Guideline Resource Unit
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Literature Review: Uveal Melanoma

Tumour Team: Cutaneous

Cancer Care Alberta

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Table 1: Initial Management of Uveal Melanoma

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
Ho, 2017[1]	Prospective ***(Level III)***	Hydroxyapatite (HA) Vs acrylic implants (AC)	UM enucleation pts b/w May 2005-Nov 2012, Liverpool Ocular Oncology Centre, UK (n=218)	No major differences b/w HA and AC implants in surgical outcomes and pt satisfaction	n/a	Higher prevalence of ptosis w AC and greater need of ocularist visits w HA at around 6 mos.
Eibl-Linder, 2016[2]	Prospective ***(Level III)***	Frameless, single-session, image-guided robotic radiosurgery (median dose: 20 Gy)	Unilateral UM (n=217)	3-yr eye retention: 86.7% (95%CI: 79.9-91.3%) 5-yr eye retention: 73.0% (95%CI: 58.1-83.3%)	Actuarial disease-specific survival: 3 yrs.: 84.8% (95% CI: 77.0–90.1) 5 yrs.: 78.4% (95% CI: 67.1–86.2)	Glaucoma (n=33), hemorrhage (n=26), macular edema (n=7)
Willerding, 2016[3]	retrospective ***(Level IV)***	Neoadjuvant proton beam RT followed by transscleral resection	UM pts (n=106)	Local recurrence: 3-yr:4.2%, 5-yr:10.4% Enucleation: 3-yr: 9.2%, 5-yr: 18.4%	Metastasis free survival: 3-yr: 28.4%, 5-yr: 40.3%	Median visual acuity: Pre-Tx: 20/50 Post-Tx: 20/400 Vitreoretinal surgery: 28.3%
Mishra, 2015[4]	phase III ***(Level I)***	Charge particle RT, n=86 vs iodine-125 plaque therapy, n=98	Choroidal and ciliary body melanoma, n=184 Median F/U times for particle and plaque arm 14.6 yrs. and 12.3 yrs., respectively (p=0.22), and for those alive at last	Local control for particle *vs* plaque Tx 100% vs 84% at 5 yrs., and 98% vs 79% at 12 yrs., respectively (log rank: p=0.0006) If pts w tumours close to disc (was lower after charged particle RT: 11% vs 22% at 5 yrs.	Using Cox regression model, likelihood ratio test, Tx most important predictor of local control (p=0.0002) and eye preservation (p=0.01) Charge particle RT significant predictor of prolonged DFS (log rank: p=0.001)	n/a

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
			F/U, 18.5 and 16.5 yrs. respectively (p=0.81)	and 17% vs 37% at 12 yrs., respectively (log rank: p=0.01)		
Takiar, 2014[5]	retrospective, ***(Level IV)***	Ruthenium-106 (^{106}Ru) compared to iodine-125 (^{125}I) brachytherapy	UM pts treated w ^{106}Ru (n=40) or ^{125}I (n=67) plaque brachytherapy b/n 2000-2008	^{125}I *vs* ^{206}Ru 5-yr LC: 83% *vs* 92% 5-yr enucleation rate: 13.4% *vs* 0%	^{125}I *vs* ^{206}Ru 5-yr OS: 80% *vs* 92% 5-yr PFS: 65% *vs* 94% 5-yr EFS: 87% *vs* 100% ^{106}Ru displays significantly improved PFS (p=0.02) and EFS (p=0.02) vs ^{125}I	^{125}I *vs* ^{106}Ru Radiation retinopathy: 26% vs 20% (p=0.03) Decreased visual acuity: 21% vs 15 % (p=0.05) Cataracts: 13% vs 1% (p<0.01)
COM Study Group, 2004, 1998	Randomized controlled trial ***(Level I)***	Pre-enucleation (n=497) vs enucleation alone (n=506)	Large choroidal melanoma (>10 mm in apical height and >16 mm in basal diameter), n=1003	576/1003 pts died w/n 10 yrs. after enrollment 10-yr. all-cause mortality rates 61% for pts in both Tx arms 10-yr. rates of death w histopathologically confirmed melanoma metastasis 45% in pre-enucleation RT arm and 40% in enucleation alone arm Older age and larger max. basal tumour diameter primary predictors of time to death from all causes and death w melanoma metastasis No differences in unadjusted or adjusted mortality rates found b/n Tx arms 32% pts eligible for 10 yrs. of F/U alive and clinically cancer-free 10 yrs. after Tx		
COM Study Group, 2006, 2001	Randomized controlled trial ***(Level I)***	Brachytherapy w iodine-125 (n=657) vs enucleation (n=660)	Medium choroidal melanoma (2.5–10 mm in apical height and ≤16 mm in basal diameter), n=1317	471/1317 pts died w/n 12 yrs. after enrollment 231/515 (45%) pts eligible for 12 yrs. of F/U alive and clinically cancer free 12 yrs. after Tx For pts in both Tx arms, 5- and 10-yr. all-cause mortality rates 19% and 35%, respectively; by 12 yrs., cumulative all-cause mortality 43% among pts in (125)I brachytherapy arm and 41% among those in enucleation arm 5-, 10-, and 12-yr. rates of death w histopathologically confirmed melanoma metastasis 10%, 18%, and 21%, respectively, in (125)I brachytherapy arm and 11%, 17%, and 17%, respectively, in enucleation arm Older age and larger max. basal tumour diameter were primary predictors of time to death from all causes and death w melanoma metastasis		
COM Study Group, 1997, 1997	Non-randomized prospective observational ***(Level IV)***	Observation	N=204, pts w choroidal melanoma too small to be eligible for COMS randomized trials (i.e., 1-3 mm in apical height and ≥	Median length of F/U 92 mos. 8% of pts treated at time of study enrollment and additional 33% treated during F/U 27 pts died; 6 deaths reported as due to metastatic melanoma. Kaplan-Meier estimate of 5-yr. all-cause mortality 6.0% (95% CI, 2.7%-9.3%) and 8-yr. all-cause mortality 14.9% (95% CI, 9.6%-20.2%)		

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
			5 mm in basal diameter)	46/188 grew during F/U to size large enough to be eligible for COMS clinical trials Kaplan-Meier estimates of proportion of tumours that grew were 21% (95% CI 14%-27%) by 2 yrs. and 31% (95% CI, 23%-39%) by 5 yrs. Factors significantly associated w time to growth = greater initial tumour thickness and diameter, presence of orange pigment, absence of drusen, and absence of areas of retinal pigment epithelial changes adjacent to tumour.		

AC, acrylic implants; COMS, The Collaborative Ocular Melanoma Study Group; DFS, disease free survival; LC, local control; EFS, enucleation-free survival; F/U, follow-up; HA, hydroxyapatite; PFS, Progression-free survival; RT, radiation therapy; OS, overall survival; UM, uveal melanoma

Table 2. Adjuvant - High-Risk Uveal Melanoma

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
Chemotherapy						
Binkley, 2020	prospective ***(Level III)***	Low-dose dacarbazine (850mg/m^2 IV days 1 and 28) and interferon-alpha-2b (3 million units SC tid/wk. for 24 wks. beginning at wk. 9) following primary therapy	Iris, ciliary body or choroidal melanoma w high-risk tumour cytogenetics (monosomy 3) Tx group: n= 33 patients Observation group: n=29	Not reported	5-yr metastasis-free survival: Tx group 64% ±9% *vs* observation group 33% ±10%, p=0.05 5-year OS rate: Tx group 66% ±9% *vs* observation group 37%±10%, p=0.02	Grade 1/2: fatigue (n=33), elevations in hepatic transaminases (n=14), depression (n=5) Grade-3 hematological toxicity observed (n=6) while on interferon-alpha-2b that was dose-limiting No grade 4 AEs
Valsecchi, 2018	retrospective ***(Level IV)***	Sunitinib for 6 mos, n=54 compared w institutional historical controls w same risk factors, n=74	Confirmed monosomy 3 and 8q or Class II. Excluded pts diagnosis before 2007 or after 2013, Sunitinib group worse cytogenetic or molecular features (monosomy 3 and 8q amplification or class 2 87% vs. 57%; p<0.001), smaller tumour sizes (T3–4 56% vs. 83%; p=0.001), and younger	Not reported	Median F/U 52.7 mos Deaths: 14 (26%) in sunitinib vs 37 (50%) in control Sunitinib group had longer OS (HR, 0.53; 95% CI, 0.29–0.99; p=0.041) Interaction b/n use of sunitinib and age as dichotomous variable highly significant (p=0.003) Variables statistically associated w prediction of OS: cytogenetic/ molecular status (p=0.015), T-size category (p=0.022), gender	No deaths attributed to sunitinib toxicity. 3 pts could not complete 6-mo course of sunitinib Tx b/c of development of systemic metastasis (n =1) and toxicity (n=2)

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
					(p=0.040), and adjuvant sunitinib in pts aged <60 yrs. (p=0.004)	
Bol, 2016[39]	phase II ***(Level II)***	Autologous, monocyte-derived dendritic cells transfected w gp100 & tyrosinase mRNA (3 biweekly ID & IV	High-risk UM pts w monosomy 3 (n=23) (distant mets excluded)	Primary myeloid DC vaccination is feasible and safe Effective antitumour immune responses which coincides w improved PFS	DFS (med): 34.5 mos. (95% CI: 27.2-41.8) 3-yr DFS: 47% OS (med): 51.8 mos. (95% CI: 27.2-41.8) 3-yr OS: 79%	Grade 1-2: Flu-like symptoms (91%), erythema at injection site (87%), Vitiligo (1) No grade 3-4 toxicities

Table 3. Adjuvant - Metastatic Uveal Melanoma

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
Chemotherapy						
McWilliams, 2018 (NCCTG N0879 [Alliance])[6]	phase II ***(Level II)***	Arm A: carboplatin AUC 5 IV, day 1 q 28 days, paclitaxel 80 mg/m^2 IV days 1,8, and 15, and bevacizumab 10mg/kg IV days 1 and 15 (n=16) Arm B: above regimen and everolimus 5 mg days 1–5, 8–12, 15–19, and 22–26 q 28 days (n=10)	Stage IV malignant melanoma not amenable to surgery, ≤1 prior chemo regimen UM (n=25 evaluable)	PR: 1 pt in Arm A	PFS (med): Arm A, 5.6 mos. vs. Arm B, 4.5 mos. Pts w UM had efficacy outcomes similar to those of pts w melanoma of cutaneous origin, w PFS of >5 mos. regardless of Tx arm (95% CI, 3.8-9.1 mos.)	Due to neutropenia and other related toxicities, everolimus dose decreased to 5 mg three times weekly
Schinzari, 2017	phase II ***(Level II)***	Cisplatin (80 mg/m^2) + dacarbazine (250 mg/m^2 daily for 3 days) + vinblastine (2 mg max) q 21 days	UM (n=25)	PR:5 pts SD: 12 pts PD: 8 pts	OS (med): 13 mos. PFS (med): 5.5 mos. Responsive pt OS: 21 mos. Progressive pt OS: 7 mos. Cumulative OS (disease controlled): 18 mos.	Grade 3-4: 20%
Bhatia, 2012 (SWOG S0512)[7]	phase II ***(Level II)***	Carboplatin (AUC 6) + paclitaxel (225 mg/m^2) IV on day 1 plus sorafenib (400 mg) PO twice daily x 6	Stage IV UM w/ 0-1 prior systemic therapy (n=25)	Overall: 0% (95% CI 0-14%)	PFS (med): 4 mos. (95% CI 1-6 mos.) PFS (6-mos.): 29% (95% CI 13%-48%) OS (med): 11 mos. (95% CI 7-14 mos.)	

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
Homsi, 2010[8]	phase II ***(Level II)***	Docosahexaenoic acid (DHA)-paclitaxel (500 mg/m²/wk.) IV for 5 wks. (6-wk cycles)	Metastatic UM chemo-naive or previously treated (n=22)	SD: 32%	OS (med): 9.8 mos.	neutropenia: 23% musculoskeletal pain: 10%
O'Neill, 2006[9]	phase II ***(Level II)***	Dacarbazine (850 mg/m^2) plus treosulfan (8 g/m^2) q 3 wks. for max of 6 cycles (1st line)	Metastatic UM (n=15)	Overall: none SD: 2 pts	DFS (med): 12 wks. OS (med): 30 wks.	Major toxicities were hematological (particularly thrombocytopenia)
Schmittel, 2006[10]	phase II ***(Level II)***	1. Gemcitabine (1000 mg/m^2) + treosulfan 2. Treosulfan alone (3500 mg/m^2)	Metastatic UM chemo-naive (n=48)	SD: 7 pts in gem-T group vs. 3 pts in treosulfan group (p=.08) PR: 1 pt in gem-T group vs. none in treosulfan group	PFS (med): 3 mos. (95% CI 1.1-4.9) for gem-T vs. 2 mos. (95% CI 1.7-2.3) for T (p=.008) PFS (12-mos): 16.7% for gem-T vs. 0% for T PFS (6 mos.): 34.8% for gem-T vs. 17.9% for T	Grade 3-4: Leukopenia: 4 gem-T vs. 0 T Nausea: 3 gem-T vs. 3 T Febrile neutropenia: 2 gem-T vs. 0 T
Schmidt-Hieber, 2004[11]	phase II ***(Level II)***	Bendamustine (120 mg/m^2 days 1 and 2) q 3 wks.	Metastatic UM; progression during or after 1st line chemo (n=11)	PD: all 11 pts	n/a	Grade 3-4: Anemia (2 pts) Thrombocytopenia (1 pt) Leukocytopenia (2 pts)
Kivelä, 2003[12]	phase II ***(Level II)***	Bleomycin, vincristine, lomustine, dacarbazine q4 w x 2 cycles + IFN alpha-2b (3 x 10^6 IU)	Metastatic UM (n=24)	objective response: 0% SD: 2 pts (8.3%) PD: 20 pts	PFS (med): 1.9 mos. (95% CI: 1.8-3.4 mos.) OS (med): 10.6 mos. (95% CI: 6.9-16.4 mos.)	Grade 3: alopecia and neurotoxicity in 13% of pts
Bedikian, 2003[13]	phase II ***(Level II)***	Temozolomide (75 mg/m^2 per day orally for 21 days) q 4 wks.	Metastatic choroidal melanoma (n=14)	CR: none PR: none SD: 2 pts	n/a	n/a
Pyrhönen, 2002[14]	phase II ***(Level II)***	Bleomycin, vincristine, dacarbazine, lomustine q 4 wks. + interferon (3 x 10^6 IU)	Metastatic UM stage IVB (n=20)	PR: 3 (15%; 95% CI 0-38) SD: 11 (55%; 95% CI 32-77) after 2+ cycles	Stage IVBa: 17 mos. (95% CI 4-37) Stage IVBb: 11 mos. (95% CI 1-23)	Grade 3-4 hematologic toxicity, either leukopenia or thrombocytopenia
Becker, 2002[15]	phase II ***(Level II)***	Fotemustine (100 mg/m^2) into hepatic artery or peripheral vein	Metastatic ocular melanoma (n=48)	Objective response: 21.7% for intra-arterial vs. 8% for peripheral vein	OS (med): 369 days for intra-arterial vs. 349 days for peripheral vein	n/a
Immune Checkpoint Inhibitors						
Pelster, 2021[16]	phase II ***(Level II)***	Nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) for 4 cycles, followed by nivolumab	Metastatic UM (n=33)	ORR was 18%, including one confirmed complete response and five confirmed partial responses.	PFS (med): 5.5 mos. (95% CI, 3.4-9.5 mos.) OS (med): 19.1 mos. (95% CI, 9.6 mos.-not reported)	40% of pts experienced grade 3-4 Tx-related AE

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
		maintenance therapy for up to 2 yrs.				
Nathan, 2019 (CheckMate 172)[17]	phase II ***(Level II)***	Nivolumab (3 mg/kg q 2 wks. up to 2 yrs.)	Advanced ocular melanoma who progressed on or after ipilimumab (n=130)	Not reported	Median OS (in mos.) 12.6 (95% CI, 10.2-15.1) for ocular melanoma w 18-mos. OS rate of 34.8% (95%CI, 24.8-45.0)	Tx-related serious AEs, Grade 3/4, n=3 (2.9%)
Rossi, 2019[18]	prospective ***(Level III)***	Pembrolizumab (2 mg/kg q.3wk.i.v.)	Advanced UM (n=17)	PR: 2 pts SD: 6 pts PD: 9 pts No CR	PFS: 3.8 mos. >5 yr. from diagnosis to metastasis PFS: 9.7 mos. <5 yr. from diagnosis to metastasis PFS: 2.6 mos. (HR: 0.2865, 95% CI: 0.0869-0.9443, p=0.039)	No grade 3-4 effects
Mouriaux, 2016[19]	phase II ***(Level II)***	Sorafenib (400 mg b.i.d. PO)	Metastatic UM (n=32)	24-wk non-progression: 31.2%	24-wk PFS: 31.2% (95% CI: 14.8-47.6%) 24-wk OS: 62.5% (95%CI: 45.4-79.6%, p>0.05)	Grade 3: 20 AE reported in 10 pts 41.2% of pts required dose modifications due to toxicities
Joshua, 2015[20]	phase II ***(Level II)***	Tremelimumab (15 mg/kg IV) on day 1 of 90-day cycle	Unresectable stage III or IV UM w/o prior immunotherapy (n=11)	Response rate: 4.3% Disease control rate: 31.9%	PFS (med): 2.9 mos. = (95% CI: 2.8-3.0) 6-mo PFS: 9.1% OS (med):12.8 mos. (95% CI: 3.8-19.7)	Grade 3 or 4: rash (9.1%), nausea (18.2%), diarrhoea (27.3%)
Zimmer, 2015 (DeCOG-Study)[21]	phase II ***(Level II)***	Ipilimumab (3 mg/kg q.3wk.i.v.) up to 4 cycles	Pretreated and Tx-naïve metastatic UM pts (n=53)	Disease control rates: 12 wk.: 47% 24 wk.: 21% SD: 47% No PR or CR	1-yr OS: 22% 2-yr OS: 7% OS (med): 6.8 mos. (95% CI: 3.7-8.1) PFS (med): 2.8 mos. (95% CI: 2.5-2.9)	Grade 3-4: 19 AE (36% of all AEs) 1 death (pancytopenia)
Molecularly Targeted Agents						
Luke, 2020 (Alliance A091201)[22]	phase II ***(Level II)***	Arm 1: cabozantinib *vs* temozolomide Arm 2: dacarbazine Arm 2X: Cross-over from Arm 2 to cabozantinib	Metastatic UM (n=46) Arm 1: n=31 Arm 2: n=15 Arm 2X: n=9	Arm 1: 0/31* Arm 2: 0/15 *1 unconfirmed response	PFS at 4 mos.: Arm 1 and Arm 2 were 32.3% and 26.7% (p=0.35), respectively, w median PFS time of 60 and 59 days (p=0.964; HR=0.99) Median OS was 6.4 mos. and 7.3 mos. (p=0.580; HR=1.21), respectively	Grade 3–4 CTCAE AEs Arm1: 61.3% Arm 2: 46.7% Arm2X: 37.5%
Shah, 2018[23]	phase II ***(Level II)***	A: Ganetespib (200 mg q wk.) vs	Stage IV UM w/o prior chemo (n=17) A: n=7	PR:1 pt SD: 4 pts PD: 11 pts	PFS: 1.6 mos. (cohort A), 1.8 mos. (cohort B) OS: 8.5 mos. (cohort A), 4.9 mos. (cohort B)	Grade 3: 17 events in 11 pts, Grade 2: 43 events in 14 pts 2/3rd of AEs GI related

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
		B: Ganetespib (150 mg q wk.)	B: n=10	ORR: 5.9% DCR: 29.4%		
Carvajal, 2018 (SUMIT)[24]	phase III ***(Level I)***	A: Selumetinib (75 mg b.i.d. PO + dacarbazine (1000 mg/m^2/ 21-day cycle IV) vs B: Dacarbazine + placebo	Stage IV UM w/o prior systemic therapy (n=129) A: n=97 B: n=32	No significant improvement of PFS compared w placebo + dacarbazine	HR (PFS): 0.78 (95% CI: 0.48–0.27, p=0.32) HR (OS): 0.75 (95% CI: 0.39–1.46, p=0.4)	Nausea: 62% vs 19% Rash: 57% vs 6% Fatigue: 44% vs 47% Diarrhea: 44% vs 22% Peripheral edema: 46% vs 6%
Daud, 2017[25]	phase II ***(Level II)***	Cabozantinib 100 mg/day during 12-wk. lead-in. Pts w SD per Response Evaluation Criteria in Solid Tumours (RECIST) at wk 12 randomized to cabozantinib or placebo	Metastatic UM (n=23), hepatic mets present in (n=16/23)	13/22 pts evaluable for change in measurable disease had ≥ 1 Ax showing reduction of measurable target lesions SD: 14/23 pts at 12 wks. PR: 0 pts Overall DCR: 61%	PFS (med): 4.8 mos. (41% PFS rate at 6 mos.) OS (med): 12.6 mos.	Most pts stayed on study Tx for 44 mos., and 6 pts stayed on Tx for >10 mos. Most common grade 3/4 AEs (≥5%) for all study pts (i.e., n=77 pts w metastatic melanoma) were fatigue, hypertension, abdominal pain, hand-foot syndrome, asthenia, back pain, hypokalaemia
Shoushtari, 2016[26]	phase II ***(Level II)***	Everolimus (10 mg daily PO) + pasireotide long-acting release (60 mg q 28 days IM	Metastatic UM, ECOG 0-1 (n=14)	Clinical benefit (≥16 wks. SD): 26% SD (med): 8 wks.	PFS (med): 16 wks. OS (med): 11 mos.	Grade 3: Hyperglycemia, mucositis, diarrhea, hypophosphatemia, anemia. 50% of pts required dose reduction due to toxicity
Carvajal, 2014[27]	phase II ***(Level II)***	Arm 1: Selumetinib (75 mg PO bid on continual basis (n=50) Arm 2: Temozolomide (150 mg/m^2 PO qd for 5 of q 28 days or dacarbazine 1000 mg/m^2 IV q 21 days; investigator choice; n=51) until disease progression, death, intolerable toxicity, or withdrawal of consent	Metastatic UM, (n=101)	No objective responses observed in Arm 1 24/49 pts in Arm 2 achieved tumour regression, 7/49 achieved objective radiographic response	PFS (med): Arm 1 and Arm 2 was 7 (95% CI, 4.3-8.4; med Tx duration of 8 wks. (IQR, 4.3-16)) and 15.9 wks. (95% CI, 8.4-21.1; med Tx duration of 16.1 wks. (IQR, 8.1-25.3)), respectively (HR 0.46; 95% CI, 0.30-0.71; p<0.001) OS (med): Arm 1 and Arm 2 was 9.1 (95% CI, 6.1-11.1) and 11.8 mos. (95% CI, 9.8-15.7), respectively (HR 0.66; 95% CI, 0.41-1.06; p=0.09)	Treatment related AEs observed in 97% pts treated w selumetinib, w 37% requiring ≥1 dose reduction 1 pt treated w chemo required dose reduction
Mahipal 2012[28]	phase II ***(Level II)***	Sunitinib malate (37.5 mg/d continuously) 4-wk cycles 2nd line in 17/20 pts	Metastatic UM expressing c-kit (n=20)	PR: 1 pt SD: 12 pts	OS (med): 8.2 mos. PFS (med): 4.2 mos.	fatigue: 90% diarrhea: 60% hemorrhage: 55% anorexia: 45% hand-foot syndrome: 25%

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
						hypothyroidism: 25% rash: 25%
Liver-Directed Therapy						
Gonsalves, 2019[29]	phase II ***(Level II)***	Radioembolization underwent unilobar (n=7), fractionated whole liver (n=1), or sequential lobar (n=16)	Histologically confirmed UM hepatic mets (≥1 cm) and an ECOG performance status of ≤ 1 Group A: Tx-naïve participants, n=23 Group B: Participants who progressed after immunoembolization w hepatic tumour burden < 50%, n=24	Group A: CR, n=0 PR, n=9 SD, n=11 achieved in 20/23 (87.0%; 95% CI: 66.4%, 97.2%) pts Group B: CR, n=0 PR, n=8 SD, n=6 achieved in 14/24 (58.3%; 95% CI: 36.3%, 77.9%) pts	Group A: - Median PFS from liver metastasis 8.1 mos. (95% CI: 6.4, 11.8; range, 3.3–33.7 mos.) - Median OS 18.5 mos. (95% CI: 11.3, 23.5; range, 6.5–73.7 mos.) Group B: - Median PFS from liver metastasis 5.2 mos. (95% CI: 3.7, 9.8; range, 2.9–22.0 mos.) - Median OS 19.2 mos. (95% CI: 11.5, 24.0; range, 4.8–76.6 os.)	Grade 3 Tx-related toxicities included transient lymphopenia (group A, n=1; group B, n=1), pain (group A, n=2) and nausea or vomiting (group A, n=1)
Valsecchi, 2015[30]	phase II, ***(Level II)***	Immunoembolization (IE) vs bland embolization (BE)	Metastatic UM to liver w no extrahepatic metastasis (IE n=25, BE: n=27)	ORR: IE, 21.2% (90% CI: 10.3-30.5%) vs. BE, 16.7% (90% CI: 6.6-26.9%) SD: IE: 12/25 vs. BE: 19/27	OS: IE: 21.5 mos. (95% CI: 18.5-24.8) BE: 17.2 mos. (95% CI: 11.9-22.4) IE: 21.5 mos. (95% CI: 18.5-24.8) BE: 17.2 mos. (95% CI: 11.9-22.4)	Grade 1-2: Abdominal pain (IE: 20.1%, BE 26.9%)
Leyvraz, 2014 (EORTC 18021)[31]	phase III ***(Level I)***	IV fotemustine, n=83 vs HIA fotemustine, n=66 at 100 mg/m^2 on days 1, 8, 15 (and 22 in HIA arm only) as induction, and after 5-wk rest period q 3 wks. as maintenance	UM w metastatic disease limited to liver Accrual stopped after randomization of 171 pts based on results of futility OS analysis	Improved response rate seen in HIA (10.5%) *vs* IV Tx (2.4%)	Total of 155 pts died and 16 still alive [median F/U 1.6 yrs. (range 0.25–6 years)] HIA did not improve OS (median 14.6 mos.) vs IV arm (median 13.8 mos.), HR 1.09; 95% CI 0.79–1.50, log-rank p=0.59. Significant benefit on PFS for HIA *vs* IV w median of 4.5 vs 3.5 mos., respectively (HR 0.62; 95% CI 0.45–0.84, log-rank p=0.002) 1-yr PFS rate 24% in HIA arm vs 8% in IV arm	In IV arm, most frequent grade ≥3 toxicity thrombocytopenia (42.1%) and neutropenia (62.6%), compared w 21.2% and 28.7% in HIA arm Main grade ≥3 toxicity related to HIA was catheter complications (12%) and liver toxicity (4.5%) apart from 2 toxic deaths
Huppert 2010[32]	phase II ***(Level II)***	Cisplatin (100mg/m^2) by transarterial	Metastatic UM; liver mets (n=14)	PR: 8 pts (57%) SD: 4 pts (29%)	OS (med): 11.5 mos./ (3-69)	

Author, year (trial)	Design	Treatment	Pts (n)	Response	Survival	Adverse Events
		chemoembolization (TACE) Carboplatin in 3/14 pts due to kidney function		progression: 2 pts (14%) (med time to progression: 8.5 mos.)	subgroup analysis (mets <25% vs. ≥25%): 17 vs. 11 mos./ (p=0.18)	
Fiorentini 2009[33]	phase II ***(Level II)***	TACE beads preloaded w irinotecan (100 mg)	Metastatic UM; liver mets (n=10)	Objective response: 100% PR: 10	Med F/U 6.5 mos. OS: 80% (8/10 alive at time of analysis)	Abdominal pain
van Iersel 2008[34]	phase II ***(Level II)***	Hyperthermic IHP w melphalan (200 mg)	Melanoma w liver mets (n=18; 12 had UMs)	UM pts: PR: 4 pts SD: 6 pts PD: 2 pts	DFS (med): 6.6 mos. OS (med): 10.0 mos.	No Tx-related mortality Grade 3-4 hepatoxicity: 10 pts (56%) Veno-occlusive disease: 4 pts
Patel 2005[35]	phase II ***(Level II)***	1,3-bis(2-chloroethyl)-1-nitrosourea dissolved in ethiodized oil for hepatic artery chemoembolization	Metastatic UM; mets to liver (n=24)	CR: 1 pt PR: 4 pts SD: 13 pts	OS (med): 5.2 mos. (0.1-27.6 mos.) OS (med) by subgroup: CR/PR = 21.9 mos. (7.4-27.6 mos.) SD: 8.7 mos. (2.9-14.4 mos.) PD: 3.3 mos. (1.6-5.6)	
Agarwala 2004[36]	phase I/II ***(Level III)***	Cisplatin (100 mg/m^2 starting; increased in 25% increments to a max 125 mg/m^2)	Metastatic UM; liver mets (n=19)	ORR: 16%	n/a	Any: renal, hepatic and hematological
Alexander, 2003[37]	phase II ***(Level II)***	Hyperthermic IHP w melphalan (1.5 mg/kg; mean total 105 mg)	Metastatic ocular melanoma; liver mets (n=29)	CR: 3 pts (10%), lasting 12-15 mos. PR: 15 pts (52%), lasting 10 mos. (mean)	Med F/U: 30.7 mos. PFS (med): 8.0 mos. OS (med): 12.1 mos.	NR
Experimental Agents						
Chandran, 2017[38]	phase II ***(Level II)***	Cyclophosphamide (60 mg/kg daily for 2 days), fludarabine (25 mg/m^2 daily for 5 days) Autologous TIL (IV + interleukin-2 (720 000 IU/kg IV)	Stage IV UM, ECOG 0-1 (n=21)	Overall response rate: 35% (95% CI: 16-59)		Grade 3: Lymphopenia, neutropenia, thrombocytopenia (100%); Anemia (67%); infection (29%); death (5%)

AE, adverse event; BE, bland embolization; CR, complete response; DCR, disease control rate; DFS, disease-free survival; IE, immunoembolization; HIA, hepatic intra-arterial; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; *SD, stable disease; TACE, transarterial chemoembolization; UM, uveal melanoma*

Table 4: Treatment of Radiation Complications

Author, year (trial)	Design	Treatment	Pts (n)	Response
Schefler, 2020[40]	phase IIb ***(Level II)***	Intravitreal 0.5 mg ranibizumab monthly, n=8 *vs* Monthly ranibizumab w targeted retinal photocoagulation, n=16 *vs* 3 monthly ranibizumab (loading doses) followed by as-needed injections and targeted retinal photocoagulation, n=16 After week 52, all subjects entered treat-and-extend protocol for ranibizumab	Active radiation retinopathy w macular edema detectable by spectral-domain OCT w resulting decrease in visual acuity below 20/20 during standard post-RT F/U; history of any of: ocular proton beam radiation, ocular plaque brachytherapy, ocular/orbital EBRT; and BCVA Snellen equivalent b/n 20/25 and 20/400 in study eye, n=40	37 pts completed mo 12 visit (92.5%), at which time change in mean BCVA was +4.0 letters, -1.9 letters, and +0.9 letters in monthly, monthly + laser, and as needed + laser cohorts, respectively Significant difference in mean BCVA at 1 yr among all 3 cohorts (p<0.001), as well as b/n cohorts in pairwise comparisons, w most significant gains in monthly group Total of 82.5% of pts retained visual acuity of 20/200 or better, and 20.0% improved 10 or more Early Treatment Diabetic Retinopathy Study letters No serious ocular AEs No cases of endophthalmitis or intraocular inflammation 2 pts developed metastatic UM during study period, and 1 developed local recurrence of UM, neither thought to be related to injection or laser protocol
Seibel, 2019[41]	phase II ***(Level II)***	Ranibizumab 0.5 mg (n=15) vs. focal laser of macula and panretinal laser Tx of ischemic retina (n=16)	Choroidal melanoma pts w radiation retinopathy and visual acuity impairment b/c of radiation maculopathy accessible for laser therapy, and BCVA < 20/32	BCVA at 6 mos.: ranibizumab superior to laser Tx, w advantage of 0.14 logMAR, 95% CI 0.01 to 0.25, p=0.030. Positive effect of ranibizumab disappeared after Tx discontinued Similar results w/o statistically significant difference found w respect to macular thickness In both groups, no change observed at 6 mos. in size of ischemia in macula or periphery compared to baseline 1 case of vitreous hemorrhage in laser group and no case of rubeosis iridis over time
Murray, 2019[42]	phase II ***(Level II)***	(1) fixed aflibercept, q6wks Tx (2) variable aflibercept, treat-and-adjust Tx centered around 6 wks	UM w documented tumour control, n= 39/40 pts completed trial (97.5%) w 1 yr. F/U All pts showed visually compromising radiation maculopathy confirmed by decline in BCVA and spectral domain OCT documentation of radiation maculopathy	Baseline study entry BCVA 20/63 and maintained at 20/62 at study conclusion at 60 wks At baseline, spectral domain OCT mean central retinal thickness 432 mm and improved to 294 mm at 60 wks (p<0.02) At study conclusion, 42.5% of eyes (17/40) showed better than 20/50 BCVA, and only 5% of eyes (2/40) showed BCVA worse than 20/200 In q 6 wks interval Tx arm, pts received 9 injections, whereas in treat-and-adjust study arm, pts received 8.4 injections (p=0.88, not significant)

Author, year (trial)	Design	Treatment	Pts (n)	Response
				1 pt experienced inflammatory response after aflibercept injection, but this did not occur again for this pt, nor for any other study injections (1/400 injections [0.0025%]) No pts demonstrated endophthalmitis during study window
Seibel, 2019[41]	phase II ***(Level II)***	Ranibizumab 0.5 mg (n=15) vs. focal laser of macula and panretinal laser Tx of ischemic retina (n=16)	Choroidal melanoma pts w radiation retinopathy and visual acuity impairment b/c of radiation maculopathy accessible for laser therapy, and BCVA < 20/32	BCVA at 6 mos.: ranibizumab superior to laser Tx, w advantage of 0.14 logMAR, 95% CI 0.01 to 0.25, p=0.030. Positive effect of ranibizumab disappeared after Tx discontinued Similar results w/o statistically significant difference found w respect to macular thickness In both groups, no change observed at 6 mos. in size of ischemia in macula or periphery compared to baseline 1 case of vitreous hemorrhage in laser group and no case of rubeosis iridis over time
Matet, 2017[43]	retrospective ***(Level IV)***	n/a – obj. to analyze microvascular and structural changes in radiation maculopathy and influence on visual acuity, using OCT and OCTA	UM pts w radiation maculopathy ≥ 12 mos after proton-beam irradiation imaged w fluorescein angiography, OCT and OCTA (n=93)	FAZ was larger, while SCP/DCP capillary density and local fractal dimension lower in 35 irradiated than in 35 fellow eyes (P<0.0001) Microvascular alterations graded on fluorescein angiography (minimally damaged/ disrupted/ disorganized) correlated to FAZ area and SCP/DCP density on OCTA (P<0.01). By univariate analysis, worse VA associated to macular detachment at presentation (p=0.024), total macular irradiation (p=0.0008), higher CMT (P=0.019), higher absolute CMT variation (p<0.0001), cystoid edema (p=0.030), ellipsoid zone disruption (p=0.002), larger FAZ (p<0.0001), lower SCP (p=0.001) and DCP capillary density (p<0.0001), and lower SCP (p=0.009) and DCP local fractal dimension (p<0.0001) 2 multivariate models w either capillary density or fractal dimension as covariate showed younger age (p=0.014/0.017), ellipsoid zone disruption (p=0.034/0.019), larger FAZ (p=0.0006/0.002), and lower DCP density (p=0.008) or DCP fractal dimension (p=0.012), respectively, associated w worse VA

BCVA, best-corrected visual acuity; CMT, central macular thickness; *DCP, deep capillary plexuses; FAZ, foveal avascular zone; F/U; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; RT, radiation therapy; SCP, superficial capillary plexuses; UM, uveal melanoma; VA, visual acuity*

Table 5: Other Studies re. Uveal Melanoma

Author, year (trial)	Design	Objective	Pts (n)	Findings
Lieb, 2020[44]	prospective (Level III)	To examine traits of pts opting for prognostication, to investigate psychosocial impact and use of psycho-oncological services over time	175 UM pts	63/175 pts obtained prognostic info; pts who opted out constituted observational group Tx method (enucleation > brachytherapy), lower social support and higher general distress could significantly predict patient's choice for prognostic testing After result announcement, perceived risk of mets significantly increased in pts w poor prognosis, while it decreased in those w good prognosis Overall, significant decrease over time appeared concerning fear of progression, general distress, depression and anxiety Mental QoL increased over time Utilization of psycho-oncological interventions increased significantly after prognostication, however equivalent in test and observational groups Female sex, higher general distress and higher anxiety predicted greater use of psycho-oncological interventions
Dalvin, 2019[45]	retrospective ***(Level IV)***	To review multimodal imaging features to calculate 5-yr. % of growth to melanoma and HR	Choroidal nevi (n=3806)	6 risk factors predictive of choroidal nevus transformation into melanoma: (1) tumour thickness >2 mm (2) subretinal fluid (3) symptoms of visual acuity loss to 20/50 or worse (4) orange pigment (5) hollow acoustic density (6) tumour largest basal diameter >5 mm Kaplan-Meier 5-yr. estimated tumour growth found in 1% of nevi with 0 risk factors, 11% (range 9%-37%) w 1 factor, 22% (12%-68%) w 2 factors, 34% (21%-100%) w 3 factors, 51% (0%-100%) w 4 factors and 55% (0%-100%) w 5 factors HR for growth = 0.1 w 0 factor, 2.1-7.8 w 1 factor, 1.8-12.1 w 2 factors, 4.0-24.4 w 3 factors, 4.6-170.0 w 4 factors and 12.0-595.0 w 5 factors Highest HR w each combination of 2, 3, 4 or 5 risk factors always included symptoms of visual acuity loss and orange pigment
Khoja, 2019 (IRCI)[46]	meta-analysis ***(Level I)***	To determine benchmarks of PFS and OS	UM in published trials from 2000-2016 (n=912)	Male sex, elevated LDH and ALP were substantially associated w shorter PFS OS (med): 10.2 mos. (95% CI: 9.5-11.0) PFS (med): 3.3 mos. (95% CI: 2.9-3.6) 6-mo PFS: 27% (95% CI: 24-30) 1-yr OS (med): 43% (95% CI: 40-47)
Rantala, 2019[47]	meta-analysis ***(Level I)***	To advance interpretation of OS	Metastatic UM on PubMed from Jan 01, 1980 to Mar 29, 2017 (n=2494)	No clinically significant difference in OS by Tx modality or decade Observed differences attributed to surveillance, selection and publication bias OS across all Tx modalities (med): 1.07 yrs. Post hepatic perfusion, OS (med): 1.34 yrs., HR: 0.92 (95% CI: 0.87-0.97, p=0.004) Post immunoembolization OS (med): 1.63 yrs., HR: 0.97 (95% CI: 0.95-1.00, p=0.008) Post-surgery OS (med): 1.43 yrs., HR: 0.94 (95% CI:0.92-0.96, p=0.0001) Post checkpoint inhibitor OS (med): 0.59 yrs., HR: 1.13 (95% CI: 1.06-1.20, p<0.001) Post conventional chemo OS (med): 0.91 yrs.
Schefler, 2019[48]	retrospective ***(Level IV)***	To examine relationship b/c clinical features, GEP class, and PRAME expression in UM	UM pts who underwent GEP and PRAME testing (n=148)	PRAME+ status was significantly associated w largest basal diameter, tumour volume and poor GEP class No association b/n higher TNM stage and positive PRAME status (p=0.129) Higher GEP class associated w higher TNM stage (<0.001) Many 1A pts may harbor increased metastatic risk
Weis, 2019[49]	prospective ***(Level III)***	To describe early experience w GEP Ax	Juxtafoveal, subfoveal, and	6 (40%) 6class 1A and 9 (60%) class 1B

Author, year (trial)	Design	Objective	Pts (n)	Findings
			peripapillary indeterminate high-risk melanocytic lesions (n=15)	Class 1A and 1B lesions had median of three and four clinical risk factors, respectively (p=0.27) No statistically significant difference for largest basal diameter b/n classes (p=0.31); however, class 1B lesions thicker than class 1A lesions (p=0.03) No class 1A lesions showed definite growth or metastasis over mean F/U period of 17.1 ± 1.8 mos. from FNA biopsy All class 1B pts opted for plaque brachytherapy, and to date no pt has developed metastasis, w mean F/U of 18.7 ± 8.4 mos.
Cai, 2018[50]	retrospective ***(Level IV)***	To compare prognostic accuracy of GEP combined w PRAME status vs. clinical TNM staging in pts w UM	UM pts who underwent GEP and PRAME testing (n=240)	GEP and PRAME demonstrated prognostic accuracy superior to AJCC TMN staging system
Nayman, 2017[51]	Review of meta-analyses ***(Level I)***	To systematically review UM risk factors	Meta-analyses and systematic reviews providing odds ratios (n=4)	Risk factors: - Atypical cutaneous nevi (OR 2.82, 95% CI 1.10-7.26) - Welding (OR 2.05, 95% CI 1.20-3.51) - Occupational cooking (OR 1.81, 95% CI 1.33-2.46) - Fair skin color (OR 1.80, 95% CI 1.31-2.47) - Light eye color (OR 1.75, 95% CI:1.31-2.34) - Common cutaneous nevi (OR 1.74, 95% CI: 1.27-2.39) - Propensity to sunburn (OR 1.64, 95% CI: 1.29-2.09) - Iris nevi (OR 1.53, 95% CI 1.03-2.27) - Cutaneous freckles (OR 1.27, 95% CI: 1.09-1.49)
Coupland, 2015[52]	Retrospective ***(Level IV)***	To compare chromosome 3 aberrations of choroidal melanoma as determined by multiplex ligation dependent probe amplification or microsatellite analysis in intraocular tumour biopsies w those results obtained from subsequent endoresection/enucleation of the same choroidal melanoma	Choroidal melanoma pts, Liverpool Ocular Oncology Centre, 2007-2014 (n=28)	Intraocular biopsy yields similar prognostic info. to larger surgical specimens. Initial evidence, that genetic testing can be successfully conducted post RT

ALP, alkaline phosphatase; CI, confidence interval; FNA, fine needle aspiration; F/U, follow-up; GEP, gene expression profiling; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; PRAME, preferentially expressed antigen in melanoma; TNM, tumour node metastasis; UM, uveal melanoma

Table 6: Summary of Existing Guideline Recommendations for the Management of Uveal Melanoma (2015-2020)

Guideline Developer/ Organization, Year	Recommendations
UptoDate, 2020	**Initial Mgmt. of Uveal Melanoma – Summary and Recommendations (Topic Updated Nov. 23, 2020)**

Guideline Developer/ Organization, Year	Recommendations

	• For asymptomatic pts w small uveal melanocytic tumours (<12 mm in diameter and <2 to 3 mm in thickness), initial period of observation for evidence of growth generally recommended until evidence of growth is documented.
	• For pts w larger tumours and for those w symptoms, initial Tx usually indicated:
	  ○ For symptomatic pts and those w medium or large tumours, Tx w RT generally recommended. RT can be administered using plaque brachytherapy, most widely available form of RT, or w charged-particle RT.
	  ○ Enucleation generally reserved for pts in whom RT unlikely to achieve adequate local tumour control or likely to result in unacceptable ocular radiation complications due to large tumour size, extrascleral extension, or risk of neovascular glaucoma.
	• Most centers use molecular prognostic testing to stratify intensity and frequency of metastatic surveillance after Tx of primary tumour. Clinical trials of adjuvant systemic therapy are increasingly becoming available in high-risk pts.
	• For pts w metastatic disease, prognosis remains poor, but clinical trials increasingly becoming available to evaluate liver-directed regional therapies, systemic targeted therapies, and immunotherapies. Clinical trial participation strongly encouraged.
	
	Mgmt. of Metastatic UV – Summary of Recommendations (Topic Updated May 4, 2020)
	• For pts who present w metastatic disease or who develop metastatic disease after Tx of their primary tumour, prognosis is poor.
	• Limited data exists re. optimal selection of pts best suited for localized, regional, or systemic therapy, but they may be performed based upon clinical factors such as number and location of metastatic lesions, disease-free interval, and availability of clinical trials.
	• Resection or ablation of oligometastatic disease can lead to long-term clinical benefit in appropriately selected pts.
	• Regional liver-directed therapy may achieve disease control that is more durable than that achieved w available systemic therapeutic options; however, does not appear to be an overall survival advantage when adjusting for prognostic factors.
	• For pts w Tx-naïve disease or disease refractory to previous therapies, offer enrollment in formal clinical trials whenever possible.
	• For pts not eligible for or who decline clinical trials, suggest initial Tx w combination immunotherapy w nivolumab + ipilimumab rather than single-agent immunotherapy.
	• Pts ineligible for combination immunotherapy may alternatively be offered single-agent immunotherapy w PD-1 inhibitors (e.g., nivolumab, pembrolizumab).

ASCO, Mar. 31, 2020	**Systemic Therapy for Melanoma** No recommendation for or against any specific systemic therapy for pts w UM may be made at this time. Pts should be offered or referred for enrollment in clinical trials where possible

NCCN, Sept. 15, 2020	**Workup and Diagnosis**
	• Clinical evaluation, including:
	  ○ H&P, including history of prior or current cancers (outside the eye)
	  ○ Color fundus photography
	  ○ Ultrasound of eye and orbit
	  ○ Comprehensive eye exam: examine front and back of eye (biomicroscopy)
	  ▪ Dilated fundus exam (indirect ophthalmoscopy)
	  ▪ Measure visual acuity
	  ▪ Measure and document location and size of tumour (diameter, thickness), distance from disc and fovea, and ciliary body involvement
	  ▪ Assess and document if present:
	  • Subretinal fluid
	  • Orange pigment
	• Additional testing options include:
	  ○ Autofluorescence of ocular fundus
	  ○ Optical coherence tomography
	  ○ Retinal fluorescein angiography of ocular fundus

Guideline Developer/ Organization, Year	Recommendations
	○ Transillumination ○ MRI occasionally needed to confirm diagnosis • Consider biopsy if needed to confirm diagnosis or for prognostic analysis for risk stratification **Clinical Staging** • Diagnosis uncertain and/or <3 risk factors for growth ○ Observe and re-evaluate for growth or features of malignancy ▪ Every 2-4 mos. as clinically indicated ▪ Then close F/U for 5 yrs. ▪ Then annually thereafter • UM ○ See Workup and Staging for UM **Workup and Staging for UM** • Ocular imaging if not previously done: ○ If large tumour, close to nerve or suspicion of extraocular involvement, MRI of orbit w and w/o IV contrast • Assess and document if present: ○ Ciliary body involvement ○ Extraocular extension • Extraocular imaging: ○ Baseline imaging to screen for distant disease • Consider biopsy of primary tumour for prognostic analysis **Following UM Diagnosis, Primary Tx Based on Tumour Size:** • Largest diameter 5-18 mm and thickness <2.5 mm, options: ○ Brachytherapy plaque ○ Particle beam radiation ○ Other options in highly select pts • Largest diameter ≤ 18 mm and thickness 2.5-10 mm, options: ○ Brachytherapy plaque ○ Particle beam radiation ○ Enucleation • Largest diameter > 18 mm (any thickness) or thickness > 10 mm (any diameter) or thickness > 8 mm w optic nerve involvement (any diameter), options: ○ RT (particle beam radiation, SRS) ○ Enucleation • Metastasis – See Tx of Metastatic Disease **Additional Primary Tx** • Extraocular extension at time of enucleation ○ Microscopically positive or close margins after enucleation (but no clinical, intraop, or radiographic evidence of gross residual disease in orbit ▪ Observe OR map biopsy AND/OR consider RT to orbit (particle beam or photon beam) ○ Visible extraocular tumour or suspicion of gross disease in orbit

Guideline Developer/ Organization, Year	Recommendations
	▪ Biopsy extraocular tissue if possible and consider ≥1 of: intraop cryotherapy, orbital exenteration, RT to orbit (particle beam or photon beam) **Standard F/U for Affected Eye AND Systemic Imaging +/- Blood Tests Based on Risk Stratification by Genetic Testing +/- Tumour Size and Histology (at Presentation)** • Low risk of distant metastasis (class 1A, disomy 3, gain of chromosome 6p, *EIF1A1* mutation, T1 (AJCC), systemic imaging: o Imaging to evaluate signs or symptoms as clinically indicated o Consider surveillance imaging q 12 mos. • Medium risk of distant metastasis (class 1B, SF3B1 mutation, T2 and T3), systemic imaging: o Imaging to evaluate signs or symptoms as clinically indicated o Consider surveillance imaging q 6-12 mos. for yrs. 6-10, then as clinically indicated • High risk of distant metastasis (class 2, monosomy 3, gain of chromosome 8q, BAP1 mutation, PRAME expression, T4 (AJCC), extraocular extension, ciliary body involvement): o Imaging to evaluate signs or symptoms o Consider surveillance imaging q 3-6 mos. for 5 yrs. then q 6-12 mos. for yrs. 6-10, then as clinically indicated **Recurrence, Tx:** • Intraocular recurrence (limited to eye, no orbital involvement) o RT (plaque brachytherapy or particle beam) OR enucleation OR laser ablation • Extraocular involvement o Surgical resection +/- RT to orbit (particle beam or photon beam) +/- cryotherapy to orbital tumour • Orbital involvement in pts w prior enucleation o Surgical resection OR cryotherapy to orbital tumour AND/OR RT to orbit (particle beam or photon beam) • Distant metastatic disease – See Tx of Metastatic Disease **Tx of Metastatic Disease** • Clinical trial (preferred), OR • Consider ≥1 of the following: o Liver-directed therapies ▪ Regional isolation perfusion of liver ▪ Embolization (chemo, RT, immunotherapy) ▪ Ablative procedures (thermal ablation, cryotherapy) ▪ Consider resection AND/OR RT (photon beam or SRS) for limited or symptomatic disease in liver o Systemic therapies ▪ Systemic therapy ▪ Consider resection AND/OR RT (photon beam or SRS) for limited or symptomatic extrahepatic disease o Best supportive/palliative care • Imaging to assess response or progression o No evidence of disease – clinical trial (preferred OR observation) Residual or progressive disease – best supportive/palliative care
National Cancer Institute, 2020	**Intraocular (Uveal) Melanoma Tx – Health Professional Version** ***Diagnosis***

Guideline Developer/ Organization, Year	Recommendations
	Careful exam by experienced clinician most important test to establish presence of intraocular melanoma. Small UM cannot be distinguished from nevus. Small uveal lesions observed for growth before making diagnosis of melanoma. Clinical findings that may help to identify melanoma include: • Orange pigment on tumour surface • Subretinal fluid • Tumour thickness of >2 mm • Low internal reflectivity on U/S exam Ancillary diagnostic testing, including fluorescein angiography and ultrasonography, can be extremely valuable in establishing and confirming diagnosis. ***Prognostic Factors*** Number of factors influence prognosis. Most important factors include: • Cell type • Tumour size • Location of anterior margin of tumour • Degree of ciliary body involvement • Extraocular extension Several additional microscopic features can affect prognosis of intraocular melanoma, including: • Mitotic activity • Lymphocytic infiltration • Fibrovascular loops (possibly) Cell type most commonly used predictor of outcome following enucleation, w spindle-A cell melanomas carrying best prognosis and epithelioid cell melanomas carrying least favorable prognosis. Nevertheless, most tumors have admixture of cell types, and no clear consensus re. proportion of epithelioid cells that constitutes designation of tumour as mixed or epithelioid. Extraocular extension, recurrence, and metastasis associated w extremely poor prognosis, and long-term survival cannot be expected. ***Cellular Classification of Intraocular UM*** Primary intraocular melanomas originate from melanocytes in uveal tract. Following 4 distinct cellular types recognized in intraocular melanoma (revised Callender classification): 1. Spindle-A cells (spindle-shaped cells w slender nuclei and lacking visible nucleoli) 2. Spindle-B cells (spindle-shaped cells w larger nuclei and distinct nucleoli) 3. Epithelioid cells (larger polygonal cells w ≥1 prominent nucleoli) 4. Intermediate cells (similar to but smaller than epithelioid cells) ***Classification and Stage Information for Intraocular (Uveal) Melanoma*** ***Tumour Size*** UM most often assumes nodular or dome-shaped configuration, but occasionally tumours can be flat or diffuse and involve extensive areas of uvea w little elevation. Tumour size classifications according to boundary lines used in Collaborative Ocular Melanoma Study (COMS) are: **Small**: Range from 1.0 mm to 3.0 mm in apical height and largest basal diameter of 5.0 to 16.0 mm. **Medium**: Range from 3.1 to 8.0 mm in apical height and a basal diameter of ≤16.0 mm.

Guideline Developer/ Organization, Year	Recommendations
	Large: >8.0 mm in apical height or basal diameter >16.0 mm, when apical height is ≥2.0 mm. Although most ocular melanomas have raised configuration, about 5% grow in diffuse pattern that also may have prognostic significance. Tumours have horizontal, flat-growth pattern, w thickness measuring approx. ≤20% than the greatest basal dimension. This uncommon variant of UM seems to have poorer prognosis, particularly when diameter large, and margins poorly defined. In clinical practice, tumour base may be estimated in average optic disc diameters (1 dd = 1.5 mm). Average elevation may be estimated in diopters (3 diopters = 1 mm). Other techniques, such as ultrasonography, should be used to provide more accurate measurements. Important function of ophthalmic ultrasonography is detection of extrascleral extension. Extrascleral extension measuring ≥2 mm in thickness can be demonstrated provided located behind equator where intraocular tumour, sclera, and adjacent orbital fat readily imaged. Orbital extraocular extension of choroidal melanoma may be found in eyes w medium and large tumours, but very rare in eyes w small melanomas. ***Metastatic Disease*** Systemic metastases evident in only 2% to 3% of pts at time of diagnosis of primary ocular melanoma. B/c uveal tract vascular structure w/o lymphatic channels, tumour spread occurs principally by local extension and by dissemination through bloodstream. Lymphatic spread rare but may occur after local extension into conjunctiva and its lymphatics. Given rarity of nodal mets, sentinel node biopsies of non-clinically involved nodes not done as part of staging procedure. Systemic mets generally hematogenous in origin, and first site identified is usually liver. Lung, bone, and subcutaneous sites also common. In pts w history of ocular melanoma who present w hepatic mets of unknown origin, metastatic melanoma considered in differential diagnosis. Particularly unusual for choroidal melanomas of any size to invade optic nerve or its meninges. Metastasis of choroidal melanoma to contralateral choroid also rare. ***Staging*** AJCC has designated staging by TNM (tumour, node, metastasis) classification to define melanoma of uveal tract. As in seventh edition of *AJCC Cancer Staging Manual*, no staging system for iris melanomas in eighth edition. However, TNM should still be recorded for this site and histology combination. ***Prognostic features*** Number of key prognostic features important to collect in malignant melanoma of uvea, even though not included in staging algorithms. These include: ***Molecular features*** 1. Chromosomal alterations. a. Chromosome 3 status (loss or no loss; complete or partial) b. Chromosome 6p status (gain or no gain) c. Chromosome 8q status (gain or no gain) Indicate: ▪ Technique used for assessing chromosome status may include: □ Karyotyping

Guideline Developer/ Organization, Year	Recommendations
	▫ Fluorescence *in situ* hybridization ▫ Comparative genomic hybridization ▫ Loss of heterozygosity using DNA polymorphism analysis (e.g., single nucleotide polymorphism, microsatellite) ▫ Other ▪ How specimen was obtained may include: ▫ Enucleation ▫ Local resection ▫ Biopsy ▫ Fine-needle aspiration biopsy ▪ For needle biopsies, whether cytopathologic evaluation performed to confirm presence of tumour cells. 2. Gene-expression profile: class 1 or class 2. Indicate: • Technique used for gene-expression profiling (e.g., microarray, pathologic complete response). • How specimen was obtained (e.g., enucleation, local resection, biopsy, fine-needle aspiration biopsy). • For needle biopsies, whether cytopathologic evaluation was performed to confirm the presence of tumour cells. ***Clinical and histopathologic features*** 1. Clinical a) PET/computed tomography • Fluorine F 18-fludeoxyglucose standardized uptake values (higher values in primary tumour may be associated w shorter survival) b) Confocal indocyanine green angiography • Identification of complex monocirculatory patterns (i.e., loops, networks, arcs w branching, parallel w cross-linking or combination of these patterns may be associated w shorter survival) 2. Histopathologic a. Mitotic count • Number of mitotic figures per 40 high-power fields (typical field area 0.15–0.19 mm2, higher counts associated w shorter survival) b. Mean diameter of 10 largest nucleoli • Mean of longest nucleoli (MLN) measured along central 5-mm long strip, e.g., after silver staining (larger values associated w shorter survival) c. Presence of extravascular matrix patterns • Loops ▫ Absent ▫ Present (shorter survival) • Loops forming networks ▫ Absent ▫ Present (shorter survival) • Other complex patterns (arcs w branching, parallel w cross-linking; absent or present) Patterns assessed w light microscopy under dark green filter after staining w periodic-acid Schiff w/o counterstain d. Microvascular density

Guideline Developer/ Organization, Year	Recommendations
	• Number of immunopositive elements labeled w markers for vascular endothelial cells (e.g., CD34 epitope, factor VIII-related antigen) in areas of densest vascularization (typical field area 0.31 mm2, higher counts associated w shorter survival) e. Insulin-like growth factor 1 receptor (IGF1-R) • % of immunopositive tumour cells (high expression associated w shorter survival) f. Tumour-infiltrating lymphocytes • Few (longest survival) • Moderate numbers • Many (shortest survival) g. Tumour-infiltrating macrophages • Few (longest survival) • Moderate numbers • Many (shortest survival) Number can be compared w standard photographs h. HLA class I expression • % of immunopositive tumour cells (low expression associated w longer survival) ***Standard Tx Options for Iris Melanoma*** 1. Observation w careful F/U - used in asymptomatic pts w stable lesions; F/U includes serial photography. 2. Local resection - used when progressive and pronounced growth documented. 3. Enucleation - used if tumour not amenable to local resection b/c of diffuse involvement of iris, involvement of ≥ 50% of iris and anterior chamber angle, intractable glaucoma, or extraocular extension. 4. Plaque RT - offered as alternative for large, diffuse, surgically nonresectable lesions of the iris. ***Standard Tx Options for Ciliary Body Melanoma*** Several options for mgmt. of ciliary body melanoma. All of them reported from case series. Choice of therapy, however, depends on many factors. 1. Plaque RT ○ Local control rates high, but Tx associated w high incidence of secondary cataract. 2. External-beam, charged-particle RT ○ Approach offered at specialized referral centers. Requires careful pt cooperation, w voluntary fixation of gaze. 3. Local tumour resection ○ Option mainly suitable for selected ciliary body or anterior choroidal tumours w smaller basal dimension and greater thickness. 4. Enucleation ○ Option generally reserved for large melanomas when no hope of regaining useful vision. Also indicated in presence of intractable secondary glaucoma and extraocular extension. ***Standard Tx Options for Small Choroidal Melanoma*** 1. Observation ○ Strategy important for pts w uncertain diagnosis or in whom tumour growth not documented. Also used for asymptomatic pts w stable lesions (particularly elderly or debilitated pts), and for pts w tumour in only useful eye. 2. Plaque RT ○ Used for small- or medium-sized UMs, amelanotic tumours, or tumours that touch optic disc for >3 clock-h of optic disk circumference. 3. External-beam, charged-particle RT

Guideline Developer/ Organization, Year	Recommendations
	○ Offered at specialized referral centers. Requires careful pt cooperation, w voluntary fixation of gaze. 4. GK radiation surgery ○ May be feasible option for small-sized to medium-sized melanomas. 5. Transpupillary thermotherapy ○ Approach has very limited use, but can be used as primary Tx or as adjunctive method to plaque RT 6. Local tumour resection ○ Used mainly for selected ciliary body or anterior choroidal tumours w smaller basal dimensions and greater thickness. **7.** Enucleation ○ Used when severe intraocular pressure elevation is factor. May also be considered w small- and medium-sized melanomas invading tissues of optic nerve. ***Standard Tx Options for Medium and Large Choroidal Melanoma*** Tumour growth pattern is factor in therapeutic decision. If diffuse melanoma or if extraocular extension, enucleation considered, but RT can be employed for less extensive disease. ***Medium-sized choroidal melanomas*** 1. Plaque RT 2. External-beam, charged-particle RT ○ Offered at specialized referral centers. Requires careful pt cooperation, w voluntary fixation of gaze. 3. Local eye-wall resection 4. Combined therapy, w ablative laser coagulation or transpupillary thermotherapy to supplement plaque Tx 5. Enucleation ○ Considered primarily for diffuse melanomas or for cases in which extraocular extension. Radiation complications or tumour recurrence may sometimes make enucleation necessary. ***Large choroidal melanomas*** 1. Enucleation when tumour judged to be too large for eye-sparing approaches. ***Extraocular Extension and Metastatic Intraocular Melanoma*** • No effective method of systemic Tx identified for pts w metastatic ocular melanoma. Available clinical trials option for these pts. ***Recurrent Intraocular Melanoma*** • Clinical trials appropriate, and eligible pts should be advised to consider participation in them whenever possible.
Steeb et al., 2020	**Guidelines for UM: Critical Appraisal of Systematically Identified Guidelines Using AGREE II and AGREE-REX Instrument** • 5 guidelines published from 2014 to 2018 by consortia of the USA, Canada and UK included • Highest scores obtained by UK guideline fulfilling 48-86% of criteria in AGREE II and 30-60% for AGREE-REX • All guidelines showed deficiencies in domains “editorial independence”, “applicability”, and “recommendation” • Subgroup differences identified only for domain “editorial independence” • UK guideline achieved highest scores w both instruments and may serve as basis for future guideline development in UM
Cancer Council Australia, 2019	**Ocular Melanoma, Evidence Summary and Recommendations** • Eye-conserving therapies for ocular melanoma result in similar rates of local control to enucleation. (Level IV) • The first surgery is most important. Inappropriate primary surgery results in upstaging of disease and worse prognosis due to inadvertent tumour seeding. (Level IV) **Evidence-Based Recommendation**

Guideline Developer/ Organization, Year	Recommendations
	Ocular melanoma is complex and uncommon form of melanoma that should be managed in specialized units where multidisciplinary ocular cancer services are available. (Grade C)
Garbe et al., 2019	**European Consensus-Based Interdisciplinary Guideline for Melanoma. Part 2: Treatment – Update 2019** ***Special Case: Metastatic UM*** • Because of preferential metastasis to liver, pts w ocular melanoma and liver mets may be candidates for local regional therapeutic measures. Few systemic schedules have been reported w objective responses, and response rates reported for Tx w checkpoint inhibitors are in lower single-digit range • In absence of effective systemic therapies, recommended that pts w metastatic disease be offered enrolment in clinical trial.
Scottish Consensus Statement Group, 2019	**Consensus Statement of Metastatic Surveillance for UM in Scotland – Executive Summary** 1. Lack of evidence and lack of consensus across UK re. specifics of metastatic surveillance for UMs. Consensus amongst clinicians involved in mgmt. of UM in Scotland will ensure uniformity of approach for these pts in Scotland 2. Early detection of these metastatic lesions may facilitate both standard and clinical trial-based Tx options 3. Good practice to offer all pts w UM 6-monthly surveillance for liver mets for first 10 yrs. after diagnosis. After 10 yrs., decision on continuing surveillance should be made after discussion b/n pt and clinician 4. In low-risk UMs, surveillance should be performed by offering serial liver ultrasounds. If any suspicious lesions seen on liver ultrasound, MRI scan w contrast (unless contraindicated) should be performed to further characterize lesion. 5. In high-risk UMs, surveillance should be performed by offering serial MRI imaging of liver. Serial ultrasound imaging may be considered as alternative modality if operator has experience of its use in uveal metastatic disease **Consensus on Definition of High-Risk UMs** • Choroidal and Ciliary Body melanomas Stage IIIA or worse as per AJCC (8th edition) staging • Cytogenetic testing confirms Monosomy 3 • Cytogenetic testing confirms abnormalities in Chromosome 8 (8p loss, 8q gain) • Cytogenetic testing confirms BAP-1 mutations • In absence of cytogenetic testing, pathological features indicating high risk include extra-scleral extension, epithelial cells and closed vascular loops – decision to be made at MDT Any other features of tumour or other factors that may indicate high risk of mets – decision to be made at MDT
Nathan et al., 2015	**Uveal Melanoma UK National Guidelines** ***3.1. Pt Choice and Shared decision-making*** 1. All specialist surgical ocular oncology MDTs should collaborate to produce an info leaflet on options available nationally. [GPP] 2. All available procedural and Tx options, local, national and international should be discussed w pt. [GPP] 3. Risks and benefits of any procedures and Tx being considered should be fully discussed w pt, including impact on QoL. [GPP] ***3.2. Service configuration*** 1. Supra-regional specialist MDTs, using network model, should be established that promote coordinated approach for care and F/U of all pts w UM. For advanced disease, specialist oncology MDT should consist of medical or clinical oncologist, interventional radiologist, diagnostic radiologist, histopathologist, liver surgeon and clinical nurse specialist, all w experience in treating UM and w direct links to ocular surgical oncology centres. MDT should make recommendations on individual pt's tumour staging and mgmt. and have available all Tx and trials locally or by referral. [GPP] 2. Any molecular testing should be carried out w/n accredited molecular pathology lab w appropriate QA in place to provide required standards and experienced interpretation of diagnostic test, in compliance w national requirements. [GPP] 3. National register, based on standardized min. data set, should be established where details of every pt w diagnosis of UM entered, w F/U data collected ≥ annually. [GPP]

Guideline Developer/ Organization, Year	Recommendations

	3.3. General guidance
	1. All local recurrences of primary UM should be reported to surgical ocular oncology centre where Tx for primary tumour took place. [GPP]
	2. All Optometrists and Ophthalmologists should receive training in recognition of UM, to allow earlier detection and timely referral of pts w UM. [GPP]
	3. Each surgical ocular oncology centre should audit results and share nationally. [GPP]
	4. Suspected diagnosis of UM by referring clinician should follow same pathways as for any other suspected cancer. Ocular oncology centre should be notified w/n 48 h of presentation and pt seen by specialist w/n 2 wks. Grade C
	5. Suspicious lesions or lesions diagnosed as UM should be referred to consultant surgical ocular oncologist in one of the surgical oncology centres for ocular malignancies. Grade D
	6. Specimens should be reported by an ophthalmic pathologist within a specialist centre. [GPP]
	7. All pts w new diagnosis of UM should be offered referral to medical or clinical oncologist w specialist interest in disease. [GPP]
	8. Pts should be informed about and recruited into clinical trials wherever possible. [GPP]
	9. Pts should be offered opportunity to participate in UM specific research. w pt consent, samples should be taken surplus to diagnostic requirements and stored in ethically approved quality biobank for research purposes. [GPP]
	
	3.4. Primary management
	3.4.1. Pre-operative investigations
	1. Make diagnosis of UM using ophthalmoscopy, fundus photography and conventional ocular U/S. Grade A
	2. Ciliary body melanoma should be imaged w Ultrasound Biomicroscopy (UBM) or anterior segment Optical Coherence Tomography (OCT). Grade D
	3. If clinical diagnosis uncertain following above-mentioned techniques diagnostic biopsy should be considered and balanced against potential risks of procedure. [GPP]
	4. Fine needle aspiration biopsy can be performed either w direct transcleral approach or using transvitreal approach. Grade D
	
	3.4.2. Staging before primary treatment
	1. A decision on staging should be made based on individual circumstances of pt, but staging should not delay primary mgmt. of the tumour. [GPP]
	2. Staging should be considered in following circumstances: pt is at particularly high-risk b/c of clinical features of presentation. Pt is particularly anxious and requires reassurance. [GPP]
	
	3.4.3. Tx of primary tumour
	1. Pts should be informed no proven survival advantage b/n any offered modalities. Grade A
	2. Treat pts as follows:
	
	RT
	• Brachytherapy Ruthenium 106 Iodine 125, Grade A
	  ○ Used for: Small/medium/large UM (as defined by Diener-West, Hawkins et al., 1992), <20 mm in basal diameter
	  ○ Outcomes: Good local tumour control
	  ○ Complications: Loss of vision, tumour recurrence
	  ○ Comments: Dose and position of plaque can be adjusted to limit loss of vision
	• Proton Beam RT, Grade C
	  ○ Used for: Medium to large UM which cannot be treated w brachytherapy or resection
	  ○ Outcomes: Good local tumour control
	  ○ Complications: Loss of vision, loss of eye from neovascular glaucoma, tumour recurrence

Guideline Developer/ Organization, Year	Recommendations
	○ Comments: Not available in all ocular oncology units • SRS, Grade C ○ Used for: Juxta-papillary UM; pts unsuitable for ruthenium plaque or unfit for surgery ○ Outcomes: Good local tumour control ○ Complications: Loss of vision, radiation related complications, tumour recurrence ○ Comments: Not available in all ocular oncology units ***Phototherapy*** • Transpupillary thermotherapy, Grade C ○ Used for: Local recurrence and of adjuvant therapy of UM ○ Outcomes: Improves local tumour control ○ Complications: Loss of vision, extraocular tumour recurrence ○ Comments: Very occasionally used by some centres for small melanoma nasal to optic disc. When considering preservation of vision, e.g., in 1 eyed-pt as it avoids RT complications. No longer recommended routinely as sole primary Tx • Photodynamic therapy, Grade D ○ Used for: Small melanoma ○ Outcomes: Uncertain tumour recurrence ○ Complications: Avoids RT complications ○ Comments: New Tx option not widely used for UM. Experimental Tx ***Surgery*** • Exoresection +/- plaque, Grade C ○ Used for: Medium to large melanoma with a narrow basal diameter ○ Outcomes: Variable ○ Complications, Retinal detachment, loss of vision, loss of the eye, tumour recurrence, risk of orbital dissemination of tumour ○ Comments: Rarely performed in UK. Only performed in limited centres. Always performed w brachytherapy to reduce risk of recurrence • Endoresection ± RT, Grade D ○ Used for: Medium-sized UM. Toxic tumour syndrome post PBR ○ Outcomes: Variable ○ Complications: Transient intraocular hemorrhage; rarely tumour seeding ○ Comments: Only performed in limited centres in UK • Enucleation Large, Grade A ○ Used for: Large UM, melanoma associated w NVG ± extensive retinal detachment ○ Outcomes: 100% local tumour control if completely excised ○ Complications: Socket related complications, orbital recurrence ○ Comments: Cosmetic results reasonably good w orbital implant and artificial eye • Exenteteration, Grade D ○ Used for: Large extra-ocular extension after UM ○ Outcomes: 100% local tumour control if completely excised ○ Complications: Orbital recurrence ○ Comments: Rarely performed in UK **3.4.4. F/U after primary Tx**

Guideline Developer/ Organization, Year	Recommendations
	1. Pts treated w plaque brachytherapy, proton beam RT or SRT should be monitored for tumour regression intensively over first 2 yrs following Tx. Long-term follow up intervals depend on response of tumour to brachytherapy and RT complications experienced. [GPP] ***3.5. Prognostication*** ***3.5.1. Prognostic factors/tool*** 1. Prognostic factors of UM multi-factorial and include clinical, morphological and genetic features. Following features should be recorded: • Age • Gender • Tumour location • Tumour height Tumour • Largest basal diameter • Ciliary body involvement • Extraocular melanoma growth (macroscopic) Following features should be recorded if tissue available: • Cell type (modified Callender system) • Mitotic count (number/40 high power fields in H&E-stained sections) • Presence of extravascular matrix patterns (particularly closed connective tissue loops; enhanced w Periodic acid Schiff staining). Grade A • Presence of extraocular melanoma growth (size, presence or absence of encapsulation). Grade A ***3.5.2. Prognostic biopsy*** 1. Should be fully informed discussion w all pts, explaining role of biopsy including benefits and risks. Discussion should include: • Risk of having biopsy • Limitations of investigation • Benefits for future Tx (including possible recruitment to trials) • Impact on QoL • Recruitment to trials • F/U [GPP] 2. Min dataset for UM from Royal College of Pathology should be recorded. Grade D 3. Tests for novel serological biomarkers should only be used w/n clinical trials or research programs. [GPP] 4. Consider collecting molecular genetic and/or cytogenetic data for research and prognostication purposes where tumour material available and where pt consent obtained as part of ethically approved research program. [GPP] 5. Use of current (i.e., 7th) Edition of TNM staging system for prognostication highly recommended. Grade A 6. Use of multifactorial prognostication models incorporating clinical, histological, immunohistochemical and genetic tumour features – should be considered. Grade D ***3.6. Surveillance*** 1. Prognostication and surveillance should be led by specialist MDT that incorporates expertise from ophthalmology, radiology, oncology, cancer nursing and hepatic services. [GPP] 2. Prognostication and risk prediction should be based on best available evidence, taking into account clinical, morphological and genetic cancer features. [GPP]

Guideline Developer/ Organization, Year	Recommendations
	3. All pts, irrespective of risk, should have holistic Ax to discuss risk, benefits and consequences of entry into surveillance program. Discussion should consider risk of false positives, emotional impact of screening as well as frequency and duration of screening. Individual plan should be developed. [GPP] 4. Pts judged at high-risk of developing mets should have 6-monthly life-long surveillance incorporating clinical review, nurse specialist support and liver-specific imaging by non-ionizing modality. [GPP] 5. Liver function tests alone inadequate surveillance tool. Grade C ***3.7. Metastatic disease*** ***3.7.1. Staging*** 1. Pts should have whole body staging (chest, abdomen and pelvis) w CT scan or PET CT. Grade D 2. Brain imaging should not be carried out in absence of symptoms. [GPP] 3. Pts who have symptomatic bony pain should have bone scan to assess presence of bony disease. [GPP] 4. Contract enhanced MRI w diffusion weight imaging should be used to stage liver disease when assessing operability. Grade D 5. CE-CT scan should be used to stage extrahepatic disease. Grade D ***3.7.2. Prognostic method*** 1. Min data set should be collected for all pts w systemic disease (Stage IV) for future validation: Metastatic Tumour Burden (site, diameter and number), LDH ALP GGT Bilirubin Presence or absence of ascites Gender Age Performance status, DFS following definitive primary therapy. [GPP] 2. Tissue sample should be taken to confirm diagnosis of metastatic UM unless contraindicated. [GPP] 3. Curative (R0) resection most important positive prognostic factor following liver resection. [GPP] ***3.7.3. Mgmt. of systemic and oligometastatic-extrahepatic disease*** 1. Pts should be considered for clinical trials wherever possible and be informed of available trial options at other centres. [GPP] 2. Pts w good performance status (PS 0-2) who decline trials or for whom no suitable clinical trials available should be offered systemic Tx and managed in specialist centres w appropriate oncology expertise in UM. [GPP] 3. Specialist centres should be involved in Tx decisions and review, but pt may prefer to receive supportive care and systemic Tx locally. [GPP] 4. Patients with liver predominant disease should be considered for regional therapy. Grade D 5. Loco-regional Tx for mgmt. of oligometastatic disease (i.e., when mets limited to single or limited number of organs) should be considered. This may include surgery, stereotactic Tx or other forms of ablation. [GPP] 6. Ipilimumab can be offered in UK following NICE approval of this drug for use in melanoma generically. ***3.7.4. Mgmt. of liver mets*** 1. For pts w technically resectable disease, Ax for curative intent hepatic resection should be offered. Grade D 2. Pre-op diagnostic laparoscopy should be performed in pts w radiologically resectable liver mets, as many of these pts will have miliary pattern of disease. Grade D 3. Regional or systemic Tx may be considered in pts w liver dominant disease where resection not suitable. [GPP] ***3.7.5. Surveillance following liver Tx*** 1. Pts treated w curative intent should be followed w regular (3–4 mo) hepatic MRI and CT of chest, abdomen and pelvis. [GPP] 2. Pt outcomes for this selected group should be collected centrally and prospectively. [GPP]
Princess Margaret, 2015	**Princess Margaret Cancer Centre Clinical Practice Guideline** ***Diagnosis***

Guideline Developer/ Organization, Year	Recommendations

	• Vision care specialists detect uveal mass suspicious for malignancy
	• Initial Ax following referral, pts undergoes complete ophthalmological exam and ancillary testing. All new pts presented to Ocular Oncology consultant group on weekly basis as part of multi-disciplinary review to formulate mgmt plan
	
	Ophthalmic Exam
	• Iris melanomas may be diagnosed earlier b/c more readily visible, posterior (ciliary body, choroidal) UMs diagnosed only after pts evaluated specifically for visual change or suspicious lesion detected incidentally during ophthalmoscopy
	• Iris melanomas better differentiated and less aggressive compared w posterior UMs
	• For posterior UMs, indirect ophthalmoscopic fundus drawing and fundus imaging performed at every visit. Lesions can be pigmented or amelanotic, in flat, dome or mushroom configuration, and can be associated w overlying orange pigment (lipofuscin) and or subretinal fluid. Simulating lesions considered in differential diagnosis
	
	Ancillary Testing
	• UM demonstrates characteristic features on echography that are highly reliable to make accurate diagnosis. Extrascleral extension can be detected using echography if ≥1.5 mm in size
	• Ultrasound biomicroscopy (UBM) can be employed for anterior uveal lesions
	• Neuroimaging (MRI, CT) helpful when lesion suspicious for posterior extrascleral extension
	• Angiographic studies including intravenous fluorescein angiography (IVFA) and indocyanine green angiography (ICGA) can show intrinsic tumour vasculature (double circulation). Abnormal leakage (i.e. hot spots) or blockage (i.e. lipofuscin) may be seen on IVFA
	• Static perimetry useful to monitor visual field changes
	• Certain pts will also undergo optical coherence tomography (OCT) when vision loss occurs secondary to sub-retinal or intra-retinal swelling
	• Patients w indeterminate lesion may be candidate for fine-needle aspiration biopsy (FNAB). Decision made on case-by-case basis in discussion w pt
	
	Systemic Metastatic Disease
	• UM should be managed as systemic disease. In addition to local spread, pts must be evaluated for metastatic lesions
	• Pts typically undergo routine blood work for hepatic enzymes (AST, ALT, bilirubin) and chest/abdominal imaging using U/S or CT
	• Lack of consensus re desired frequency and choice of testing for metastatic screening
	
	Genetic Testing
	• Gene expression profiling separates UM patients into 1 of 2 groups; those who are likely (class 2) vs those who are unlikely (class 1) to undergo metastasis
	  ○ Class 1: well-differentiated chr 6p gain (disomy 3), chromosomal aneuploidy low, Ki-67 antibody positivity low, spindle cell type, met rate low
	  ○ Class 2: stem-cell like ectodermal cells loss of heterozygosity for chr 3 (monosomy 3), chromosomal aneuploidy high, Ki-67 antibody positivity high, epithelioid cell type, met rate high
	• Predictive value of molecular class supersedes clinical, histologic, and cytologic prognosticators. However, important limitations include lack of accuracy due to tumour heterogeneity (i.e. sampling error), lack of availability of various molecular genetic tests, and fact that progression from class 1 to class 2 cannot be anticipated
	• Currently, genetic analysis accomplished off-site when considered advisable
	
	Mgmt Algorithms
	Decision to treat

Guideline Developer/ Organization, Year	Recommendations

	• If systemic work-up negative, mgmt options involve serial observation or local therapy (radiation, surgery, or laser)
	• Tx goals = to prevent metastasis and maintain vision for lesions that are growing or exhibit high-risk features for growth
	• Pts w lesion demonstrating clinical and echographic features consistent w UM (≤Stage IIIC) offered RT or surgery
	• Histopathological diagnosis only available from enucleation specimen or by FNAB
	• Although most agree medium and large tumours should be treated promptly, decision re mgmt of smaller indeterminate tumours more difficult
	• Pts may be offered serial observation, FNAB (for select cases), or occasionally surgery
	• Most agree small tumour can be observed unless it demonstrates growth or has high-risk features for growth
	
	Surgery
	• UM can be treated by enucleation surgery when clinical diagnosis clear. However, when globe-preserving therapy viable option, every effort made to present risks vs benefits of all options to pt
	• Enucleation = definitive procedure whereby entire eyeball removed w sclera intact, w disinsertion of extraocular muscle attachments and optic nerve
	• Tumours that progress despite prior RT often treated by enucleation
	• Permanent orbital implant inserted during surgery, which replaces orbital volume and covered by Tenon's fascial and conjunctival layers after extraocular muscles attached
	• Temporary plastic conformer left in place for 6 weeks after which time ocularist fashions customized prosthetic shell to rest on mucous membrane tissue
	• Some iris or ciliary body melanomas can be excised by local resection
	• Exenteration for recurrence of limited value
	
	Chemotherapy
	• No role for systemic chemotherapy in treating primary intraocular tumour
	
	RT
	• I-125 plaque brachytherapy employed for medium-sized tumours w minimal optic nerve involvement and no to limited extraocular extension, and stereotactic arcs utilized for peripapillary tumours not suitable for I-125 plaques
	• Iodine-125 Plaques
	  ○ Tumours w height of 2-10 mm and basal diameter < 16 mm eligible for brachytherapy
	  ○ Plaque diameter 4 mm wider than widest basal dimension of melanoma, to provide 2 mm clearance circumferentially (plaque range 10-22 mm in 2 mm increments)
	  ○ Prescription point: 85 Gy to tumour apex
	  ○ Dose rate: 50 cGy/hr, delivered over 7 days
	• External Beam RT:
	  ○ Posterior peripapillary medium size tumours (height 2-10 mm, basal diameter < 16 mm, anterior edge of tumour does not cross equator of eye)
	  ○ Immobilization: relocatable stereotactic GTC frame w eye fixation device
	  ○ Simulation: CT, MRI Technique: VMAT, 2 partial arcs
	  ○ Daily image guidance w cone beam CT
	  ○ Dose: 50 Gy/5 fractions, delivered on alternate days over 10 days
	
	Other therapy

Guideline Developer/ Organization, Year	Recommendations
	• Transpupillary thermotherapy (TTT), non-invasive laser Tx, found to be of limited benefit as primary therapy for choroidal melanoma and used only as adjunctive therapy for select cases • Pts w vision loss secondary to macular edema may be treated w intravitreal injection of anti-VEGF agents (bevacizumab or ranibizumab) ***Oncology nursing practice*** Pts seen at Ocular Oncology clinic invariably outpatients. Initial history and Ax of visual acuity and pupil reactivity performed by clinic RN. RN proceeds to instill dilating eye drops in 1 or both eyes prior to photography, echography, and exam by consultant. RN often used as initial point of contact by pts when new symptoms develop or other questions arise ***Clinic Coordination/Mgmt*** Identification of specific disease complex and direction to appropriate subspecialty care usually accomplished by trained ocular oncology clinic coordinator/manager. Individual frequently experienced ophthalmic assistant. Knowledge of vision care referral base and collection of investigational materials for new pts of paramount importance as first steps to providing optimal pt care. Coordinator also serves invaluable function in supporting both pt and family during investigation, therapy, and convalescence ***Supportive Care*** ***Pt education*** • Pts and family members educated on one-on-one basis by consultant during initial Ax and at every F/U visit. ***Psychosocial care*** • When pts express or display emotional, psychological, or social concerns, effort made to address these during clinical encounter. In rare instances when this is insufficient to deal w all issues, pt may be referred to Department of Psychosocial Oncology ***Symptom Mgmt.*** • Pts w UM may/may not present w visual symptoms including visual field loss, blurriness, or flashes of light • Pts treated by radiation educated about short-term symptoms including eye redness, double vision, and discomfort while recovering, and about long-term possibility of dry eyes, cataract formation, or vision loss related to RT • Pts undergoing enucleation surgery educated about possibility of pain, discharge, and swelling that can last several wks after surgery • Pts encouraged to discuss ocular symptoms during every clinical encounter and managed accordingly ***Clinical Nutrition*** • Role of nutritional advice and support in ocular oncology pt population very limited • Pts w dry eye syndrome may be educated about value of omega-3-fatty acid and flax seed intake while those w age-related macular degeneration may be encouraged to eat green leafy vegetables ***Palliative care*** • When systemic metastasis detected, primary UM may be untreated. However, in cases of intractable ocular pain, palliative enucleation surgery may be considered • Pts w systemic mets typically succumb to disease b/c currently no effective therapies • Radiation and medical oncology groups facilitate end-of-life palliative care ***F/U Care and Surveillance*** ***Monitoring for growth***

Guideline Developer/ Organization, Year	Recommendations
	• Natural history of UM is to progress locally and systemically • Growth of tumour can be horizontal, vertical, focal or diffuse. Over time, tumours may extend anteriorly through Bruch's membrane, posteriorly through sclera, or undergo extraocular extension via neurovascular or aqueous channels • Horizontal growth best observed by comparing serial fundus images of lesion while vertical growth by comparing serial measurements of thickness using echography. Rate of growth variable amongst pts. Pts demonstrating faster doubling time and growth rate have greater likelihood of developing metastatic disease and tend to be less responsive to RT • Overall, I-125 plaque brachytherapy achieves good local tumour control • Pts followed every 3 to 6 months for first 5 yrs. after Tx and annually thereafter. Pts encouraged to come in sooner if new visual symptoms develop during interval b/n F/U visits • Pts who undergo enucleation surgery monitored yearly after postop recovery period

References

1. Ho VWM, Hussain RN, Czanner G, Sen J, Heimann H, Damato BE. Porous Versus Nonporous Orbital Implants After Enucleation for Uveal Melanoma: A Randomized Study. *Ophthalmic Plast Reconstr Surg*. Nov/Dec 2017;33(6):452-458. doi:10.1097/iop.0000000000000824
2. Eibl-Lindner K, Fürweger C, Nentwich M, et al. Robotic radiosurgery for the treatment of medium and large uveal melanoma. *Melanoma Res*. Feb 2016;26(1):51-7. doi:10.1097/cmr.0000000000000199
3. Willerding GD, Cordini D, Moser L, Krause L, Foerster MH, Bechrakis NE. Neoadjuvant proton beam irradiation followed by transscleral resection of uveal melanoma in 106 cases. *Br J Ophthalmol*. Apr 2016;100(4):463-7. doi:10.1136/bjophthalmol-2015-307095
4. Mishra KK, Quivey JM, Daftari IK, et al. Long-term Results of the UCSF-LBNL Randomized Trial: Charged Particle With Helium Ion Versus Iodine-125 Plaque Therapy for Choroidal and Ciliary Body Melanoma. *Int J Radiat Oncol Biol Phys*. Jun 1 2015;92(2):376-83. doi:10.1016/j.ijrobp.2015.01.029
5. Takiar V, Voong KR, Gombos DS, et al. A choice of radionuclide: Comparative outcomes and toxicity of ruthenium-106 and iodine-125 in the definitive treatment of uveal melanoma. *Pract Radiat Oncol*. May-Jun 2015;5(3):e169-e176. doi:10.1016/j.prro.2014.09.005
6. McWilliams RR, Allred JB, Slostad JA, et al. NCCTG N0879 (Alliance): A randomized phase 2 cooperative group trial of carboplatin, paclitaxel, and bevacizumab ± everolimus for metastatic melanoma. *Cancer*. Feb 1 2018;124(3):537-545. doi:10.1002/cncr.31072
7. Bhatia S, Moon J, Margolin KA, et al. Phase II trial of sorafenib in combination with carboplatin and paclitaxel in patients with metastatic uveal melanoma: SWOG S0512. *PLoS One*. 2012;7(11):e48787. doi:10.1371/journal.pone.0048787
8. Homsi J, Bedikian AY, Papadopoulos NE, et al. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. *Melanoma Res*. Dec 2010;20(6):507-10. doi:10.1097/CMR.0b013e3283403ce9
9. O'Neill PA, Butt M, Eswar CV, Gillis P, Marshall E. A prospective single arm phase II study of dacarbazine and treosulfan as first-line therapy in metastatic uveal melanoma. *Melanoma Res*. Jun 2006;16(3):245-8. doi:10.1097/01.cmr.0000205017.38859.07
10. Schmittel A, Schmidt-Hieber M, Martus P, et al. A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. *Ann Oncol*. Dec 2006;17(12):1826-9. doi:10.1093/annonc/mdl309
11. Schmidt-Hieber M, Schmittel A, Thiel E, Keilholz U. A phase II study of bendamustine chemotherapy as second-line treatment in metastatic uveal melanoma. *Melanoma Res*. Dec 2004;14(6):439-42. doi:10.1097/00008390-200412000-00001
12. Kivelä T, Suciu S, Hansson J, et al. Bleomycin, vincristine, lomustine and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma. *Eur J Cancer*. May 2003;39(8):1115-20. doi:10.1016/s0959-8049(03)00132-1
13. Bedikian AY, Papadopoulos N, Plager C, Eton O, Ring S. Phase II evaluation of temozolomide in metastatic choroidal melanoma. *Melanoma Res*. Jun 2003;13(3):303-6. doi:10.1097/00008390-200306000-00013
14. Pyrhönen S, Hahka-Kemppinen M, Muhonen T, et al. Chemoimmunotherapy with bleomycin, vincristine, lomustine, dacarbazine (BOLD), and human leukocyte interferon for metastatic uveal melanoma. *Cancer*. Dec 1 2002;95(11):2366-72. doi:10.1002/cncr.10996
15. Becker JC, Terheyden P, Kämpgen E, et al. Treatment of disseminated ocular melanoma with sequential fotemustine, interferon alpha, and interleukin 2. *Br J Cancer*. Oct 7 2002;87(8):840-5. doi:10.1038/sj.bjc.6600521

16. Pelster MS, Gruschkus SK, Bassett R, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. *J Clin Oncol*. Feb 20 2021;39(6):599-607. doi:10.1200/jco.20.00605
17. Nathan P, Ascierto PA, Haanen J, et al. Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172). *Eur J Cancer*. Sep 2019;119:168-178. doi:10.1016/j.ejca.2019.07.010
18. Rossi E, Pagliara MM, Orteschi D, et al. Pembrolizumab as first-line treatment for metastatic uveal melanoma. *Cancer Immunol Immunother*. Jul 2019;68(7):1179-1185. doi:10.1007/s00262-019-02352-6
19. Mouriaux F, Servois V, Parienti JJ, et al. Sorafenib in metastatic uveal melanoma: efficacy, toxicity and health-related quality of life in a multicentre phase II study. *Br J Cancer*. Jun 28 2016;115(1):20-4. doi:10.1038/bjc.2016.119
20. Joshua AM, Monzon JG, Mihalcioiu C, Hogg D, Smylie M, Cheng T. A phase 2 study of tremelimumab in patients with advanced uveal melanoma. *Melanoma Res*. Aug 2015;25(4):342-7. doi:10.1097/cmr.0000000000000175
21. Zimmer L, Vaubel J, Mohr P, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naïve patients with metastatic uveal melanoma. *PLoS One*. 2015;10(3):e0118564. doi:10.1371/journal.pone.0118564
22. Luke JJ, Olson DJ, Allred JB, et al. Randomized Phase II Trial and Tumor Mutational Spectrum Analysis from Cabozantinib versus Chemotherapy in Metastatic Uveal Melanoma (Alliance A091201). *Clin Cancer Res*. Feb 15 2020;26(4):804-811. doi:10.1158/1078-0432.ccr-19-1223
23. Shah S, Luke JJ, Jacene HA, et al. Results from phase II trial of HSP90 inhibitor, STA-9090 (ganetespib), in metastatic uveal melanoma. *Melanoma Res*. Dec 2018;28(6):605-610. doi:10.1097/cmr.0000000000000509
24. Carvajal RD, Piperno-Neumann S, Kapiteijn E, et al. Selumetinib in Combination With Dacarbazine in Patients With Metastatic Uveal Melanoma: A Phase III, Multicenter, Randomized Trial (SUMIT). *J Clin Oncol*. Apr 20 2018;36(12):1232-1239. doi:10.1200/jco.2017.74.1090
25. Daud A, Kluger HM, Kurzrock R, et al. Phase II randomised discontinuation trial of the MET/VEGF receptor inhibitor cabozantinib in metastatic melanoma. *Br J Cancer*. Feb 14 2017;116(4):432-440. doi:10.1038/bjc.2016.419
26. Shoushtari AN, Ong LT, Schoder H, et al. A phase 2 trial of everolimus and pasireotide long-acting release in patients with metastatic uveal melanoma. *Melanoma Res*. Jun 2016;26(3):272-7. doi:10.1097/cmr.0000000000000234
27. Carvajal RD, Sosman JA, Quevedo JF, et al. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *Jama*. Jun 18 2014;311(23):2397-405. doi:10.1001/jama.2014.6096
28. Mahipal A, Tijani L, Chan K, Laudadio M, Mastrangelo MJ, Sato T. A pilot study of sunitinib malate in patients with metastatic uveal melanoma. *Melanoma Res*. Dec 2012;22(6):440-6. doi:10.1097/CMR.0b013e328358b373
29. Gonsalves CF, Eschelman DJ, Adamo RD, et al. A Prospective Phase II Trial of Radioembolization for Treatment of Uveal Melanoma Hepatic Metastasis. *Radiology*. Oct 2019;293(1):223-231. doi:10.1148/radiol.2019190199
30. Valsecchi ME, Terai M, Eschelman DJ, et al. Double-blinded, randomized phase II study using embolization with or without granulocyte-macrophage colony-stimulating factor in uveal melanoma with hepatic metastases. *J Vasc Interv Radiol*. Apr 2015;26(4):523-32.e2. doi:10.1016/j.jvir.2014.11.037
31. Leyvraz S, Piperno-Neumann S, Suciu S, et al. Hepatic intra-arterial versus intravenous fotemustine in patients with liver metastases from uveal melanoma (EORTC 18021): a multicentric randomized trial. *Ann Oncol*. Mar 2014;25(3):742-746. doi:10.1093/annonc/mdt585
32. Huppert PE, Fierlbeck G, Pereira P, et al. Transarterial chemoembolization of liver metastases in patients with uveal melanoma. *Eur J Radiol*. Jun 2010;74(3):e38-44. doi:10.1016/j.ejrad.2009.03.064
33. Fiorentini G, Aliberti C, Del Conte A, et al. Intra-arterial hepatic chemoembolization (TACE) of liver metastases from ocular melanoma with slow-release irinotecan-eluting beads. Early results of a phase II clinical study. *In Vivo*. Jan-Feb 2009;23(1):131-7.
34. van Iersel LB, Hoekman EJ, Gelderblom H, et al. Isolated hepatic perfusion with 200 mg melphalan for advanced noncolorectal liver metastases. *Ann Surg Oncol*. Jul 2008;15(7):1891-8. doi:10.1245/s10434-008-9881-6
35. Patel K, Sullivan K, Berd D, et al. Chemoembolization of the hepatic artery with BCNU for metastatic uveal melanoma: results of a phase II study. *Melanoma Res*. Aug 2005;15(4):297-304. doi:10.1097/00008390-200508000-00011
36. Agarwala SS, Panikkar R, Kirkwood JM. Phase I/II randomized trial of intrahepatic arterial infusion chemotherapy with cisplatin and chemoembolization with cisplatin and polyvinyl sponge in patients with ocular melanoma metastatic to the liver. *Melanoma Res*. Jun 2004;14(3):217-22. doi:10.1097/01.cmr.0000129377.22141.ea
37. Alexander HR, Jr., Libutti SK, Pingpank JF, et al. Hyperthermic isolated hepatic perfusion using melphalan for patients with ocular melanoma metastatic to liver. *Clin Cancer Res*. Dec 15 2003;9(17):6343-9.
38. Chandran SS, Somerville RPT, Yang JC, et al. Treatment of metastatic uveal melanoma with adoptive transfer of tumour-infiltrating lymphocytes: a single-centre, two-stage, single-arm, phase 2 study. *Lancet Oncol*. Jun 2017;18(6):792-802. doi:10.1016/s1470-2045(17)30251-6
39. Bol KF, van den Bosch T, Schreibelt G, et al. Adjuvant Dendritic Cell Vaccination in High-Risk Uveal Melanoma. *Ophthalmology*. Oct 2016;123(10):2265-7. doi:10.1016/j.ophtha.2016.06.027

40. Schefler AC, Fuller D, Anand R, et al. Randomized Trial of Monthly Versus As-Needed Intravitreal Ranibizumab for Radiation Retinopathy-Related Macular Edema: 1-Year Outcomes. *Am J Ophthalmol*. Aug 2020;216:165-173. doi:10.1016/j.ajo.2020.03.045
41. Seibel I, Vollhardt D, Riechardt AI, et al. Influence of Ranibizumab versus laser photocoagulation on radiation retinopathy (RadiRet) - a prospective randomized controlled trial. *Graefes Arch Clin Exp Ophthalmol*. Apr 2020;258(4):869-878. doi:10.1007/s00417-020-04618-7
42. Murray TG, Latiff A, Villegas VM, Gold AS. Aflibercept for Radiation Maculopathy Study: A Prospective, Randomized Clinical Study. *Ophthalmol Retina*. Jul 2019;3(7):561-566. doi:10.1016/j.oret.2019.02.009
43. Matet A, Daruich A, Zografos L. Radiation Maculopathy After Proton Beam Therapy for Uveal Melanoma: Optical Coherence Tomography Angiography Alterations Influencing Visual Acuity. *Invest Ophthalmol Vis Sci*. Aug 1 2017;58(10):3851-3861. doi:10.1167/iovs.17-22324
44. Lieb M, Tagay S, Breidenstein A, et al. Psychosocial impact of prognostic genetic testing in uveal melanoma patients: a controlled prospective clinical observational study. *BMC Psychol*. Jan 31 2020;8(1):8. doi:10.1186/s40359-020-0371-3
45. Dalvin LA, Shields CL, Ancona-Lezama DA, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. *Br J Ophthalmol*. Oct 2019;103(10):1441-1447. doi:10.1136/bjophthalmol-2018-312967
46. Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. *Ann Oncol*. Aug 1 2019;30(8):1370-1380. doi:10.1093/annonc/mdz176
47. Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. *Melanoma Res*. Dec 2019;29(6):561-568. doi:10.1097/cmr.0000000000000575
48. Schefler AC, Koca E, Bernicker EH, Correa ZM. Relationship between clinical features, GEP class, and PRAME expression in uveal melanoma. *Graefes Arch Clin Exp Ophthalmol*. Jul 2019;257(7):1541-1545. doi:10.1007/s00417-019-04335-w
49. Weis E, Roelofs K, Larocque M, Murtha A. Gene Expression Profiling as an Adjunctive Measure to Guide the Management of Indeterminate, High-Risk Choroidal Melanocytic Lesions: A Pilot Study. *Ocul Oncol Pathol*. Feb 2019;5(2):102-109. doi:10.1159/000490252
50. Cai L, Paez-Escamilla M, Walter SD, et al. Gene Expression Profiling and PRAME Status Versus Tumor-Node-Metastasis Staging for Prognostication in Uveal Melanoma. *Am J Ophthalmol*. Nov 2018;195:154-160. doi:10.1016/j.ajo.2018.07.045
51. Nayman T, Bostan C, Logan P, Burnier MN, Jr. Uveal Melanoma Risk Factors: A Systematic Review of Meta-Analyses. *Curr Eye Res*. Aug 2017;42(8):1085-1093. doi:10.1080/02713683.2017.1297997
52. Coupland SE, Kalirai H, Ho V, Thornton S, Damato BE, Heimann H. Concordant chromosome 3 results in paired choroidal melanoma biopsies and subsequent tumour resection specimens. *Br J Ophthalmol*. Oct 2015;99(10):1444-50. doi:10.1136/bjophthalmol-2015-307057

Appendix A: Search Strategy

Database	Date	Search Strategy	Results
PubMed	Mar 3 2021	**Search:** uveal melanoma [MeSH Terms]	1595
		Filters: Clinical Trial, Phase II, Clinical Trial, Phase III, Meta-Analysis, Observational Study, Practice Guideline, Systematic Review, English, Adult: 19+ years, from 2014/1/1 - 2021/3/2	82
		Exclusions: outcomes not related to treatment efficacy or imaging modalities, studies with <10 patients, studies of non-uveal ocular melanomas	52

Appendix B: Levels of Evidence

- Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
- Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
- Level III – prospective cohort studies
- Level IV – retrospective cohort studies or case-control studies
- Level V – studies without a control group, case reports, or expert opinions