancer Network (NCCN). Unless clinically evident, dose comparison plans will be required.

3. Treatment schedules with photons and/or electrons should be matched to the clinical circumstance, including size and depth of the lesion, histology, cosmetic goal, and risk of damage to underlying structures. The radiation dose schedules used with non-melanoma skin cancers are commonly employed. However, dose schedules may include hypofractionated regimens with large fraction size that take advantage of theoretical radiobiological characteristics. Schedules such as 5 fractions of 6 Gy (two fractions per week) have been reported as having acceptable acute toxicity and increased response rates, but may be at the expense of long term side effects.
4. Requests to use highly conformal techniques such as Stereotactic Body Radiation Therapy (SBRT) to treat melanoma metastasesrequire individual review and must also satisfy criteria set forth in the guideline on Radiation Therapy for Extra-cranial Oligometastasis.
5. The radiation prescription is to be made by a qualified radiation oncologist who is familiar with the nuances of the dose deposition that accompany the physical characteristics of the radiation beams and techniques. Dose prescription for electrons is at the 90% isodose line, and for superficial or orthovoltage radiation at the Dmax. When sophisticated Complex photon, 3D, or IMRT treatments are used, attention is to be paid to the skin dose, and may require the use of bolus.

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Radiation Therapy for Soft Tissue Sarcomas

POLICY

This policy applies to sarcomas of soft tissues in the adult population. Soft tissue sarcomas are grouped in the following categories:

- Extremity, trunk, head and neck
- Retroperitoneal, intra-abdominal
- Gastrointestinal stromal tumor (GIST)
- Desmoid tumor (aggressive fibromatoses)
- Rhabdomyosarcoma

I. Extremity, trunk, head and neck sites

A. Preoperative radiation therapy with photons and/or electrons

Radiation therapy with photons and/or electrons is medically necessary when delivered prior to resection or attempted resection of a soft tissue sarcoma of an extremity, the trunk, or a head and neck site. At the time of surgery, the surgeon is encouraged to place clips both to identify the periphery of the surgical field and also to identify any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation.

The medically necessary preoperative dose is 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day followed by a postoperative boost that depends on the extent of any disease remaining after resection.

Indications and doses medically necessary for a boost due to positive margins are the following:

1. External beam radiation therapy with photons and/or electrons
   a. For microscopic residual disease (R1 resection) 16 Gy to 18 Gy
   b. For gross residual disease (R2 resection) 20 Gy to 26 Gy
2. Brachytherapy - low dose rate (LDR)
   a. For microscopic residual disease (R1 resection) 16 Gy to 18 Gy
   b. For gross residual disease (R2 resection) 20 Gy to 26 Gy
3. Brachytherapy - high dose rate (HDR)
   a. For microscopic residual disease (R1 resection) 3 Gy to 4 Gy given twice daily for a total of 14 Gy to 16 Gy
   b. For gross residual disease (R2 resection) 3 Gy to 4 Gy given twice daily for a total of 18 Gy to 24 Gy
4. Intra-operative radiation therapy (IORT) with photons and/or electrons
   a. For microscopic residual disease (R1 resection) 10 Gy to 12.5 Gy
   b. For gross residual disease (R2 resection) 15 Gy

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B. Postoperative radiation therapy with photons and/or electrons (all radiation treatments planned to be given during and/or after resection)

C. Radiation therapy is medically necessary when delivered at the time of or subsequent to resection or attempted resection of a soft tissue sarcoma of an extremity, the trunk, or a head and neck site. It is expected that the surgeon will have placed clips both to identify the periphery of the surgical field and also to identify any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation, if anything other than an R0 (negative margins) was anticipated.

Indications and doses medically necessary for postoperative radiation therapy are the following:

1. External beam radiation therapy with photons and/or electrons - 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day followed by a boost:
   a. For microscopically positive margins 16 Gy to 18 Gy
   b. For gross residual disease 20 Gy to 26 Gy
2. LDR Brachytherapy
   a. For positive surgical margins 16 Gy to 20 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons with conventional fractionation of 1.8 Gy to 2 Gy per day
   b. For negative margins 45 Gy. No boost is medically necessary.
3. HDR Brachytherapy
   a. For positive surgical margins 3 Gy to 4 Gy given twice daily for a total of 14 Gy to 16 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons using conventional fractionation of 1.8 Gy to 2 Gy per day
   b. For negative margins 36 Gy given in 10 fractions on a twice-daily basis, 3.6 Gy per fraction. No boost is medically necessary.
4. IORT with photons and/or electrons - 10 Gy to 16 Gy followed by 50 Gy external beam radiation therapy using photons and/or electrons with conventional fractionation of 1.8 Gy to 2 Gy per day

II. Retroperitoneal and intra-abdominal sites (excluding desmoid tumors):

A. Preoperative radiation therapy with photons

With the exception of desmoid tumors, radiation therapy with photons is medically necessary when delivered prior to resection or attempted resection of a soft tissue sarcoma of a retroperitoneal or intra-abdominal location. At the time of subsequent surgery, the surgeon is encouraged to place clips both to identify the periphery of the surgical field and any potential sites of microscopic or gross residual disease that may be in need of higher amounts of radiation.

Two dose schedules/techniques are medically necessary:

1. The preoperative dose is 50 Gy using conventional fractionation with

photons of 1.8 Gy to 2 Gy per day, followed by a postoperative boost of photons that depends on the extent of any disease remaining after resection.

2. A preoperative dose-painting technique with photons is medically necessary to deliver the following:
   a. Coverage of the entire clinical target volume (CTV) to a dose of 45 Gy to 50 Gy in 25 to 28 once-daily fractions
   b. Simultaneous integrated boost to anticipated high risk margins to a dose of 57.5 Gy

B. Intraoperative radiation therapy with photons and/or electrons
   1. IORT with photons and/or electrons: 10 Gy to 16 Gy followed by external beam radiation with photons and/or electrons of 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day
      a. IORT with photons and/or electrons
         i. For microscopically positive margins: 10 Gy to 12.5 Gy
         ii. For gross residual disease: 15 Gy

C. Postoperative radiation therapy with photons
   Radiation therapy with photons is medically necessary when delivered subsequent to resection or attempted resection of a soft tissue sarcoma of a retroperitoneal or intra-abdominal location. It is expected that the surgeon will have placed clips both to identify the periphery of the surgical field and to help define potential sites of microscopic or gross residual disease that may benefit from additional radiation.

   Indications and doses medically necessary for postoperative radiation therapy with photons are the following:
   1. External beam radiation therapy with photons of 50 Gy using conventional fractionation of 1.8 Gy to 2 Gy per day, followed by a boost:
      a. For selected cases with negative margins (R0): 10 Gy with photons
      b. For microscopically positive margins (R1): 16 Gy to 18 Gy with photons
      c. For gross residual disease (R2 and re-resection not possible): 20 Gy to 26 Gy with photons

III. Treatment of primary or metastatic sites for salvage or palliation

Palliation of recurrent or metastatic sites of soft tissue sarcoma may be medically necessary when other alternatives are less appropriate. The use of radiation in such circumstances must balance between expedience, the need and ability to relieve symptoms, the high doses that are required to achieve a response, and the potential normal tissue damage that can be inflicted. All requests for the palliative use of radiation with photons that involve Intensity-Modulated Radiation Therapy (IMRT), Stereotactic Body Radiation Therapy (SBRT), or more than 15 fractions

require medical review. Palliative treatment with electrons is done with Complex Radiation Therapy technique and should not exceed 15 fractions as well.

IV. Radiation techniques

A. Complex
Complex technique with photons and/or electrons is medically necessary most commonly in the palliative setting in which a simple, expeditious approach is required to relieve symptoms.

B. Three-dimensional conformal radiation therapy (3DCRT)
3DCRT with photons is medically necessary in all cases of curative intent in order to limit the radiation dose to normal nearby organs at risk (OARs). 3DCRT is also medically necessary in the palliative treatment of soft tissue sarcomas.

C. IMRT
IMRT is considered medically necessary when 3DCRT is unable to protect adequately the nearby OARs from doses of radiation that exceed published constraints. This is commonly the situation in cases of curative intent where the clinical circumstance requires doses in excess of 50 Gy. IMRT is medically necessary when a dose-painting technique is appropriate to deliver a simultaneous integrated boost. IMRT will be approved when comparative 3D and IMRT plans demonstrate that a 3D plan does not meet the "Acceptable" normal tissue constraints using standard metrics published by the Radiation Therapy Oncology Group (RTOG)/National Comprehensive Cancer Network (NCCN).

D. IORT
IORT is medically necessary when given in conjunction with external beam radiation therapy with photons and/or electrons and is not regarded as medically necessary as a sole means of delivering radiation therapy to a soft tissue sarcoma. IORT requires special technology in that it is delivered in a single fraction to the tumor or tumor bed during the surgical procedure being performed to resect the sarcoma.

E. Brachytherapy
Brachytherapy may be given using an HDR approach or an LDR approach and is medically necessary in cases in which a boost is required or as the sole means of delivering radiation for tumors that have been completely resected with clear margins.

When HDR is utilized, afterloading catheters are placed at the time of surgery, and the radioactive sources are briefly placed within them multiple times, most commonly twice daily, for several days. One placement of HDR afterloading

catheters is medically necessary, as is up to six loadings of the radioactive sources into them.

When utilized, LDR brachytherapy is performed by placing radioactive material permanently into the region of the tumor. As the radioisotope decays fully, the radiation dose is delivered; the material becomes non-radioactive and can be left in place. One LDR insertion is medically necessary.

F. SBRT
SBRT with photons is medically necessary to treat a locally recurrent soft tissue sarcoma that is within or immediately adjacent to an area that has received radiation treatments as part of the primary management.
For SBRT treatment of metastases, please refer to the separate Radiation Treatment of Extra-Cranial Oligometastases clinical guideline.

G. Image-Guided Radiation Therapy (IGRT)
Please refer to the separate IGRT criteria.

Key Clinical Points

Radiation therapy with photons and/or electrons is medically necessary in all potentially curable cases of soft tissue sarcoma of the extremity, trunk, head and neck, retroperitoneal and intra-abdominal sites, with the exceptions of retroperitoneal or intra-abdominal desmoid tumors, and of low grade, stage I sarcomas that have been resected and oncologically appropriate margins have been achieved.

Radiation therapy with photons and/or electrons is medically necessary in palliative cases of soft tissue sarcoma of the extremity, trunk, head and neck, retroperitoneal and intra-abdominal sites when other simpler methods of palliation are inadequate, ineffective, or not available.

Radiation therapy is not medically necessary in the initial management of GIST but does have a role in management of refractory or unresectable cases.

Radiation therapy with photons and/or electrons may play a role in the management of desmoid tumors but is generally limited to sites other than retroperitoneal or intra-abdominal.

Of the rhabdomyosarcomas, management of the pleomorphic variety is similar to that of other soft tissue sarcomas. The non-pleomorphic variety often occurs in the pediatric population, and its management is less well defined.

Treatment is to be given in a multi-disciplinary environment in which the radiation oncologist is consulted prior to a resection attempt.

Medically necessary radiation therapy with photons and/or electrons employs the use of highly sophisticated treatment planning and the use of highly conformal delivery techniques to achieve a suitable therapeutic ratio of target coverage versus protection of normal tissues. Radiation dose is to be influenced by normal tissue tolerance, i.e. doses listed herein may require modification based on normal tissue constraints.

Radiation therapy is not a substitute for completeness of resection. Re-resection may be indicated in some cases. However, further resection may not be feasible for medical or technical reasons and this may serve as an indication for additional radiation (boost) in selected cases. Examples include extremely large tumors, high-grade lesions, or the morbidity of further surgery. The risk and feasibility of administering additional radiation must be weighed against that of additional surgery. Means to mitigate radiation to nearby structures, such as tissue displacement using omentum, biologic or synthetic material, may be incorporated into the resection procedure when additional postoperative radiation is contemplated.

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Radiation Therapy for Testicular Cancer

POLICY

External beam photon radiation therapy is medically necessary for the following:

I. Stage IA, IB, IIA, and IIB testicular seminoma

Fractionation

I. For seminoma stages IA-IB in the adjuvant setting, regimens of 20 Gy in 10 fractions or 25.5 Gy in 17 fractions are medically necessary

II. For seminoma stages IIA-IIB in the adjuvant setting, up to 18 fractions is medically necessary

Technique

I. External beam photon radiation therapy with three-dimensional conformal radiation therapy (3DCRT) is medically necessary in the treatment of seminoma

In stages IA-IB, the treatment prescription is to the para-aortic nodes to a dose of 20 Gy in 10 fractions delivered with an AP-PA field arrangement.

In stages IIA-IIB, the initial treatment prescription is to a modified dog-leg field to 20 Gy in 10 fractions followed by a boost of 10 to 16 Gy in 5 to 8 fractions with an AP-PA field arrangement, in two phases.

Key Clinical Points

I. Seminoma

In an individual with stage I seminoma, radical orchiectomy serves as the initial treatment for testicular malignancies (Groll et al, 2007). Following orchiectomy, the management of the individual is dependent on the histologic type and whether residual disease is present.

Treatment options for those who have a pure seminoma with no sign of residual disease (stage I) include active surveillance, radiation therapy to the para-aortic lymph nodes or single agent carboplatin (Bernard et al., 2015). Cure rates with orchiectomy alone approach 85% (Mortensen, et al., 2014). Furthermore, salvage therapies for seminoma are very effective and administered with curative intent. Therefore, active surveillance is the recommended treatment option in an individual with stage I seminoma because it

avoids unnecessary treatment and the treatment-related side effects that are associated with radiation and chemotherapy (Kollmannsberger et al., 2015).

For an individual who refuses active surveillance, chemotherapy or radiation therapy is a treatment option. A phase III trial studied both treatment approaches in 1,477 patients with stage I seminoma and found similar relapse free rates with one cycle of carboplatin vs. radiation (94.7% vs. 96%, respectively) (Oliver et al., 2011). Radiation therapy may be associated with worse long term complications including an increased risk of secondary malignancies and increased risk for cardiovascular disease. In an individual who refuses active surveillance and chemotherapy, radiation can be administered to a dose of 20 Gy to the para-aortic lymph nodes (Jones et al., 2005).

For an individual with stage II seminoma, radiation therapy can be effective in the treatment of stage IIA and non-bulky IIB disease (nodes < 3cm) (Classen et al., 2003). Chemotherapy is recommended for an individual with bulky nodal disease. Studies in patients with IIA and non-bulky IIB seminoma show 5-year disease free results of greater than 90%. Treatment with radiation consists of 20 Gy in 10 fractions to the para-aortic and superior ipsilateral pelvis followed by a boost of 10 to 16 Gy in 5 to 8 fractions to the involved nodal areas, in two phases (Schmoll et al., 2004).

An individual receiving radiation therapy for seminoma should be treated with a scrotal shield and with an AP-PA technique to limit dose the kidneys, liver and small bowel. Intensity modulated radiation therapy is not medically necessary because it increases the amount of tissue receiving a low dose of radiation which may increase the risk of second cancers relative to an AP-PA beam arrangement.

II. Nonseminoma

Nonseminomatous germ cell tumors are primarily managed with surgery and chemotherapy (Kollmannsberger et al., 2010). Men at low risk of relapse can be managed with an orchiectomy alone. Those with a higher risk of relapse are managed with chemotherapy. In general, there is no established role for the routine use of radiation therapy in the management of nonseminomatous germ cell tumors.

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Radiation Therapy for Urethral Cancer and Upper Genitourinary Tract Tumors

POLICY

External beam photon radiation therapy (EBRT) is medically necessary for the following:

I. Definitively in urethral cancer in an individual with T2-T4 disease or node positive
II. Postoperatively in urethral cancer in an individual with T3-T4 disease, node positive, or positive surgical margins
III. Palliation
IV. Radiation therapy is not considered medically necessary in the definitive treatment of cancers of the ureter or renal pelvis

Fractionation

I. In the definitive setting up to 39 fractions is medically necessary
II. In the adjuvant setting in an individual with no high risk features, up 30 fractions is medically necessary
III. In the adjuvant setting in and individual with positive margins or extra-nodal extension, up to 39 fractions is medically necessary
IV. In the palliative setting up to 20 fractions is medically necessary

Techniques

I. EBRT with three-dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) is medically necessary in the definitive treatment of urethral cancer. Treatment prescriptions include the pelvic and inguinal lymph nodes to 40 to 45 Gy followed by a boost to 70 Gy to areas of gross disease in 2 to 3 phases of treatment
II. 3DCRT is medically necessary in the palliative setting

Key Clinical Points

Treatment for urethral cancer is dependent on gender, tumor location and tumor size (Dayyani, 2014). In males, surgical options include a distal urethrectomy, partial penectomy, or a urethrectomy with a cystoprostatectomy in males. In females, surgical options include a urethrectomy with or without a cystectomy.

Adjuvant radiation can be delivered for an individual with a high risk of recurrence including one with positive nodes, positive margins or T3-T4 disease.

In an individual who refuses surgery or one with advanced disease, concurrent chemoradiation can be used (Gakis, 2013; Grivas, 2012). Often the draining lymphatics will include the pelvic and inguinal lymph nodes and appropriate techniques include 3DCRT or IMRT. Brachytherapy can also be utilized and will be considered on a case-by-case basis.

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Radioimmunotherapy with Zevalin®

POLICY

I. Indications

A. Radioimmunotherapy (RIT) with Zevalin® is medically necessary for an individual with any of the following:
   1. Relapsed low grade B-cell CD20-positive follicular Non-Hodgkin's lymphomas (NHLs)
   2. Refractory low grade B-cell CD20-positive follicular NHLs
   3. Newly diagnosed (consolidation after chemotherapy) low grade B-cell CD20-positive NHLs after at least a partial response (PR) to therapy
   4. Newly diagnosed (initial treatment) low grade B-cell CD20-positive follicular NHLs for the elderly or infirm when no other option is expected to be tolerated
   5. Transformed B-cell follicular NHLs that are CD20-positive (off-label for Zevalin®, recommended in National Comprehensive Cancer Network [NCCN] Guidelines®)

B. NCCN Guidelines® consider RIT an option:
   1. In primary cutaneous diffuse large B-cell Lymphoma, LEG type (T3, generalized disease only with either PR or relapse after R-CHOP +/- local RT)
   2. For stage III/IV non-gastric MALT lymphoma with extranodal disease and multiple nodal sites as well as post RT recurrent gastric MALT lymphoma [through follicular lymphoma (FL) pathway]
   3. For progressive splenic marginal zone lymphoma (through FL pathway)
   4. In an individual with transformed B-cell FLs who has received multiple prior therapies, and
   5. In an individual with minimal or no prior chemotherapy with progression of disease, no response, or partial response to chemotherapy +/- rituximab +/- radiation therapy.

II. Contraindications

A. Poor bone marrow reserve (platelet count < 100,000/microL, absolute neutrophil count < 1,500/microL, bone marrow cellularity < 15%)

B. High tumor burden in the bone marrow (lymphoma bone marrow involvement > 25%). Bilateral cores are recommended and the pathologist should provide the percent of cellular elements involved in the marrow. Cytogenetics +/- fluorescence in situ hybridization (FISH) for known Myelodysplastic syndrome (MDS) markers. A trend towards an increased risk of MDS with RIT has been suggested

C. Previous radiation to > 25% of active marrow sites

D. In an individual with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended.
E. An individual who is pregnant

III. Investigational

A. Newly diagnosed (consolidation after chemoimmunotherapy)
   1. It is not known whether the addition of RIT improves the outcome of an individual receiving chemoimmunotherapy. The role in the frontline setting is under investigation. NCCN Guidelines® on FL (grade 1-2) consider radioimmunotherapy after induction with chemotherapy or chemoimmunotherapy a category 1 recommendation but adds the following footnotes:
      a. "f First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied."
      b. "g The full impact of an induction regimen containing rituximab on RIT consolidation is unknown."
B. RIT as single-agent (initial therapy/previously untreated disease)
C. Preparative regimens for hematopoietic cell transplantation (HCT)
D. Any type of NHL other than mentioned above
E. Solid tumors

Key Clinical Points

I. Agent

Currently, there is one Food and Drug Association (FDA) approved RIT agent in the United States (US), ^{90}Y ibritumomab tiuxetan (Zevalin®). Tositumomab (Bexxar™) was withdrawn permanently from the US market in February 2014. Zevalin® has FDA approval for relapsed or refractory CD20 positive follicular NHL and as a frontline adjuvant agent for CD20 positive follicular NHL achieving a complete response (CR) or partial response (PR) to induction chemotherapy (consolidation after chemotherapy). It contains murine Immunoglobulin-G (IgG) monoclonal antibodies (mAbs) that target the CD20 surface antigen on CD20 positive follicular NHL.

Zevalin® utilizes ^{90}Y, a pure β-particle emitter with a physical half-life of 2.7 days. The β-particle has an energy of 2.3 megaelectronvolts (MeV) and a maximum tissue penetration of approximately 12.0 mm (R_{90} = 5.2 mm). As such, physical contact with loved ones after administration is not limited except that sexual intercourse and kissing should be avoided in the first 24 hours. Tiuxetan is a DTPA-type chelate that attaches ^{90}Y to the mAb, ibritumomab. Because there is no gamma emission in the spectrum of this isotope, it is not visualized by gamma camera scans. As a result, a biodistribution assessment cannot be performed. Therefore, a surrogate imaging radionuclide that emits gamma radiation (^{111}In) is required.

The treatment is delivered over 1 to 2 weeks. On day 1, an infusion of nonradioactive (cold) rituximab is delivered. This is designed to saturate the CD20 antigen sink (depletion of peripheral B-cells and the binding of nonspecific sites in the liver and spleen) and provide antibody mass, which improves biodistribution and tumor targeting.

The administered activity for Zevalin® is based on weight (0.4 mCi/kg for a platelet count ≥ 150,000; 0.3 mCi/kg for a platelet count of 100,000 to 149,000; maximum of 32 mCi). A single gamma scan (^{111}In ibritumomab tiuxetan) is used to confirm a normal biodistribution on days 3 to 4. A review of the Zevalin® imaging registry reveals that only 0.6% of scans exhibited an altered biodistribution. An eligible individual is also required to have an absolute neutrophil count (ANC) ≥ 1,500 and a bone marrow biopsy that reveals < 25% involvement with lymphoma.

II. Discussion of indications

A. Relapsed or refractory setting

There is no standard therapy for an individual with relapsed or refractory FL, and practice varies widely; as such, an individual should be encouraged to participate in clinical trials whenever possible.

The main treatment options for an individual with relapsed or refractory FL include:

1. Clinical trials of new agents or new combinations of existing agents
2. Immunotherapy either with single agent rituximab or rituximab plus chemotherapy
3. RIT with radiolabeled antibodies
4. Re-challenge of original therapy
5. High dose chemotherapy with autologous hematopoietic cell transplantation (HCT) rescue
6. Allogeneic HCT

RIT has demonstrated response rates of approximately 60% to 80%. However, RIT is not recommended for an individual with poor bone marrow reserve or high tumor burden in the bone marrow and requires coordination with physicians trained in the safe use of radionucleotides.

Prospective trials of RIT demonstrate response rates of 60% to 80% in previously treated disease (Buchegger et al., 2006; Davies et al., 2004; Davis et al., 2004; Fisher et al., 2005; Horning et al, 2005; Leahy et al., 2006; Vose et al., 2000; Wiseman et al., 2002). Median progression-free survival (PFS) is less than 1 year, but an individual who achieves a complete response has a median time to progression of close to 4 years (Gordon et al., 2004; Witzig et al., 2007).

A phase III study comparing Zevalin® versus rituximab for patients with relapsed or refractory low-grade follicular B-cell NHL or transformed NHL was performed (Witzig, et al., 2002). Patients were randomized to either a single intravenous (IV) dose of Zevalin® 0.4 mCi/kg (n = 73) or IV rituximab 375 mg/m^2 weekly for 4 doses (n = 70). The RIT group was pre-treated with 2 rituximab doses (250 mg/m^2) to improve biodistribution and tumor targeting. After the first rituximab dose on day 1, ^{111}In ibritumomab tiuxetan was administered to assess biodistribution and to aide in dosimetry. No patients received the therapeutic dose of Zevalin® if > 20 Gy or 3 Gy was calculated to any non-tumor organ or the red marrow, respectively. Zevalin® was administered after the second rituximab dose approximately 1 week (days 7 to 9) after the first dose of rituximab and ^{111}In ibritumomab tiuxetan. The administered activity of Zevalin® was capped at 32 mCi. Patients in both arms of the study received 2 prior chemotherapy regimens. The overall response rate (ORR) was 80% for Zevalin® and 56% for rituximab (p = 0.002). The CR rates were 30% and 16% (p = 0.04), respectively, in the Zevalin® and rituximab group. Durable responses ≥ 6 months were 64% versus 47% (p = 0.030) for Zevalin® versus rituximab. The conclusion of the study was that RIT with Zevalin® was well tolerated and resulted in statistically significant and clinically significant higher ORRs and CRs than rituximab alone.

In a pivotal, nonrandomized, phase III multicenter trial (Kaminski et al., 2001), patients with relapsed, refractory, or transformed follicular B-cell NHL were treated with Bexxar™ (n = 60). A single dose resulted in an overall response rate of 65% (20% CR). Eligible patients were required to have been treated with at least two prior protocol-specific chemotherapy regimens (median of four regimens in the study) and to either have not responded or progressed within 6 months of therapy. A PR or CR was observed in 39 patients (65%) after Bexxar™ compared to 17 patients (28%) after last qualifying chemotherapy (LQC) (p < 0.001). The median duration of response was 6.5 months for Bexxar™ and 3.5 months for the LQC group (p < 0.001). The CR rate was 20% for Bexxar™ and 3% for the LQC group (p < 0.001). The conclusion of the study was that a single dose of Bexxar™ was significantly more efficacious than the LQC received by heavily pre-treated patients with relapse or refractory follicular B-cell NHL.

Early evidence suggests that an individual relapsing following treatment with RIT may tolerate other treatment approaches including chemotherapy, external beam radiation therapy (EBRT) with photons and/or electrons, and autologous HCT.

B. Frontline therapy

Seventy to 85 percent of individuals present with advanced stage disease. Individuals with advanced stage disease are usually not cured with conventional treatment. While remissions can be attained, repeated relapses are common. Treatment focuses on the alleviation of symptoms, reversal of cytopenias, and improvement of quality of life. The disease course is variable with some individuals demonstrating stable disease for years and others progressing more rapidly. Rarely, individuals may have spontaneous remissions lasting longer than one year.

Considering the concerns about RIT for treating large bulky tumors (tumor penetration, overall required dose, non-uniform dose distribution), it would appear that bringing RIT into a frontline therapeutic setting after induction chemotherapy and maximum cyto-reduction would be the next logical direction.

A phase III first-line indolent trial (FIT) of consolidation with Zevalin® compared to no additional therapy after first remission was reported for follicular B-cell NHL (Morschhauser et al., 2013; Morschhauser et al., 2008).

Patients with CD20+ stage III/IV follicular B-cell NHL who achieved a PR or CR to induction chemotherapy were randomized to Zevalin® (n = 208) or to the control arm, representing no further treatment (n = 206). After a median follow-up of 7.3 years, consolidation with Zevalin® resulted in an estimated 8-year PFS advantage of 41% versus 22% in the control arm ($p < 0.0001$). The median PFS was 4.1 years vs. 1.1 years, respectively ($p < 0.001$). No significant difference in overall survival (84% vs. 81%) was observed between treatment arms. The incidence of secondary malignancies was higher in the RIT arm but the difference was not statistically significant (13% vs. 7%). Incidence of MDS/AML was significantly higher in RIT arm with an actuarial 8-year incidence rate of 4.2% vs. 0.6% ($p < 0.042$). Only 14% of patients in this study received rituximab in combination with chemotherapy as induction. The estimated eight-year PFS advantage was 56% versus 45% in the control arm. The median PFS was 7.9 years vs. 4.9 years, respectively. The difference in PFS outcomes was not significant in this subgroup; however, the trial was not statistically powered to detect differences in subgroups based on induction therapies. Since only a small portion of patients enrolled in the FIT trial received rituximab-containing induction therapy, the effects of RIT consolidation following rituximab-containing regimens cannot be fully evaluated.

The phase III randomized intergroup study by the SWOG/CALGB (S0016) evaluated the role of RIT consolidation following R-CHOP. In this study, 554 patients with newly diagnosed FL were randomly assigned to chemoimmunotherapy alone (RCHOP for 6 cycles) or to chemotherapy plus a radioimmunoconjugate (CHOP for 6 cycles followed by ^{131}I. When compared with R-CHOP, CHOP plus Bexxar™ resulted in similar rates of overall (84% each) and complete (45% vs. 40%) remissions. Severe (grade 3/4) thrombocytopenia was greater (18% vs. 2%) among those who received a radioimmunoconjugate. At a median follow-up of 4.9 years, chemoimmunotherapy alone resulted in similar rates of PFS (76% vs. 80%) and OS (97% vs. 93%) at 2 years.

These trials suggest that consolidation with a radioimmunoconjugate may be able to improve the quality of remission by converting PRs into CRs. Indication of RIT in relapsed or refractory disease as well as consolidation in frontline therapy when chemotherapy alone has been used for induction is well supported in literature. However, it is not known whether the addition of an anti-CD20 radioimmunoconjugate improves outcomes of patients already receiving chemoimmunotherapy. The role in the frontline setting is under investigation.

NCCN Guidelines® (Follicular Lymphoma [grade 1-2], FOLL-B 1 of 3, First-line Consolidation or Extended Dosing [optional]) consider RIT after induction with chemotherapy or chemoimmunotherapy a category 1 recommendation but adds the following footnotes:

- “f First-line consolidation with radioimmunotherapy or extended dosing of rituximab after bendamustine + rituximab has not been studied.”
- “g The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.”

In frontline setting, RIT is also indicated for the elderly or infirm when no other option is expected to be tolerated.

C. Off-label use of radioimmunoconjugates as single-agent therapy for the management of previously untreated disease

Nonrandomized trials support use of radioimmunoconjugates as single-agent therapy for the management of previously untreated disease. While initial reports suggest good response rates and tolerability, long-term follow-up of such an approach is limited. The following describes the largest phase II trials evaluating RIT for initial management of advanced stage FL.

In an international phase II trial (Scholz et al., 2013) of 59 older patients (> 50) with stage II to IV FL, Zevalin® was used as first line therapy and

resulted in an ORR of 87% at 6 months with 56% of patients achieving a CR. After a median follow-up of 31 months, the median PFS was 26 months and the median overall survival had not been reached. Rates of PFS at 1 and 2 years were 77% and 54%, respectively. Severe (grade 3/4) thrombocytopenia, leukopenia, neutropenia, and lymphopenia were seen in approximately 48%, 34%, 32%, and 20%. Non-hematologic toxicities were mostly mild to moderate and included infections (20%) and gastrointestinal toxicities (10%).

In an international phase II trial (Illidge et al., 2014), 74 patients with previously untreated FL (78% advanced stage) received two cycles of Zevalin®. Patients with > 20% bone marrow infiltration were pretreated with four cycles of rituximab. The overall response rate was 94% (CR/complete response unconfirmed [CRu] 58%). At a median follow-up of 3 years, the estimated rates of PFS and OS at 3 years were 58% and 95%, respectively. Median PFS was 40 months. Toxicity was mild with the most common side effects being lethargy and gastrointestinal side effects.

In another phase II trial evaluating Bexxar™ (Kaminski et al., 2005) in 76 patients with stage III or IV FL requiring therapy, the ORR was 95% with 75% CRs. The median PFS was 6 years and the 10-year PFS rate was 40%. One patient developed MDS 8 years after treatment.

D. Histologic transformation of follicular lymphoma
The most commonly employed treatment regimens for an individual with histologic transformation (HT) include conventional chemotherapy with immunotherapy (e.g., R-CHOP), RIT, and high-dose therapy followed by autologous HCT. An individual who is not a candidate for HCT may be considered for RIT.

An individual with HT of FL who is resistant to initial therapy or who relapses following initial therapy, is expected to do poorly. Available treatment options include enrollment in a clinical trial, use of chemotherapy regimens similar to that employed in relapsed/resistant diffuse large B cell lymphoma (DLBCL), or RIT. An individual with disease that responds to treatment may be a candidate for autologous or allogeneic HCT.

There are no prospective trials evaluating the use of RIT as consolidation in individuals with chemotherapy sensitive HT or DLBCL. Some clinicians offer the off-label use of RIT as consolidation in individuals with chemotherapy sensitive HT who have received extensive prior therapy and who are not candidates for autologous HCT. Given the paucity of data regarding this approach, RIT should be used in the context of a clinical trial.

NCCN Guidelines® consider RIT an option for an individual with multiple prior therapies and for an individual with minimal or no prior chemotherapy with progression of disease, no response, or partial response to chemotherapy +/- rituximab +/- radiation therapy.

E. Preparative regimens for HCT – (Experimental/Investigative/Unproven [EIU])
The maximally tolerated dose of total body irradiation (TBI) is approximately 15 Gy. A randomized trial comparing 12 and 16 Gy found that the higher dose was associated with a lower relapse rate (12% vs. 35% at three years in patients with acute myeloid leukemia) (Clift, et al., 1991). One approach to achieving this goal has been the administration of mAbs radiolabeled with high energy emitting radioisotope. This would permit targeting of the radiation dose to the tumor cells and marrow with potential reduction in dose to other organs, such as the liver, lungs and kidneys.

RIT has been added to standard preparative regiments in the autologous setting for the treatment of patients with B cell NHL, with encouraging preliminary results and tolerable toxicity profiles (Gopal et al., 2007, Gopal et al., 2011; Krishnan et al., 2008). A randomized trial comparing Bexxar™-BEAM with BEAM has been conducted by the Bone Marrow Transplantation Clinical Trials Network (BMT-CTN 0401). Patient accrual has been completed but results have not yet been released.

III. Toxicities

The most profound side effects of RIT are potentially prolonged and significant cytopenias with cell count nadirs ranging from four to nine weeks post-therapy with recovery one to four weeks post-nadir. The most common cytopenias are leucopenia and thrombocytopenia, which are easily managed in the majority of individuals. RIT causes a transient depletion of B cells for approximately 6 to 9 months but has not been associated with significant increases in severe infections or hospitalizations. RIT can be associated with an infusion reaction similar to that seen with other monoclonal antibodies.

Although initial reports suggested a possible risk of treatment-related MDS (t-MDS) and acute myeloid leukemia (t-AML), the rate of t-MDS and t-AML does not appear to be increased. An evaluation of 746 patients treated for NHL with Zevalin® found that the rates of t-MDS and t-AML were not increased compared with historic rates in those who had received multiple chemotherapeutic regimes (Czuczman et al., 2007).

A bilateral bone marrow biopsy is required prior to the initiation of RIT to assess bone marrow involvement. RIT is not recommended in an individual with inadequate marrow reserve (i.e., platelet count < 100,000/microL, absolute neutrophil count < 1,500/microL, bone marrow cellularity < 15%), lymphoma

bone marrow involvement > 25%, or previous radiation to > 25% of active marrow sites. Due to the risk of delayed hematologic toxicity, an individual should have blood count monitoring at least weekly following treatment until hematologic recovery.

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Selective Internal Radiation Therapy (SIRT)

Overview

Selective internal radiation therapy (SIRT), also known as radioembolization with microsphere brachytherapy device (RMBD) and transarterial radioembolization (TARE), is a form of arterially directed therapy for primary and secondary liver cancer. The treatment involves catheter-based injection of radioactive Yttrium-90 (^{90}Y) microspheres, in either glass or resin form, through the arterial branch feeding the affected portion of the liver. Although radioembolization with Yttrium-90 (^{90}Y) microspheres involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia.

POLICY

I. Indications

Selective internal radiation therapy (SIRT), using radioactive Yttrium-90 (^{90}Y) microspheres, is indicated in an individual with:

A. Unresectable and/or medically inoperable primary or metastatic liver malignancies
   1. Unresectable liver only or liver dominant metastases from neuroendocrine tumors (e.g., carcinoids, pancreatic islet cell tumors, endocrine tumor)
   2. Unresectable primary hepatocellular carcinoma (HCC)
   3. Unresectable metastatic liver tumors from primary colorectal cancer
   4. Requests for the treatment of liver metastases from other primary malignancies, including breast carcinoma, ocular melanoma, cutaneous melanoma, and intrahepatic cholangiocarcinoma, will be considered on a case-by-case basis. These requests should be based on the lack of any known systemic or liver-directed treatment options for this individual in an effort to relieve symptoms and/or possibly extend life expectancy

B. The tumor burden should be liver dominant, not necessarily exclusive to the liver

C. Eastern Cooperative Oncology Group (ECOG) performance status should be 0 or 1 or Karnofsky Performance Status (KPS) of 70 or more

D. Life expectancy should be at least 3 months

E. Radioactive Yttrium-90 (^{90}Y) microspheres treatment is allowed only in the outpatient setting unless the documentation supports the medical necessity of inpatient treatment

Repeat radioembolization may be used for new or progressive primary or metastatic liver cancers when:

A. The individual has had a previous satisfactory response to an initial radioembolization treatment as evidenced on results of a computed tomography (CT) scan or positron emission tomography (PET)-CT scan performed 3 months following the previous procedure. Response should be graded according to the revised RECIST guideline (Version 1.1)
B. The disease still must be liver dominant
C. Life expectancy of at least 3 months
D. ECOG performance status no greater than 2 or KPS of 70 or more
E. There are no other effective systemic or liver-directed treatment options
F. The individual has compensated liver function tests (LFTs)
G. Estimated lung dose and combined lung dose from previous embolizations are within acceptable dose volume constraints. Exclude an individual with lung shunting in which the lung radiation dose is greater than 35 to 30 Gy per treatment or greater that 50 Gy cumulatively for all treatments
H. Treatment should be given to a targeted tumor volume
I. Repeat whole liver irradiation is considered experimental, investigational, or unproven (EIU) and will not be certified
J. Requests for a third radioembolization will not be certified
K. All requests for repeat radioembolization are subject to medical review and will be judged on a case-by-case basis

Key Clinical Points

Radioembolization with Yttrium-90 microspheres has proven safe and effective in palliation of symptoms as well as possible increase in survival in selected cancer patients. Given this proven effect, consideration is now being given to repeating the procedure in an individual who has responded well previously, has good performance status, and has liver dominant disease without other treatment options. In their series of 148 patients diagnosed with neuroendocrine tumor metastases to the liver treated with Yttrium-90 microspheres, Vyleta et al. (2011) noted a subgroup of 33 patients who were retreated to the same liver lobe with very low toxicity and no evidence of radiation-induced liver disease (RILD). They also commented on other published studies in which a few patients even received a third treatment. In their analysis, increased duration of tumor responses was noted and most deaths were attributed to progression of extrahepatic disease. Similarly, Lewandowski et al. (2006) noted further palliation and prolongation of survival in individuals retreated for viable residual or recurrent liver metastases. Favorable prognostic indicators for longer survival in their entire series of 82 initial and retreated patients included a lower pretreatment level of alpha-fetoprotein (AFP) and a higher tumor to baseline uptake ratio.

Lam et al. (2013) attempted to correlate the occurrence of RILD in a population of 247 patients treated to a targeted area with Yttrium-90 microspheres within univariate

analyses of multiple variables. This population included 8 patients who were retreated. Two of these patients received a second treatment to the whole liver and died shortly after the second treatment with signs and symptoms of RILD. Cumulative doses of 3.08 and 2.66 GBq were noted respectively. The remaining 6 patients experienced minor side effects with cumulative doses of 2.41 to 3.88 GBq. Objective responses were noted in all patients. Risk factor analysis disclosed repeat radioactive remobilization, serum total bilirubin and baseline serum aspartate aminotransferase as significant factors in the development of RILD but only repeat radioembolization proved to be an independent indicator. The authors noted objective tumor responses but commented on the need for improved safety limits, which will require better dosimetric measurement.

At this time, requests for a second radioembolization treatment will be considered on a case-by-case basis. Third treatment requests will not be certified nor will requests for a second radioembolization procedure to the whole liver.

I. Absolute contraindications

A. Inability to catheterize the hepatic artery
B. Fulminant liver failure (Childs-Pugh status late B or C)
C. ^{99m}Technetium-Albumin Macroaggregates (^{99m}Tc-MAA) hepatic arterial perfusion scintigraphy demonstrating significant reflux or non-target deposition to the gastrointestinal organs that cannot be cannot be corrected by angiographic techniques. It is important that liver injection of ^{99m}Tc-MAA is delivered with flow rates and catheter position that mimic the anticipated ^{90}Y infusion rate catheter position
D. ^{99m}Tc-MAA hepatic arterial perfusion scintigraphy demonstrating the potential > 30 Gy radiation exposure to the lung

II. Relative contraindications

A. Excessive tumor burden in the liver with greater than 70% of the parenchyma replaced by tumor
B. Prior extensive liver resection
C. Total bilirubin greater than 2 mg/dL in the absence of reversible cause (e.g. obstruction), which indicates severe liver function impairment. Nonobstructive bilirubin elevations generally indicate that liver metastases have caused liver impairment to a degree at which risks outweigh benefits for this therapy. In contrast, patients with hepatocellular carcinoma (HCC) and elevated bilirubin may be treated with radioembolization if a segmental or subsegmental infusion can be performed
D. Prior radiation therapy to the liver or upper abdomen that included a significant volume of the liver (clinical judgment by the authorized used required). Based on a study by Lam et al. (2013) the fraction of liver exposed to $\geq$ 30 Gy (V30) is the strongest predictor of hepatotoxicity. All patients with V30 > 13% experienced hepatotoxicity

E. Concurrent or prior capecitabine chemotherapy (within the previous two months)
F. If the patient is known to be pregnant, the potential radiation risks to the fetus and clinical benefits of the procedure required before, during, and after RMBD, and any scatter radiation from the hepatic implant should be considered before proceeding with treatment
G. Portal vein thrombosis (PVT): Tsi et al. suggests ^{90}Y microspheres are tolerated in patients with HCC and major PVT. Kulik et al. (2008) reported more grade 3/4 adverse events in patients with main portal vein thrombosis. Schwartz et al. (2010) states ^{90}Y is a safe microembolization treatment that can be used as an alternative to TACE in patients in case of PVT

III. Chemotherapy (adjuvant or concurrent) for case-by-case requests

A. Requests submitted on a case-by-case basis for the use of SIRT as a debulking agent will not be certified. There are currently no national guidelines, such as those of the National Comprehensive Cancer Network (NCCN), for the use of SIRT in this manner. As both the clinical effectiveness and toxicity of combined treatment is not known, treatment in this setting is considered experimental, investigational, or unproven (EIU). Results from the Phase III SIRFLOX trial (van Hazel, 2016) showed no difference in PFS. A prolonged liver response was demonstrated in the FOLFOX/Y-90 arm 20.5 months vs. 12.6 months for chemotherapy alone. As data fail to show an impact on survival, current NCCN Guidelines® recommend SIRT as an option in carefully selected chemotherapy-resistant or refractory disease in patients with predominant liver metastases.

IV. Treatment target planning

A. Treating multiple tumors within the entire liver in a single treatment session is termed whole liver delivery. Treating the entire liver by first treating one lobe and then the other in separate sessions is termed sequential delivery; both are described in the literature. Treatment to a single lobe only is termed lobar delivery. In the sequential treatment, a 30 to 45 day interval is the generally accepted practice
B. Treatment to additional lobes may be done if a positive response of the first is achieved as evidenced by any of the following:
    1. Stability in tumor size
    2. Tumor shrinkage
    3. Necrosis within the tumor with or without shrinkage
    4. Improvement in liver function test results
    5. Improvement in performance status or pain

    Repeat treatment of a lobe/segment may be necessary in a previously treated vascular bed (lobe), such as recurrent disease or incompletely treated disease. A 90-day interval before retreatment of the PTV is recommended for adequate hepatic healing.

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