Appendix A. Supplementary data

Table A.1
Glaucoma following radiotherapy.

Treatment	Dose Mean, median (range), dose to/as	Dose fractions and dose rate	Follow-up Mean, median (range)	Subjects Patients (eyes)	Glaucoma post-RT Eye retained	Enucleated	Onset post-RT	Reference (year reported)
Malignant disase								
External beam RT								
Single session								
^{60}Co								
Uveal melanoma	66 ± 11[a], NA (NA) Gy	1–6 shots	24 ± 4[a], NA (NA) mo	10 (NA)	0 –	– 1 Pt (NVG)	– 1 yr	[S1] (1996)
Uveal melanoma	53 ± 11[a], NA (NA) Gy	1–6 shots	16 ± 2[a], NA (NA) mo	9 (NA)	0	0	–	[S1] (1996)
Uveal melanoma	54 ± 6[a], NA (NA) Gy	1–6 shots	6 ± 3[a], NA (NA) mo	17 (NA)	1 Pt (NVG)	0	NA	[S1] (1996)
Uveal melanoma	NA, NA (45–80) Gy, tumor margin	Mean 2.7 (1–4) shots	NA, NA (16–94) mo	60 (NA)	21 Pt (NVG)	0	NA	[S2] (2000)
Uveal melanoma	NA, NA (30–80) Gy, tumor margin	1 Fr	NA, NA (12–79) mo	64 (NA)	9% at 41.5 Gy, 48% at 52.1 Gy (NVG)	0	NA	[S3] (2002)
Uveal melanoma	NA, 31.4 (20–76.5) Gy, tumor margin	1 Fr	NA, 32 (10–74) mo	75 (NA)	14 Pt (NVG)	4 Pt (NVG)	NA	[S4] (2002)
Uveal melanoma	50, NA (NA) Gy, max dose	1 Fr	NA, NA (1–3) yr	100 (NA)	0	7 Pt at 1 yr, 1 Pt at 2 yr 0 Pt at 3 yr (SG)	NA	[S5] (2003)
Uveal melanoma	NA, 35 (35–40[b]) Gy, tumor margin	1 Fr in 3–4 h	NA, 31.3 (17.6–60.6[b]) mo	78 (78)	18.7% Pt (NVG)	1–4 Pt (NVG)	NA	[S6] (2009)
Posterior uveal melanoma	70, NA (NA) Gy, tumor periphery	1 Fr	NA, 23.5 (18–36) mo	14 (14)	5 Pt (SG)	2 Pt (SG)	NA	[S7] (1996)
Posterior uveal melanoma	30, NA (NA) Gy, 50% isodose	1 Fr	NA, 40 (16–78) mo	50 (50)	14% Pt (NVG) –	– 4 Pt (NVG)	NA Mostly ≤ the first 3 yr	[S8] (2013)
Choroidal melanoma	NA, 50 (40–80) Gy, tumor margin	1 Fr	38, NA (6–81) mo	32 (NA)	9 Pt (NVG)	6 Pt (NVG)	NA	[S9] (2002)
Ocular melanoma	50–70, NA (NA) Gy, 50% isodose	1 Fr	NA, 63.5 mo (0.5–20 yr)	24 (NA)	20.83% (NVG)	0	NA	[S10] (2012)
Ocular melanoma	45, NA (NA) Gy, 50% isodose	1 Fr	NA, 63.5 mo (0.5–20 yr)	71 (NA)	19.72% (NVG)	0	NA	[S10] (2012)
Ocular melanoma	35, NA (NA) Gy, 50% isodose	1 Fr	NA, 63.5 mo (0.5–20 yr)	62 (NA)	8.06% (NVG)	0	NA	[S10] (2012)
X-rays								
Posterior uveal melanoma	NA, 49 (37–52) Gy, max dose	1 Fr	NA, NA (≤5) yr	96 (NA)	0 –	– 11 Pt (SG)[c]	– 3–5 yr	[S11] (2014)
Uveal melanoma	35, NA (NA) Gy [12 Gy, NA (NA) Gy, ON] [10 Gy, NA (NA) Gy, CB]	1 Fr	NA, NA (≤2) yr	40 (NA)	17.5% Pt (SG)	0	NA	[S12] (2015)
Uveal melanoma	NA, NA (18–22) Gy, 70% isodose	1 Fr in 3 h	13, NA (6–22) mo	20 (NA)	0	0	–	[S13] (2008)
Uveal melanoma	20.3, 20 (17–22) Gy	1 Fr in 3 h	29.6, 26.4 (5.9–84) mo	217 (NA)	33 Pt (glaucoma) –	– 5 Pt (NVG)	Med 20.8 (5.8–54) mo NA	[S14] (2016)
Choroidal or CB melanoma	35 Gy, NA (NA) [NA, 45 (37–51) Gy, max dose] [NA, NA (<8) Gy, ON and OD]	1 Fr	NA, NA (6–110) mo	150 (NA)	0	20 Pt (SG)	NA	[S15] (2017)
Hypofractions								
^{60}Co								
Uveal melanoma	54 ± 8[a], NA (45–70) Gy	1–3 Fr	NA, 28.3 (12–51) mo	62 (62)	3 Pt (SG), 4 Pt (NVG)	6 Pt (NVG)	NA	[S16] (2000)
X-rays								
Juxtapapillary choroidal melanoma	70, NA (NA) Gy [NA, 73.8 (58.7–76.7) Gy, tumor apex] [NA, 72.4 (60.1–77.8) Gy, ON]	5 Fr in 10 d	NA, 18.5 (5–37) mo	28 (28)	20% Pt (NVG) –	– 2 Pt (NVG)	9–15 mo NA	[S17] (2004)
Juxtapapillary choroidal melanoma	70, NA (NA) Gy [NA, 74.6 (47.2–78.6) Gy, max dose to tumor] [NA, 72.9 (60.1–77.2) Gy, max dose to ON]	5 Fr in 10 d	NA, 26 (6–72) mo	64 (64)	NVG incidence 28% at 26 mo –	– 4 Pt (NVG)	Med 20 (9–36) mo NA	[S18] (2009)
Juxtapapillary choroidal melanoma	70, NA (NA) Gy [NA, 74.6 (47.2–78.6) Gy, max dose to tumor] [NA, 72.9 (60.1–77.2) Gy, max dose to ON]	5 Fr in 10 d	NA, 37 (6–106) mo	64 (NA)	NVG incidence 42% –	– 6 Pt (NVG)	Med 20 (9–36) mo NA	[S19] (2009)
Juxtapapillary choroidal melanoma	70, NA (NA) Gy	5 Fr in 10 d	NA, 31.7 (12–48) mo	10 (10)	– 0	6 Pt (NVG) –	Med 19.7 (13–26) mo –	[S20] (2011)
Juxtapapillary choroidal melanoma	60, NA (NA) Gy	10 Fr in 2 wk	NA, 29 (1–77) mo	50 (NA)	9 Pt (NVG) Actuarial rate 18% at 2 yr, 38% at 5 yr	1 Pt (NVG)	NA	[S21] (2011)
Uveal melanoma	NA, NA (60 or 70) Gy, 80% isodose	5 Fr in 10 d	NA, 20 (1–48) mo	90 (90)	8 Pt (NVG) –	– 6 Pt (NVG)	Mostly ≤21 mo ≤4 yr	[S22] (2003)
Uveal melanoma	NA, NA (25–55) Gy	1–4F in 1–16 d	NA, 66 (3–100) mo	16 (NA)	0	3 Pt (SG)	NA	[S23] (2005)
Uveal melanoma	50, NA (NA) Gy	5 Fr in 5 d	NA, 32 (2–92) mo	102 (NA)	1 Pt (NVG) –	– 8 Pt (NVG)	NA Med 33 (16–55) mo	[S24] (2012)
Choroidal melanoma	50, 62 or 70, NA (NA) Gy	5 Fr	NA, 64.5 (40.7–97.4[b]) mo	212 (NA)	21 Pt (NVG)	25 Pt (NVG)	NA	[S25] (2012)

Table A.1 (cont'd)

Treatment	Dose Mean, median (range), dose to/as	Dose fractions and dose rate	Follow-up Mean, median (range)	Subjects Patients (eyes)	Glaucoma post-RT Eye retained	Enucleated	Onset post-RT	Reference (year reported)
Malignant disase								
External beam RT								
Hypofractions								
X-rays								
Juxtapapillary choroidal melanoma	70, NA (NA) Gy, tumor apex [69.7, NA (NA) Gy, OD center] [10.8 Gy, NA (NA) Gy, CB]	5 Fr in 10 d	51, 46 (6–105[b]) mo	64 (NA)	Actuarial rate 47% at 50 mo (NVG)	0	NA	[S26] (2013)
Posterior choroidal melanoma	50, NA (NA) Gy	5 Fr in 5–7 d	NA, 37.8 (19.2–49.9[b]) mo	91 (NA)	9 Pt (NVG)	6 Pt (NVG)	NA	[S27] (2013)
Choroidal metastasis	20, NA (NA) Gy	5 Fr in 5 d	12, NA (1–49) mo	55 (71)	1 eye (NVG)	0	NA	[S28] (2017)
Protons								
Metastatic choroidal tumors	14, NA (NA) GyE	2 Fr, 7–14 GyE/min	10, 8 (1–34) mo	46 (55)	3 eyes (NVG) –	– 0	Mean 18 mo –	[S29] (2005)
Iris melanoma	53.1, NA (NA) Gy	4 Fr in 4 d	NA, 2.7 (NA) yr	88 (NA)	0	0	–	[S30] (2005)
Iris melanoma	60, NA (NA) GyE	4 Fr in 4 d, 12.9–20 GyE/min	NA, 33 (8–72) mo	21 (NA)	0	0	–	[S31] (2006)
Uveal melanoma	54.6, NA (NA) Gy	4 Fr in 4 d	5, NA (NA) yr	20 (NA)	0	7 Pt (NVG)	4–12 mo	[S32] (1998)
Uveal melanoma	52, NA (NA) Gy	4 Fr in 4 d, 50–60 Gy/min	NA, NA (12–78) mo	538 (538)	37 Pt (NVG)	18 Pt (NVG)	NA	[S33] (1999)
Uveal melanoma	60, NA (NA) Gy	4 Fr	NA, 38 (NA) mo	75 (75)	41 Pt (NVG)	0	NA	[S34] (2006)
Uveal melanoma (with TTT)	60, NA (NA) Gy	4 Fr	NA, 38 (NA) mo	76 (76)	38 Pt (NVG)	0	NA	[S34] (2006)
Uveal melanoma	56, NA (NA) GyE	4 Fr	NA, 58.3 (6–194) mo	704 (NA)	48 Pt (NVG) 5-yr rate 12.7%	29 Pt (NVG) 5-yr rate 4.9%	NA	[S35] (2013)
Parapapillary choroidal melanoma	60, NA (NA) GyE [NA, NA (≥50) GyE, OD]	4 Fr in 4 d	78, 77 (4–140) mo	147 (NA)	10 Pt (SG)[d] –	– 7 Pt (SG)[d]	31 ± 30[a] (3–131) mo NA	[S36] (2014)
Parapapillary melanoma	52, NA (NA) Gy	4 Fr in 4 d	69, 53.3 (6–240) mo	865 (NA)	17.9% Pt (glaucoma)	0	NA	[S37] (2016)
Ocular melanoma	50, NA (NA) GyE [10.1, NA (NA) GyE, ON]	5 Fr in 5 d	NA, 31 (18–40) mo	26 (26)	1 Pt (NVG)	0	NA	[S38] (2016)
Choroidal melanoma	60, NA (NA) cGy[e]	4 Fr in 4 d	NA, NA (5–57) mo	105 (NA)	6 Pt (SG)	0	NA	[S39] (2016)
Helium ions								
Uveal melanoma	NA, NA (50) GyE	5 Fr in 8–11 d	14.0, NA (7–23) mo	14 (NA)	0	0	NA[f]	[S40] (1986)
Uveal melanoma	NA, NA (60) GyE	5 Fr in 8–11 d	16.4, NA (6–26) mo	59 (NA)	5 Pt (NVG)	0	NA[f]	[S40] (1986)
Uveal melanoma	NA, NA (70) GyE	5 Fr in 8–11 d	53.4, NA (8–82) mo	25 (NA)	1 Pt (NVG)	0	NA[f]	[S40] (1986)
Uveal melanoma	NA, NA (80) GyE	5 Fr in 8–11 d	38.3, NA (22–58) mo	71 (NA)	16 Pt (NVG)	0	NA[f]	[S40] (1986)
Uveal melanoma	NA, NA (48–80) GyE	4 or 5 Fr in mean 7 (3–15) d	NA, 8.5 (1–17) yr	347 (NA)	35% Pt (NVG)	16% Pt[g]	NA	[S41] (1997)
Carbon ions								
Choroidal melanoma	NA, NA (60–85) GyE	5 Fr	NA, 35 (11–60) mo	55 (NA)	20 Pt (NVG) 3-yr cumulative rate 42.6 ± 6.8%[a]	3 Pt (NVG)	NA	[S42] (2007)
Choroidal melanoma	NA, NA (60–85) GyE, 1 port	5 Fr	NA, 4.6 (0.5–10.6) yr	63 (NA)	30 Pt (NVG) 3-yr incidence rate 41.6% 5-yr incidence rate 49.0%	3 Pt (NVG) at 60 or 77 GyE	NA	[S43] (2013)
Choroidal melanoma	NA, NA (60–85) GyE, 2 ports	5 Fr	NA, 4.6 (0.5–10.6) yr	51 (NA)	6 Pt (NVG) 3-yr incidence rate 13.9% 5-yr incidence rate 13.9%	0	NA	[S43] (2013)
Conventional fractions								
^{60}Co or X-rays								
Choroidal metastasis	NA, NA (30–40) Gy	10–20 Fr. 2 or 3 Gy/Fr	NA, 9 (1–42) mo	39 (52)	1 Pt (acute glaucoma)	0	NA	[S44] (1989)
^{60}Co, ^{137}Cs or X-rays								
CCH	20, NA (NA) Gy	2 Gy/Fr	4.5, 4.0 (0.3–24) yr	36 (36)	0	0	–	[S45] (1997)
DCH in SWS	20, NA (NA) Gy	2 Gy/Fr	5.3, 4.8 (1.5–17) yr	12 (15)	8 eyes (SG)	0	NA	[S45] (1997)
^{60}Co, electrons or X-rays								
Primary extracranial H&N tumors	NA, NA (<30– >75) Gy	N.A.	9, 8 (3–26) yr	64 (68)	5 Pt (NVG)	6 Pt (NVG)	NA	[S46] (1994)
Primary orbital NHL	34.8, 40 (20–50) Gy	Med 2 (1.8–3) Gy/Fr	7.6, 6.2 (0.4–24.3) yr	17 (28)	0	1 Pt (glaucoma) at 36 Gy	NA	[S47] (1996)
Primary orbital NHL	NA, NA (20–51) Gy	1.7–2 Gy/Fr, 5 Fr/wk	NA, 55 (6–232) mo	47 (52)	1 Pt (NVG) at 34.2 Gy (19 Fr in 4 wk)	0	NA	[S48] (2002)
Posterior uveal metastasis	NA, NA (30–40) Gy	2–3 Gy/Fr	NA, 5.8 (0.7–170) mo	483 (578)	1 eye (narrow angle glaucoma)	1 eye (narrow angle glaucoma)	NA	[S49] (1997)
X-rays								
Retinoblastoma	NA, NA (40 or 44) Gy	20 or 22 Fr	NA, 14 (NA) mo	14 (28)	0 –	– 2 Pt (NVG)	– 5–9 mo	[S50] (1996)
NPC (with operation)	67.7, 72 (56–80) Gy, retina	2–2.5 Gy/Fr	66, 62 (48–125) mo	90 (90)	5 Pt (NVG)	0	NA	[S51] (1997)
Nasal and paranasal cancer	NA, NA (50–72) Gy, primary lesion	1.2 or 2 Gy/Fr, 5 Fr/wk	4.5, 3.3 (2.0–11) yr	25 (43)	3 eyes (NVG) at 54–72 Gy –	– 0	Med 22 (16–26) mo NA	[S52] (1999)
PNSNC carcinoma	NA, NA (50–80) Gy	N.A.	39.7, NA (10–108) mo	32 (NA)	1 Pt (glaucoma)	0	NA	[S53] (1996)

Table A.1 (cont'd)

Treatment	Dose Mean, median (range), dose to/as	Dose fractions and dose rate	Follow-up Mean, median (range)	Subjects Patients (eyes)	Glaucoma post-RT Eye retained	 Enucleated	 Onset post-RT	Reference (year reported)
Malignant disase								
External beam RT								
Conventional fractions								
X-rays								
PNSNC tumors	62, NA (54–68) Gy, prescription dose	2 Gy/Fr, 5 Fr/wk	NA, 19 (3–48) mo	40 (NA)	1 Pt (NVG) –	– 0	3 yr –	[S54] (2000)
Sinonasal tumors	NA, 70 (42–70) Gy	35 Fr	NA, 40 (8–106) mo	84 (NA)	1 Pt (NVG) –	– 0	24 mo –	[S55] (2009)
Sinonasal tumors	NA, NA (60–70) Gy	30–35 Fr in 6–7 wk	NA, 52 (15–121) mo	130 (NA)	1 Pt (NVG) –	– 0	24 mo –	[S56] (2012)
Electron or X-rays								
Choroidal metastasis	NA, 35.5 (20–53) Gy	10–30 Fr	NA, NA (1.5–3.5) yr	58 (80)	1 Pt (hemorrhagic glaucoma)	0	NA	[S57] (1998)
POAML	NA, 30.6 (30–50) Gy	15–25 Fr	NA, 66 (3–234) mo	68 (NA)	1 Pt (glaucoma)	0	NA	[S58] (2012)
Internal beam RT								
^{60}Co								
Choroidal melanoma	NA, NA (100–200) Gy	1 Fr	NA, NA (5–18) yr	157 (157)	27 Pt (NVG) –	– 44 patiens (NVG)	Mostly 1–5 yr NA	[S59] (1991)
^{60}Co or ^{106}Ru								
Uveal melanoma	95, NA (43–328) Gy, tumor apex	1 Fr	99, NA (11–169) mo	65 (NA)	15% Pt (NVG)	0	NA	[S60] (1998)
^{60}Co, ^{106}Ru, ^{125}I or ^{192}Ir								
Posterior uveal melanoma	80[h], NA (NA) Gy, tumor apex	1 Fr in mean 8 (2–16) d[h]	42, NA (11–115) mo[h]	1019 (NA)	0 –	– 18 Pt (NVG) at mean 78 Gy	– Mean 38 mo	[S61] (1989)
CB uveal melanoma	84.6, 87.6 (34.9–156) Gy, tumor apex [14.6, 13.7 (1.0–29.8) Gy, OD]	1 Fr	75, 70 (25–212) mo	136 (NA)	17 Pt (NVG) –	– 4 Pt (NVG)	Mean 34 med 32 (5–65) mo NA	[S62] (1999)
^{60}Co or ^{125}I								
Juxtapapillary choroidal melanoma	NA, 85 (45–155) Gy, tumor apex [NA, 120 (13.7–878) Gy, OD]	1 Fr in med 98 (87–298) h, med 86 (23–325) cGy/h Med 119 (18–418) cGy/h	56, 46 (3–249) mo	141 (141)	10 eyes (NVG)	14 eyes (NVG)	NA	[S63] (2008)
^{90}Sr								
Corneal SCC (with operation)	120, NA (NA) Gy	Single daily dose 10 Gy	3.5, NA (NA) yr	1 (1)	0	0	–	[S64] (2009)
^{103}Pd								
Choroidal melanoma (some with HT)	81, NA (39–101) Gy, tumor apex	1 Fr in 5–7 d	38, NA (4–91) mo	80 (80)	0	1 Pt (NVG) at 81 Gy	NA	[S65] (1999)
Choroidal melanoma	85, NA (69.3–164) Gy, tumor apex	1 Fr in 5–7 d	23, 22 (4–64) mo	24 (NA)	0	0	–	[S66] (2012)
Uveal melanoma	73.3, NA (NA) Gy, tumor apex	1 Fr in 5–7 d	51.1, NA (–205) mo	400 (NA)	1 Pt (NVG)	9 Pt (NVG)	NA	[S67] (2009)
^{103}Pd or ^{125}I								
Choroidal melanoma (with HT)	NA, NA (40–88) Gy, tumor apex	1 Fr, 0.37–1.4 Gy/h	22.2, NA (6–55) mo	44 (NA)	0	0	–	[S68] (1992)
Uveal melanoma (with HT)	52.5, NA (39–88) Gy, tumor apex	1 Fr, 0.7–1.2 Gy/h	45, NA (2–90) mo	48 (NA)	0	2 Pt (NVG) at 40–50 Gy (^{125}I)	NA	[S69] (1996)
Uveal melanoma (with TTT)	52.6, NA (NA) Gy, tumor apex	1 Fr	60, NA (8–120) mo	48 (48)	0	4 Pt (NVG)	NA	[S70] (1997)
^{106}Ru								
Choroidal melanoma	150, NA (NA) Gy, tumor apex	1 Fr	NA, NA (≥12) mo	67 (NA)	0	1 Pt (NVG)	NA	[S71] (1986)
Uveal melanoma	NA, 100 (15–200) Gy, tumor apex	1 Fr in med 5.5 (1–23) d	NA, 2.0 or 2.8 (0.1–10) yr	100 (100)	10 eyes (NVG) –	– 0	Med 2.6 (0.5–5.6) yr –	[S72] (1996)
Choroidal melanoma (with TTT)	600 or 800, NA (NA) Gy	1 Fr	20.5, NA (6–49) mo	21 (21)	1 Pt (NVG) at 800 Gy	0	NA	[S73] (1998)
Posterior choroidal melanoma	150, NA (NA) Gy, tumor apex	1 Fr	NA, 5.6 (3–9) yr	52 (52)	0	1 Pt (SG)	NA	[S74] (2002)
Posterior choroidal melanoma	NA, 100 (43.3–207) Gy, tumor apex	1 Fr in med 72 (48–288) h, ≥0.6 Gy/h	NA, 39 (6–83) mo	83 (NA)	3% Pt (glaucoma)	0	NA	[S75] (2013)
Ocular tumors	NA, NA (50–100) Gy	1 Fr	NA, NA (≥5) yr	187 (NA)	0	2 Pt (hemorrhagic glaucoma)	NA	[S76] (2005)
Iris or iridociliary melanoma	152, 145 (70.4–315) Gy, tumor apex	1 Fr in mean 4.4 med 3.5 (1.5–8) d	NA, 6.5 (2–11) yr	36 (NA)	1 Pt (glaucoma)	0	NA	[S77] (2012)
DCH in SWS	38.9, 41.2 (31.0–47.4) Gy, tumor apex	1 Fr in mean 68.9 (46.3–92.5) h	NA, 62 (22–122) mo	5 (5)	1 Pt (SG) –	– 0	75 mo –	[S78] (2015)
^{125}I								
Ocular melanoma	NA, NA (74.3–83.7) Gy, tumor apex	1 Fr, 0.6–1 Gy/h	NA, 46 (25–90) mo	144 (NA)	8 Pt (NVG) –	– 0	Med 15 (4–39) mo –	[S79] (1993)
Retinoblastoma	NA, NA (20–40) Gy	1 Fr in 25–187 h, 0.18–0.8 Gy/h	NA, 29 (2–157) mo	22 (24)	– 0	1 eye (NVG) –	1 yr –	[S80] (2001)
Iris melanoma	NA, 91 (78.6–350) Gy, tumor apex [NA, 4.9 (1.9–11.9) Gy, OD]	1 Fr in med 96 (67–121) h, med 97 (81–368) cGy/h Med 5 (2–12) cGy/h	75, 79 (5–190) mo	38 (38)	4% at 1 yr, and 8% at 5 and 10 yr (NVG)	0	NA	[S81] (2003)

Table A.1 (cont'd)

Treatment	Dose Mean, median (range), dose to/as	Dose fractions and dose rate	Follow-up Mean, median (range)	Subjects Patients (eyes)	Glaucoma post-RT Eye retained	Enucleated	Onset post-RT	Reference (year reported)
Malignant disase								
Internal beam RT								
^{125}I								
Uveal melanoma	NA, 87 (42–109) Gy, tumor apex	1 Fr in med 147 (42–599) h, 57 cGy/h	NA, 3.5 (0.3–10.4) yr	96 (96)	45 Pt (NVG or second glaucoma) 3-yr incidence 55% 5-yr incidence 60%	6 Pt (glaucoma)	NA	[S82] (2004)
Uveal melanoma	100, NA (80–120) Gy	1 Fr	NA, NA (1–12) mo	147 (NA)	20.5% Pt (glaucoma)	0	NA	[S83] (2005)
Juxtapapillary choroidal melanoma	85, NA (NA) Gy, tumor apex [61.9, NA (NA) Gy, OD center] [13.9, NA (NA) Gy, CB]	1 Fr in 7 d, mean 50 (49.5–52.2) cGy/h	51, 46 (6–105) mo	30 (NA)	Actuarial rate 8% at 50 mo (NVG)	0	NA	[S26] (2013)
Conjunctival SCC (postoperative)	56, 50 (50–80) Gy, tumor apex	1 Fr in mean 133 med 142 (93–170) h	42, 46 (7–96) mo	15 (15)	1 Pt (glaucoma)	0	NA	[S84] (2014)
Combined analysis[i]								
Uveal melanoma	88.3, 74 (56–305) Gy, tumor apex	1 Fr (^{60}Co or ^{125}I), 4 Fr (protons)	116, 103 (23–257) mo	23 (23)	0	2 Pt (NVG)	NA	[S85] (2008)
Benign disease								
Externa beam RT								
Hypofractions								
Soft X-rays								
Pterygium (with operation)	NA, NA (5–30) Gy	1–7 Fr	31 or 52, 26 or 57 (NA) mo	65 (NA)	0	0	–	[S86] (2001)
X-rays								
Age-related macular degeneration	NA, NA (<15– >28.5) Gy	4–8 Fr	15, NA (NA) mo	270 (295)	1 Pt (bilateral NVG) at 28.8 Gy (8 Fr)	0	NA	[S87] (2000)

Abbreviations: CB, ciliary body; CCH, circumscribed choroidal hemangioma; d, day(s); DCH, diffuse choroidal hemangioma; Fr, fraction; GyE, absorbed dose in Gy weighted by the relative biological effectiveness value; h, hour(s); H&N, head and neck; HT, hyperthermia; max, maximum; med, median; min, minute(s); mo, month(s); NA, not available; NHL, non-Hodgkin's lymphoma; NPC, nasopharyngeal carcinoma; NVG, neovascular glaucoma; OD, optic disc; ON, optic nerve; PNSNC, paranasal sinus and nasal cavity; Pt, patient(s); POAML, primary ocular adnexal mucosa-associated lymphoid tissue lymphoma; RT, radiotherapy; SCC, squamous cell carcinoma; SG, secondary glaucoma; SWS, Sturge-Weber syndrome; TTT, transpupillary thermotherapy; wk, week(s); yr, year(s).

The numbers in parentheses following means and/or medians indicate a range unless otherwise specified.

[a] Means and standard deviations.

[b] Interquartile range.

[c] This number includes neuropathy in addition to secondary glaucoma.

[d] These numbers include retinopathy and optic neuropathy in addition to secondary glaucoma.

[e] cGy may be Gy.

[f] Mean 14.1 (range 7–31) months applying to all 22 neovascular glaucoma patients in aggregate.

[g] These were mostly due to neovascular glaucoma but also included other complications (those not specified in the paper).

[h] These numbers apply to all 59 enucleated patients in aggregate (of which 18 were due to neovascular glaucoma) but not to all 1019 patients.

[i] Hypofractionated external beam radiotherapy (protons) or internal beam radiotherapy (^{60}Co or ^{125}I).

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Appendix A. Supplementary data

Table A.2
Susceptibility loci for glaucoma.

Glaucoma type	Loci	Function	References
POAG	ABCA1	Integral membrane ABC transporter protein mediating cellular efflux of cholesterol and phospholipid. Mutations in Tangier's disease. Upregulated in the hippocampus following IR. Related to IR-induced dermatitis.	[S88–S93]
	AFAP1	Binds to filamentous actin. Downstream signaling component of TGF-β1 for Src activation, CTGF/CCN2 induction and collagen XIIa.	[S89,S93,S94]
	ANKRD55-MAP3K1[a]	ANKRD55 is a multiple sclerosis risk gene. MAP3K1 related to ocular development and involved in IR-induced apoptotic signaling.	[S93,S95]
	ARHGEF12	Binds to ABCA1. Involved in the RhoA/RhoA-activated kinase pathway.	[S96]
	ASB10	Involved in ubiquitin-mediated protein degradation pathways. Upregulated by TNFα and IL1α.	[S97,S98]
	ATOH7	Transcription factor central to the RGC fate and optic nerve formation. Promotes the differentiation of retinal Müller cells into RGCs.	[S99,S100]
	ATXN2	Involved in endocytosis, mRNA repair, ribosomal translation, mTOR signaling and mitochondrial function.	[S101,S102]
	CAV1, CAV2	Caveolins in caveolae and lipid rafts play critical roles in transcellular transport, endocytosis, mechanotransduction, cell proliferation, membrane lipid homeostasis, and signal transduction. Overexpressed in tumors leading to radioresistance.	[S103–S105]
	CDC7-TGFBR3[a]	p53 downregulates CDC7 kinase leading to G_1/S arrest. TGFBR3 transmembrane proteoglycan regulates TGF-β signaling in fibrotic process.	[S99,S106–S108]
	CDKN2B	Cyclin dependent kinase inhibitor controling G_1 progression. Induced by TGF-β. Mutated/deleted in tumors.	[S99]
	CDKN2B-AS1/CDKN2BAS	Functional RNA molecule whose polymorphisms associated with CVD, CeVD, type 2 diabetes, and endometriosis.	[S93,S106, S109–S111]
	CACNA2D1	Calcium channel involved in various calcium-dependent processes. Mutations in this gene can cause cardiac deficiencies.	[S112]
	CYP1B1	Cytochrome P450 monooxygenase located in ER, catalyzing various reactions in drug metabolism and synthesis of cholesterol, steroids and lipids. Minor alleles cause a boaderline increased risk of breast cancers and significantly increase the dose response relationship assuming a recessive model in USRT. Upregulated by UV exposure.	[S113–S115]
	DLG2	Involved in neuronal signaling and development.	[S116]
	EFEMP1	ECM glycoprotein with tandemly repeated EGF-like repeats. Mutations in Doyne honeycomb retinal dystrophy.	[S117]
	FNDC3B/FAD104	Fibronectin domain containing protein required for craniofacial development. Regulates adipogenesis. Overexpression promotes cancer proliferation.	[S88,S93, S118–S120]
	FOXC1	Transcription factor with a DNA-binding forkhead domain. Regulates embryonic and ocular development. Locus specific DNA methylation occurs following fractionated IR exposures.	[S101,S121]
	GAS7	A putative role in neuronal development. Connects microtubules with actin filaments. Susceptibility gene for schizophrenia.	[S122,S123]
	GMDS	Catalyzes the first step in the synthesis of GDP-fucose from GDP-mannose.	[S89]
	HMGA2	Related to ocular develoment. Delays the clearance of IR-induced foci of phosphorylated histone H2AX.	[S93,S124]
	LHPP	Protein histidine phosphatase. Tumor suppressor.	[S93]
	LMX1B	Related to ocular development.	[S93]
	LOXL1	Involved in elastogenesis and collagen crosslinking. Upregulated in TCFs following UV exposure, oxidative stress, and TGF-β1.	[S93]
	MEIS2	Interacts with FOXC1. Expressed in the trabecular meshwork.	[S93]
	MYOC/TIGR	Mutations cause aggregation and misfolding of proteins resulting in ER stress. A role in cytoskeletal function. Expressed in the trabecular meshwork and other ocular tissues. Secretion modulated by FOXC1.	[S125,S126]
	PMM2	Catalyzes the isomerization of mannose 6-phosphate to mannose 1-phosphate, which is a precursor to GDP-mannose. Involved in glycoprotein biosynthesis.	[S90]
	SALL1	Zinc finger transcriptional repressor. Mutations in Townes-Brocks syndrome.	[S99]
	SIX1	Homeobox protein involved in limb development. Required for eye formation. Overexpressed in cancers leading to radioresistance.	[S99,S111,S127]
	SIX6	Homeobox protein involved in eye development. Upregulates $p16^{CDKN2A/INK4A}$ leading to RGC senescence.	[S93,S110, S111,S128]
	TMCO1	Transmembrane protein serving as an ER Ca^{2+} load-activated Ca^{2+} channel. Mutations associated with craniofacial dysmorphism, skeletal anomalies, and cognitive disability.	[S109,S122,S129]
	TXNRD2/TrxR2	Selenocysteine-containing flavoenzyme reducing thioredoxins. Important for scavenging ROS in mitochondria. Associated with IR-induced subcutaneous fibrosis. Activated by UV exposure.	[S101,S130,S131]
	WDR36	WD repeat protein involved in retinal homeostasis.	[S132,S133]
	8q22	N.A.	[S111]
NTG	OPTN	Coiled-coil containing protein involved in membrane trafficking, protein secretion, autophagy, cell division and negative regulation of the interferon response.	[S134,S135]
	TBK1	Serine/threonine kinase similar to IκB and mediates NF-κB activation. Upregulates $p16^{CDKN2A/INK4A}$ leading to RGC senescence. Regulates IR-induced EMT of lung cancer cells.	[S136–S138]
PACG	CHAT	Involved in acetylcholine generation. Upregulated in the hippocampus following IR.	[S91,S139]
	COL11A1	Extracellular minor fibrillar collagen regulating the diameter of major collagen fibrils. Mutations in Stickler syndrome and Marshall syndrome. Overexpressed in cancers leading to chemoresistance.	[S140,S141]
	DPM2-FAM102[a]	N.A.	[S139]
	EPDR1	Transmembrane protein similar to protocadherins and ependymins. Genetic risk factor for late urinary morbidity after IR therapy.	[S139,S142,S143]
	FERMT2/kindlin-2	Integrin regulation. Mutations in Kindler syndrome characterized by photosensitivity and mechanical skin fragility.	[S139,S144]
	GLIS3	Krüppel-like zinc finger transcription factor. Involved in development of pancreas, thyroid, liver, kidney and eye. Mutations in neonatal diabetes and congenital hypothyroidism syndrome.	[S139,S145]
	PCMTD1-ST18[a]	N.A.	[S140]
	PLEKHA7	Component of adherens junction and tight junction. Implicated in hypertension.	[S140,S146]
XFG	AGPAT1	Enzyme converting lysophosphatidic acid into phosphatidic acid. Localizes in ER. Involved in diacylglycerol/triacylglycerol biosynthesis.	[S147]
	CACNA1A/Cav2.1	Calcium channel involved in various calcium-dependent processes. Mutations cause diverse neurological phenotypes. Involved in IR-induced adaptive response.	[S148,S149]
	LOXL1	Involved in elastogenesis and collagen crosslinking. Upregulated in TCFs following UV exposure, oxidative stress, and TGF-β1.	[S150,S151]
	POMP	Proteasome specific chaperone required for 20S proteasome assembly and for efficient NF-κB signaling.	[S147,S152]
	RBMS3	RNA binding protein controlling RNA metabolism. Tumor suppressor. Regulates G_1/S progression.	[S147,S153]
	TMEM136	Transmemberane protein. Mutations occur in cancers.	[S147,S154]
	5q23 (near SEMA6A)	N.A.	[S147]

Abbreviations: ABC, ATP binding cassette; ABCA1, ATP binding cassette subfamily A member 1; AFAP1, actin filament associated protein 1; AGPAT1, 1-acylglycerol-3-phosphate *O*-acyltransferase 1; ANKRD55, ankyrin repeat domain 55; ARHGEF12, Rho guanine nucleotide exchange factor 12; ASB10, ankyrin repeat and SOCS box containing 10; ATOH7/MATH5, atonal bHLH transcription factor 7; ATP, adenosine triphosphate; ATXN2, ataxin 2; bHLH, basic helix loop helix; CACNA1A, a P/Q type voltage dependent calcium channel subunit α1A; CACNA2D1, an L type calcium voltage-gated channel auxiliary subunit α2δ 1; CAV1/2, caveolin 1/2; CDC7 cell division cycle 7; CDKN2A/B, cyclin dependent kinase inhibitor 2A/B; CDKN2B-AS1/CDKN2BAS, CDKN2B antisense RNA 1; CeVD, cerebrovascular disease; CHAT, choline acetyltransferase; CIP1B1, cytochrome P450 family 1 subfamily B member 1; COL11A1, collagen type XI α1 chain; CTGF/CCN2, connective tissue growth factor; CVD, cardiovascular disease; DLG2, discs large MAGUK scaffold protein 2; DPM2, dolichyl-phosphate mannosyltransferase subunit 2; ECM, extracellular matrix; EFEMP1, EGF containing fibulin-like extracellular matrix protein 1; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; EPDR1, ependymin related 1; ER, endoplasmic reticulum; FAD104, factor for adipocyte differentiation 104; FERMT2, fermitin family member 2; FNDC3B, fibronectin type III domain containing 3B; FOXC1, forkhead box C1; GAS7, growth arrest specific 7; GDP, guanosine diphosphate; GLIS3, GLI-similar 3; GMDS, GDP-mannose 4,6-dehydratase; HMGA2, high mobility group AT-hook 2; IκB, inhibitor of NF-κB; IL1α, interleukin 1α; INK4A/B, inhibitor of kinase 4A/B; IR, ionizing radiation; LHPP, phospholysine phosphohistidine inorganic pyrophosphate phosphatase; LIM, lin-11, Isl-1 and mec-3; LMX1B, LIM homeobox transcription factor 1β; LOXL1, lysyl oxidase like 1; MAGUK, membrane-associated guanylate kinase; MAP3K1, mitogen-activated protein kinase kinase kinase 1; MEIS2, Meis homeobox 2; mTOR, mammalian target of rapamycin; MYOC, myocilin; N.A., not available; NF-κB, nuclear factor κB; NTG, normal-tension glaucoma; OPTN, optineurin; PACG, primary angle-closure glaucoma; PCMTD1, protein-L-isoaspartate (D-aspartate) *O*-methyltransferase domain containing 1; PLEKHA7, pleckstrin homology domain containing A7; PMM2, phosphomannomutase 2; POAG, primary open-angle glaucoma; POMP, proteasome maturation protein; RBMS3, RNA binding motif single stranded interacting protein 3; RGC, retinal ganglion cell; ROS, reactive oxygen species; SALL1, spalt like transcription factor 1; SEMA6A, semaphorin 6A; SIX1/6, Sine oculis homeobox 1/6; SOCS, suppressor of cytokine signaling; ST18, suppression of tumorigenicity 18; TANK, TRAF-associated NF-κB activator; TBK1, TANK-binding kinase 1; TCF, Tenon's capsule fibroblast; TGFBR3/TβRIII, transforming growth factor β receptor 3; TGF-β1, transforming growth factor β1; TIGR, trabecular meshwork-inducible glucocorticoid response; TMCO1, transmembrane and coiled-coil domains 1; TMEM136, transmembrane protein 136; TNFα, tumor necrosis factor α; TRAF, tumor necrosis factor receptor associated factor; TXNRD2/TrxR2, thioredoxin reductase 2; USRT, US radiologic technologist; UV, ultraviolet light; WD, Trp-Asp; WDR36, WD repeat domain 36; XFG, exfoliation glaucoma.

[a] Loci located between these two.

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