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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Uveal Melanoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Uveal Melanoma

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Uveal Melanoma, Version 1.2019

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Uveal Melanoma include recommendations for staging, treatment, and follow-up of patients diagnosed with uveal melanoma of the choroid or ciliary body. In addition, because distinguishing between uveal melanoma and benign uveal nevi is in some cases difficult, these guidelines also contain recommendations for workup of patients with suspicious pigmented uveal lesions, to clarify the tests needed to distinguish between those who should have further workup and treatment for uveal melanoma versus those with uncertain diagnosis and low risk who should to be followed and later reevaluated. These NCCN Guidelines Insights describe recommendations for treatment of newly diagnosed nonmetastatic uveal melanoma in patients who have already undergone a complete workup.

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Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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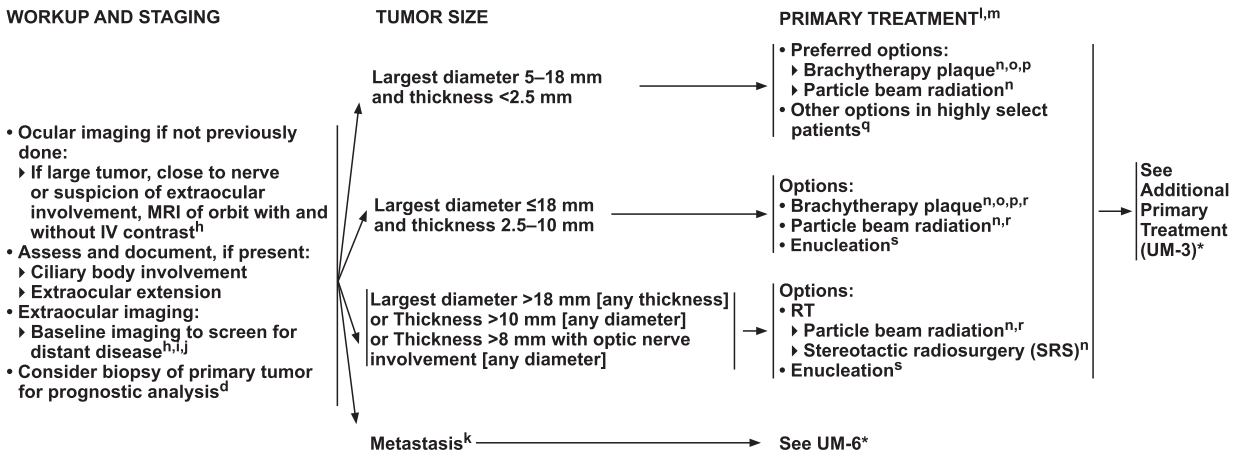

For footnotes d, h, i, j, and n, see full NCCN Guidelines online at NCCN.org.

[k]Patients may be considered for palliative local therapy to the primary tumor in the setting of metastatic disease. Patients who present with advanced metastatic disease and limited life expectancy may elect to have no treatment to their primary tumor.

[l]An essential feature of high-quality care is that clinical decisions are informed by a variety of case-specific factors (eg, patient characteristics and preferences like age, status of the other eye among others, disease characteristics, medical history), such that for some patients the best clinical approach may be other than one of the listed options.

[m]For small ciliary body and iris tumors (less than 3 clock hours), surgical excision may be considered.

[o]The plaque should cover the tumor with a ≥2-mm circumferential margin. The exception is for tumors near the optic nerve where it may be impossible to achieve adequate coverage of the margins. The largest commercially available brachytherapy plaque is 22 mm in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter <18 mm.

[p]Brachytherapy with scleral patch graft for cases with limited extraocular extension.

[q]Consider laser ablation or enucleation for patients who are not good candidates for brachytherapy or particle beam radiation.

[r]Consider additional treatment with resection, laser ablation, transpupillary thermotherapy, or cryotherapy if concerned that adequate response was not achieved from initial radiation.

[s]While there is a trend toward avoiding enucleation, it is recommended for patients with neovascular glaucoma, tumor replacing >50% of globe, or blind, painful eyes. Consider enucleation in cases of extensive extraocular extension.

*Available online, in these guidelines at NCCN.org

UM-2

Overview

The NCCN Guidelines for Uveal Melanoma are the first and only NCCN Guidelines on an ocular cancer, and include recommendations for staging, treatment, and follow-up of patients diagnosed with uveal melanoma of the choroid or ciliary body. In addition, because distinguishing between uveal melanoma and benign uveal nevi is in some cases difficult, these guidelines also contain recommendations for workup of patients with suspicious pigmented uveal lesions, to clarify the tests needed to distinguish between those who should have further workup and treatment for uveal melanoma versus those with uncertain diagnosis and low risk who should to be followed and later reevaluated (page UM-1, available in the full guidelines at NCCN.org). These NCCN Guidelines Insights describe recommendations for treatment of newly diagnosed nonmetastatic uveal melanoma, as shown on UM-2 (see above) and UM-3 (available at NCCN.org), in patients who have already undergone a complete workup.

Treatment of Uveal Melanoma

Treatment of Localized Primary Uveal Melanoma

Most uveal melanomas are localized at first presentation, and only a small percentage of cases present with metastases (<3%).[1–6] Local treatment of primary uveal melanoma is effective in preventing local recurrence in >85% of cases,[7,8] yet the rate of metastasis within 20 years after treatment is approximately 20% to 70% in patients who present with localized uveal melanoma, depending on tumor stage/size at diagnosis.[3,9–11] Although surgical approaches are the mainstay of treatment of localized cutaneous melanoma, and historically most uveal melanomas were treated with surgery, the field has moved away from using surgery in all patients,[12,13] because different modalities, primarily various forms of radiation therapy (RT), have been found to be just as safe and effective for those with limited disease, and can preserve the affected eye. Some surgical approaches are still used in patients with extensive local disease, but most patients with localized primary uveal melanoma are treated with some form of radiation.[14] A number of other ablative techniques are occasionally used for localized primary melanoma, including laser therapy, cryotherapy, and photodynamic therapy. The NCCN Guidelines Insights describes each of these primary treatment modalities in more detail. Selection among these techniques is guided by many case-specific factors, including the size and location of the tumor,

presence of extraocular extension, visual potential, and patient age and preference.

Surgical Options

Prior to the development of effective RT options, surgery was used to treat most uveal melanomas.

Local Resection

A variety of methods for local resection of uveal melanoma are aimed at conserving the eye and useful vision,[15–17] including transretinal (endoresection) and transscleral (exoresection) approaches.[17] These methods can be technically challenging,[17,18] with high rates of immediate postoperative complications, such as hemorrhage, retinal detachment, ocular hypertension, and proliferative vitreoretinopathy, which may require repeat surgery.[15–17,19,20]

Local resection is not recommended in the NCCN Guidelines for Uveal Melanoma as a primary treatment option for choroidal or ciliary body melanoma. For patients with primary tumors amenable to eye-conserving approaches, radiation-based approaches are preferred. For tumors too large for brachytherapy, enucleation is preferred over local resection, because the latter is technically difficult for large tumors.

Enucleation

Enucleation is a technically less challenging procedure than local resection of uveal melanoma, and historically is the most widely used treatment of uveal melanoma. Results from the prospective Collaborative Ocular Melanoma Study (COMS) suggest that enucleation is associated with a very low risk of local recurrence (~1%),[21,22] notably lower than the rate of local recurrence reported for retrospective studies in patients treated with primary local resection.[8,23–31] Enucleation procedures have been standardized; they involve complete removal of the eye and in most cases include insertion of an orbital implant.[16,17,32,33] Both porous and nonporous implants have been shown to result in similar outcomes, although there may be a higher incidence of ptosis with acrylic implants, and a greater need for ocularists' treatment (topical antibiotics, polishing or refitting of prosthesis) with hydroxyapatite implants.[34]

Complications of enucleation reported in the COMS during or <24 hours after surgery include pain, hemorrhage, nausea/vomiting, cardiovascular or pulmonary issues, urinary retention, fever, local surgical problems.[21] Complications 1 to 6 weeks after surgery included pain requiring longer hospital stay, pain requiring medication, conjunctival wound dehiscence, infection, decreased facial sensation, eyelid swelling, inflammation, implant displacement, loss of hair, ptosis, conjunctival chemosis, ecchymosis, and orbital or conjunctival hemorrhage.[21] Long-term follow-up has shown that other problems after enucleation include poor motility of prosthesis, poor alignment of prosthesis, severe ptosis, and displacement of implant.[21] Enucleation can also result in phantom eye syndrome, including visual sensations, seeing, and pain, which can be distressing to some patients.[35]

Pre-enucleation radiation is generally not used because results from a COMS randomized trial in large tumors (height ≥2 mm and diameter ≥16 mm; or height ≥10 mm and any diameter; or height ≥8, any diameter, if proximal tumor border <2 mm to optic disc) showed that pre-enucleation radiation had no impact on survival (death from melanoma metastasis, all-cause death) compared with enucleation alone,[21,36,37] confirming results of prior retrospective studies.[38] The COMS randomized trial for large tumors reported a 5-year tumor-related mortality of 28% for patients treated with enucleation.[36]

In a COMS randomized trial in medium choroidal melanoma tumors (height 2.5–10 mm, diameter ≤16 mm, no extrascleral extension ≥2.0 mm thick), outcomes (cumulative mortality, melanoma-specific mortality) for enucleation were similar to those for iodine-125 (^{125}I) brachytherapy.[39,40] For medium tumors, the 5-year disease-specific survival rate was 11% for patients treated with enucleation (14% and 5% for patients with tumor diameter >11 and ≤11 mm, respectively).[40] One prospective and several retrospective studies also found that survival was similar after enucleation versus cobalt plaque brachytherapy,[41–45] a mix of brachytherapy plaque types,[46] or proton-beam RT.[47] Retrospective studies suggest that outcomes (overall survival, metastasis-free survival, melanoma-related mortality) are similar for enucleation versus proton-beam radiation or stereotactic radiosurgery (SRS).[48–51] Despite the negative aspects of enucleation (relative to RT therapy), including worse effects on certain visual functions (peripheral vision, night driving, judging distances), greater decrease in role functioning, and larger reductions in physical and functional well-being, some studies have found that patients undergoing enucleation appear to have similar quality of life as those treated with RT.[52–57]

Based on results of the prospective studies comparing enucleation with brachytherapy, enucleation is generally only recommended for patients with tumors that are unsuitable for brachytherapy treatment, such as those that are too large to be effectively treated by commercially available plaques, or that have optic nerve involvement. For tumors such as these, enucleation is an option, but other types of RT (particle beam, stereotactic radiation) are also possibilities. Enucleation is sometimes reserved for cases that would be difficult to treat using only radiation, such as those with neovascular glaucoma, tumor replacing >50% of the globe, blindness, painful eyes, or extensive extraocular extension. In addition to use as a primary treatment, enucleation is also often used as a secondary

therapy for patients who develop local recurrence or complications after eye-sparing primary treatment.

Radiation Therapy

RT is the most commonly used first-line treatment for uveal melanoma,[12] because several approaches have been shown to have similar efficacy as enucleation for reducing the risk of metastasis and death from disease.[39–51] Brachytherapy and charged-particle RT are the RT modalities considered appropriate as primary therapy for most cases uveal melanoma, whereas photon RT and stereotactic radiation are less often used as primary treatment for uveal melanoma. SRS is sometimes used for large primary tumors, and photon RT is generally only used as an adjuvant to surgery.

Plaque Brachytherapy

Plaque brachytherapy is a commonly used form of definitive RT for the primary tumor.[13,14,58,59] Brachytherapy is often used (for localized primary uveal melanoma) based on results of a large prospective randomized COMS trial showing that long-term outcomes were not significantly different with plaque brachytherapy (n=657) versus enucleation (n=660) in patients with small- to medium-sized choroidal melanomas (2.5–10.0 mm in apical height [2.5–8.0 mm if peripapillary] and ≤16 mm in maximum basal diameter, no extrascleral extension ≥2.0 mm thick).[39,40] In this study, the 5-year risk of treatment failure after brachytherapy was 10.3%.[60] Treatment failure was defined as tumor expansion (≥15% increase in height, ≥250 μm in any tumor boundary) or extrascleral extension (>2 mm). Risk factors for treatment failure were older age, greater tumor thickness, and proximity of the tumor to the foveal avascular zone. Other more recent studies have reported local failure rates ranging from 0% to approximately 20% for patients treated with ^{125}I plaques, and local failure rates were in this range for patients treated with other types of brachytherapy plaques (ruthenium-106, palladium-103, cesium-131).[8,61–64] It is important to note that late treatment failures (up to 12 years) after brachytherapy have been observed.[63]

In the COMS randomized trial in medium choroidal melanoma tumors (height 2.5–10.0 mm, diameter ≤16 mm, no extrascleral extension ≥2.0 mm thick), after a minimum of 5 years of follow-up (range, 5–15 years), there were no treatment-dependent differences in all-cause mortality or death with confirmed melanoma metastasis.[40] There was no difference across arms in the rate of death with histologically confirmed metastasis (enucleation vs brachytherapy, respectively: 11% vs 10% at 5 years and 17% vs 18% at 10 years) or all-cause mortality (19% at 5 years and 35% at 10 years in each arm).[40] The only factors correlated with these outcomes were age and maximum basal diameter, but even after adjustment for these variables, there were no treatment-dependent differences in all-cause mortality or mortality with confirmed melanoma metastasis at time of death.[40]

In the COMS randomized trial in medium choroidal melanoma tumors, intraoperative/immediate postoperative complications observed with similar frequency across brachytherapy and enucleation arms included anesthetic complications; pain requiring medication; other hemorrhage; cardiovascular or pulmonary problems; urinary problems; and local surgical problems.[39] Immediate complications seen only in the brachytherapy arm included intraocular hemorrhage, scleral perforation, and vortex vein rupture.[39] In the brachytherapy arm, the most common long-term complications were loss of visual acuity and growth of tumor or other indications that lead to enucleation.[39] After 3 years of follow-up, approximately half of the patients (49%) treated with brachytherapy lost ≥6 lines of visual acuity (compared with before treatment), and among patients with visual acuity better than 20/200 before treatment, 43% had visual acuity of 20/200 or worse.[65] Factors associated with loss of visual acuity included greater baseline tumor apical height, shorter distance between the tumor and the foveal avascular zone, presence of tumor-associated retinal detachment, non–dome-shaped tumor, and patient history of diabetes.[65] During the first 5 years of follow-up, cataracts developed in 68% of eyes treated with brachytherapy and 12% had undergone cataract surgery.[66] Cataract surgery resulted in visual acuity improving by ≥2 lines in 66% of patients and stabilizing in 26%.[66] The 5-year cumulative rate of enucleation was approximately 12%,[39,60] most often due to treatment failure during the first 3 years after brachytherapy and to eye pain beyond 3 years after treatment.[60]

When evaluating patients for brachytherapy, it is important to consider the entry criteria and treatment parameters used in the COMS randomized trial that compared brachytherapy with enucleation, which included only patients with tumors that were choroidal[39]; those with tumors contiguous with the optic disc were excluded, as were those with metastases from melanoma or another cancer (except nonmelanoma skin cancers).[40] Only 16% of patients had tumors <2.0 mm from the optic disc.[39] Most of the tumors included were dome-shaped on B-scan ultrasound (77%), and approximately half had nonrhegmatogenous retinal detachment (54%–55%); a few (<1%) had rhegmatogenous retinal detatchment.[39]

Prospective studies in patients with small choroidal tumors treated with ^{125}I brachytherapy also found that most patients experienced tumor regression (98%),[67] <3% experienced recurrence, and 98% achieved globe conservation.[68] Melanoma-specific mortality at 5 years was 3.9%.[68]

Although the plaques used in the COMS randomized trial were all ^{125}I, one prospective and several retrospective studies also found that survival was similar after

enucleation versus cobalt plaque[41–45] or a mix of brachytherapy plaque types.[46] A meta-analysis of studies testing ruthenium plaques in patients with uveal melanoma reported a 5-year melanoma-related mortality rate of 6% for small and medium tumors (T1/T2) and 26% for large tumors (T3).[69] Palladium-103 brachytherapy plaques also appear to perform similarly to ^{125}I plaques.[70]

Recent prospective studies aimed at identifying factors associated with loss of visual acuity after brachytherapy have had varying results. Factors identified in ≥1 studies include applicator size, tumor basal diameter, juxtapapillary location, dose (close to foveola, or retinal), increased tumor height, radiation maculopathy, and radiation optic neuropathy.[71–73] Some studies have reported adjustments to technique that may reduce the risk of vision decline.[64] One prospective study of 650 patients with medium-sized choroidal melanoma found that retinal hemorrhage in the macular and peripapillary zone, optical disc hemorrhage, microaneurysms, and foveal retinal pigment epithelium atrophy were more prevalent and severe after brachytherapy than before treatment.[74] Macular angiographic leakage tended to worsen after brachytherapy, and optic neuropathy was present in 27% of patients 5 years after treatment.[74]

NCCN Recommendations

Plaque brachytherapy is appropriate as an upfront therapy after initial diagnosis, or after local recurrence following a prior local therapy. Plaque brachytherapy is appropriate for patients with tumors ≤18 mm in largest base diameter and ≤10 mm in thickness, based on the size of the largest commercially available plaques. The plaque margin on the tumor border should be ≥2 mm when feasible (diameter of plaque ≥4 mm larger than largest base diameter of tumor; the plaque should cover the tumor with a ≥2-mm circumferential margin). The exception is for tumors near the optic nerve where it may be impossible to achieve adequate coverage of the margins. The largest commercially available brachytherapy plaque is 22 mm in diameter; thus, plaque brachytherapy is recommended only for tumors with largest basal diameter ≤18 mm. Brachytherapy plaque is a recommended first-line option for all tumors that have a largest diameter of at least 5 mm but no more than 18 mm, with thickness up to 10 mm. Round plaques are most commonly used, although nonround plaques (eg, notched) can be considered for tumors in specific locations (eg, peripapillary). Preliminary data from a prospective study suggest that slotted plaques provide local control of choroidal melanomas adjacent to the optic nerve, but with a high risk of radiation optic neuropathy.[75] Plaque brachytherapy should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and brachytherapy physicist.[76] Tumor localization for brachytherapy may be performed using indirect ophthalmoscopy, transillumination, light pipe diathermy, and/or ultrasonography (intraoperative and/or preoperative).[77] MRI may be used for preoperative planning. A summary of NCCN recommendations regarding brachytherapy, as well as recommended dosing, can be found on UM-B, 1 of 3 (available at NCCN.org).

Particle Beam RT

Particle beam RT includes radiation with protons, carbon ions, or helium ions and is a common form of definitive RT for the primary tumor.[58] Prospective studies and a systematic review found that disease-specific survival in patients with uveal melanoma treated with particle beam RT was similar or better compared with those treated with plaque brachytherapy.[78–80] Compared with brachytherapy, particle beam RT was associated with higher rates of local control and similar or lower rates of enucleation during follow-up.[78–80] Across studies, local recurrence rates reported with charged-particle therapy ranged from 3% to 10%.[8,81] However, multivariate analysis of a real-world database found that treatment with protons was associated with poorer overall survival compared with brachytherapy treatment.[82]

Decrease in visual acuity and loss of vision can occur with particle beam RT.[81,83] Toxicities include vitreous hemorrhage, subretinal exudation in macula, posterior subcapsular opacity, radiation keratopathy, rubeosis/neovascular glaucoma, radiation maculopathy, and papillopathy.[81,84]

NCCN Recommendations

Particle beam RT should be performed by an experienced multidisciplinary team including an ophthalmic oncologist, radiation oncologist, and particle beam physicist.[85] In settings where the appropriate expertise is available, particle beam therapy (proton, carbon ion, or helium ion) is appropriate as upfront therapy after initial diagnosis, after margin-positive enucleation, or for intraocular or orbital recurrence. It is important that the clinical team have experience treating uveal melanoma with the specific type of particle beam used (proton, carbon ion, or helium ion). Particle beam RT is an option regardless of the size of the primary lesion, and is the preferred method of RT for tumors that are too large or too near the optic nerve to be effectively treated with brachytherapy. Tumor localization for particle beam RT may be performed using indirect ophthalmoscopy, transillumination, and/or ultrasonography (intraoperative and/or preoperative), MRI, and/or CT. Recommendations regarding particle beam RT, as well as recommended dosing, can be found on UM-B, 1 and 2 of 3 (available at NCCN.org).

Stereotactic Radiation

Stereotactic radiation includes both single-fraction and hypofractionated stereotactic techniques, referred

to collectively as SRS in these NCCN Guidelines. Compared with brachytherapy and particle beam RT, there are fewer prospective comparative study data on SRS for treatment of primary uveal melanoma. Available data suggest that SRS may be as effective as other radiation modalities, but may also be associated with a higher risk of complications. One series that compared SRS with ^{125}I brachytherapy found that rates of tumor recurrence, distant metastasis, and secondary enucleation were similar across treatments.[86] Risk of cataract appeared similar across treatments, but SRS appeared to be associated with higher rates of certain complications, including neovascular glaucoma, radiation retinopathy, and radiation papillopathy.[86,87] Another study also reported similar rates of local control with brachytherapy versus SRS.[88] A retrospective study comparing ruthenium-106 brachytherapy versus SRS found a nonsignificant trend toward increased secondary glaucoma after SRS.[89] A retrospective study comparing SRS versus proton beam RT reported similar rates of local control and eye retention across treatment, but higher rates of visual acuity decline with SRS.[90]

Studies using SRS as primary treatment of uveal melanomas have reported local failure rates ranging between 2% to 16%.[8,86,88,90–104] Rates of 5-year metastasis-free survival after SRS ranged from 69% to 84%.[86,92,94,105] Overall survival 5 years after SRS has been reported to be 55% to 98%.[93,94,99,105,106] These large ranges likely reflect differences in the populations studied; thus, in the absence of randomized trial data it is difficult to know whether these outcomes are better or worse than those reported for other treatment modalities.

In studies testing SRS as primary treatment of uveal melanoma, eye retention rates ranged from 73% to 98%.[90,93,96,98–101,104–108] In addition to causing decline in visual acuity, complications associated with SRS reported across multiple studies include cataracts, neovascular glaucoma, radiation retinopathy, radiation papillopathy, radiation maculopathy, hemorrhage, macular edema, optic neuropathy, and keratitis sicca (dry eye).[86,87,92,93,95,96,101–103,108–112] Some studies have linked the rate and/or severity of complications to the radiation dose, tumor location, tumor size, and visual acuity before treatment.[95,98,101,110,113,114]

NCCN Recommendations

Due to the lack of randomized prospective data (compared with other RT techniques described earlier), SRS is the least often used form of definitive RT for the treatment of primary or recurrent intraocular tumors. Like particle beam RT, SRS can be used to treat large choroidal melanomas. The choice between these 2 options generally depends on the radiation oncology facilities available. In rare cases when both particle beam RT and SRS facilities are available, some NCCN panel members prefer particle beam RT because of more supporting data for this approach. Tumor localization, fiducial marker use, and planning for SRS are generally consistent with particle beam RT approaches. Using fractionated SRS, 45 to 70 Gy in 2 to 5 fractions should be prescribed. Using single-fraction SRS, 18 to 45 Gy in 1 fraction should be prescribed (UM-B, 2 of 3, available at NCCN.org).

Treatment of Extraocular/Extrascleral Extension

Extraocular/extrascleral extension has been reported to be present in approximately 3% of patients at uveal melanoma diagnosis,[115–118] is more common among tumors with higher T stage (12% of T4 tumors),[9] and is associated with poor prognosis.[7,10,119–122] Extrascleral/extraocular extension can be detected by preoperative imaging, or found or confirmed at the time of enucleation.[21,123] Sometimes the evidence of extraocular extension is microscopically positive or close margins after enucleation, without clinical, intraoperative, or radiographic evidence of gross residual disease to the orbit. In other cases, extraocular tumor is visible intraoperatively or intraoperative findings suggest that there may be gross disease to the orbit. In the COMS trial of patients with large uveal melanomas that tested enucleation with versus without pre-enucleation radiation, unexpected extrascleral extension was found in 2% of patients who underwent enucleation, despite extensive clinical and imaging workup.[21,37]

Orbital Exenteration

Orbital exenteration is surgical removal of the globe and adjacent orbital contents, for cases with extraocular extension and/or orbital invasion.[18,76,124–127] Retrospective studies of large databases suggest that exenteration is used in <1% of patients,[10] and among patients undergoing enucleation, 2.5% need orbital exteneration.[128] The value of orbital exenteration is disputed in the literature, largely based on low-quality data such as case reports and retrospective studies. Some studies support orbital exenteration because it provided superior outcomes to other (nonsurgical) approaches,[129] whereas others report poor outcomes after orbital exenteration, arguing that it may not be justified.[130,131]

RT for Extraocular/Extrascleral Extension

A retrospective study (n=202) found that in patients treated with enucleation, postoperative RT improved survival, particularly in young patients (age <30 years) and those with choroidal tumor height >3 mm.[128] Another retrospective study (n=17) reported a local recurrence rate of 6% in patients with extrascleral extension who were treated with enucleation followed by adjuvant external-beam RT to the orbit.[132] For patients with limited extraocular extension <3 mm thick, brachytherapy may also be an option based on a retrospective study (n=17) showing no intraocular or extraocular

tumor relapse after a median follow-up of 63 months (range, 23–164 months).[133]

NCCN Recommendations for Treatment of Localized Uveal Melanoma

After workup and staging, patients with localized uveal melanoma should be treated. Treatment options depend on tumor size (diameter and thickness) and proximity to the optic nerve (UM-2, page 122).

Tumor Size: Largest Diameter 5–18 mm and Thickness <2.5 mm

For thin tumors (<2.5 mm) with largest diameter ranging from 5 to 18 mm, recommended preferred primary treatment options are brachytherapy plaque or particle beam RT. For patients who are not good candidates for brachytherapy or particle beam RT, other options to consider include laser therapy or enucleation.

Tumor Size: Largest Diameter ≤18 mm and Thickness 2.5–10 mm

Brachytherapy and particle beam RT are also options for treating tumors with largest diameter ≤18 mm and thickness 2.5 to 10 mm. If there is concern that adequate response was not achieved from initial radiation, then further treatment should be considered. Recommended options for further treatment include laser therapy or cryotherapy. In highly select cases, resection is sometimes considered. Tumors in this size range may also be treated with enucleation. Although there is a trend toward avoiding enucleation, it is recommended for patients with neovascular glaucoma, tumor replacing >50% of globe, or blind, painful eyes. Enucleation should also be considered in cases of extensive extraocular extension.

Tumors Not Appropriate for Brachytherapy

Given the limitations in the size and RT penetrance of commercially available brachytherapy plaques (diameter ≤22 mm), this method is not appropriate (and not recommended) for tumors that are too large in diameter (>18 mm; any thickness), too thick (>10 mm; any diameter), or have optic nerve involvement and thickness >8 mm (any diameter). RT options for such tumors include particle beam RT and SRS. The choice between these 2 RT modalities usually depends on which modality is available at the treating institution. In the rare scenario that the institution has both SRS and particle beam facilities, some practitioners would opt for particle beam because there are more data supporting its efficacy. Enucleation is also a recommended option, especially in cases with extensive extraocular extension, neovascular glaucoma, tumor replacing >50% of globe, or blind, painful eyes.

Additional Treatment Considerations

An essential feature of high-quality care is that clinical decisions are informed by a variety of case-specific factors (eg, patient preferences and characteristics, such as age; status of the other eye; disease characteristics; medical history), such that for some patients the best clinical approach may not be one of the listed options. The recommended treatment options are largely based on data from choroidal melanomas. For small ciliary body and iris tumors (<3 clock hours), surgical excision may be considered.

Additional Primary Treatment of Extraocular Extension

For patients with limited extraocular extension, brachytherapy with scleral patch graft should be considered. For patients treated with enucleation for their primary tumor, additional treatment may be needed if extraocular extension is present (UM-3, available at NCCN.org). For patients with microscopically positive or close margins after enucleation, but no clinical, intraoperative, or radiographic evidence of gross residual disease to the orbit, recommended options include observation (no further treatment), mapping biopsy, and/or consideration of RT to the orbit (using particle beam or photon beam therapy). For patients with visible extraocular tumor or suspicion of gross disease in the orbit at the time of enucleation, biopsy of the extraocular tissue is recommended, if possible. Additional treatment options to consider include one or more of the following: intraoperative cryotherapy, orbital exenteration, and/or RT to orbit using particle beam or photon beam therapy. For photon or proton beam RT to the orbit (after enucleation), a dose of 20 to 30 Gy in 5 fractions should be prescribed to the clinical target volume at risk for recurrence[21,134] using intensity-modulated or conformal techniques with image guidance.

NCCN Recommendations for Treatment of the Primary Tumor in Patients With Metastatic Disease

Palliative local therapy to the primary tumor may be considered in the setting of metastatic disease. In general, if the metastatic disease is being treated, the primary tumor should also be treated. Patients who present with advanced metastatic disease and limited life expectancy may elect to have no treatment to their primary tumor. Recommendations for treatment of distant metastatic disease in patients with uveal melanoma can be found on UM-6 (available at NCCN.org).

Conclusions

Most uveal melanomas are localized at first presentation, and local treatment of primary uveal melanoma is effective in preventing local recurrence in most patients but fail to prevent distant metastasis. Although historically most primary uveal melanomas were treated with surgery, RT has been shown to be equally effective, and is

now more widely used than surgical approaches. Due to technical limitations with RT approaches, selection of primary treatment depends largely on the size and location of the primary tumor. Clinical decisions should also take into account case-specific factors (eg, patient preferences and characteristics, such as age; status of the other eye; disease characteristics; medical history).

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