The 8th Edition of the AJCC Staging for Retinoblastoma: Mallipatna, et al.

The recently published staging of retinoblastoma by the American Joint Committee on Cancer provides an evidence based clinical staging. When there was insufficient published evidence, the international staging survey data from 18 centres (2802 eyes of 2079 patients) was considered. The TNM system of staging is unique in providing intraocular and extraocular aspects in the same system. The 8th edition is also is the first cancer in AJCC staging to recognize that genetic predisposition (germline *RB1* gene mutation) affects outcome as a risk category, adding the stage group H.

The pathological classification system has also been drastically modified from the previous system, with a logical progression to the tumour stages, making it easier for centres to identify children at risk of developing metastasis.

Summary of Clinical Staging Systems

	AJCC Clinical Staging[1] 8th edition, 2017	IIRC Group [2] Murphree, 2005	ICRB Group [3] Shields, 2006	IRSS Stage [4] Chantada, 2006
cT1	**Intra-retinal tumour(s)** with subretinal fluid ≤5 mm from base of any tumour			
cT1a	Tumours ≤3 mm and further than 1.5 mm from disc and fovea	A, > 3mm to fovea or B, 1.5 to 3 mm	A, > 3mm to fovea or B, 1.5 to 3 mm	-
cT1b	Tumours >3 mm or closer than 1.5 mm from disc or fovea	B	B, ≤3 mm or C, 3 to 5 mm	-
cT2	**Intraocular tumour(s)** with retinal detachment, vitreous seeding, or subretinal seeding.			
cT2a	Subretinal fluid >5 mm from the base of any tumour	C, >5 mm or D, > 1 quadrant	C, or E, tumour >50% of eye volume	-
cT2b	Vitreous seeding and/or subretinal seeding	C, "local" or D, "diffuse"	C, ≤3 mm or D, > 3 mm or E, tumour >50% of eye volume	-
cT3	**Advanced intraocular tumour(s)**			
cT3a	Phthisis or pre-phthisis bulbi	E	E	I or II
cT3b	Tumour invasion of choroid, pars plana, ciliary body, lens, zonules, iris, or anterior chamber	E	E	I or II
cT3c	Raised intraocular pressure with neovascularization and/or buphthalmos	E	E	I or II
cT3d	Hyphaema and/or massive vitreous haemorrhage	E	E	I or II
cT3e	Aseptic orbital cellulitis	E	E	I or II
cT4	**Extraocular tumour(s)** involving orbit, including optic nerve			
cT4a	Radiologic evidence of retrobulbar optic nerve involvement or thickening of optic nerve or involvement of orbital tissues			I or II
cT4b	Extraocular tumour clinically evident with proptosis and/or an orbital mass			IIIa
N1	Evidence of preauricular, submandibular, and cervical **lymph node involvement**			IIIb
cM1	Clinical signs of **distant metastasis**			
cM1a	Tumour(s) involving any distant site (e.g., bone marrow, liver) on clinical or radiologic tests			IVa
cM1b	Tumour involving the CNS on radiologic imaging (not including trilateral retinoblastoma)			IVb
H	**Hereditary Trait**			
HX	Unknown or insufficient evidence of a constitutional RB1 gene mutation			
H0	Normal RB1 alleles in blood tested with demonstrated high-sensitivity assays			
H1	Bilateral retinoblastoma, retinoblastoma with an intracranial primitive neuroectodermal tumour (i.e., trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of a constitutional *RB1* gene mutation			

Summary of Pathological Staging Systems

	AJCC Clinical Staging[1] 8th edition, 2017	IRSS Stage [4] Chantada, 2006
pT1	Intraocular tumour(s) without any local invasion, or with focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head	C0 or C1 N0 or N1
pT2	Intraocular tumour(s) with **local invasion**	
pT2a	Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head	C1 and N1
pT2b	Tumour invasion of stroma of iris and/or trabecular meshwork and/or Schlemm's canal	-
pT3	Intraocular tumour(s) with **significant local invasion**	
pT3a	Massive choroidal invasion (>3 mm in largest diameter, or multiple foci of focal choroidal involvement totalling >3 mm, or any full-thickness choroidal involvement)	C2
pT3b	Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve	N2
pT3c	Any partial-thickness involvement of the sclera within the inner two thirds	S1
cT3d	Full-thickness invasion into the outer third of the sclera and/or invasion into or around emissary channels	S1
cT4	**Extraocular tumour(s)** involving orbit, including optic nerve	
cT4a	Evidence of extraocular tumour: tumour at the transected end of the optic nerve, tumour in the meningeal spaces around the optic nerve, full thickness invasion of the sclera with invasion of the episclera, adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids.	N3 and/or S2

Considerations of evidence from the international staging survey:

1. Tumour Size:

Tumours < 3 mm, > 3 mm, and > 50% and > 2/3 of the eye were compared. The failure-free probability (ie; probability of avoiding enucleation or external beam radiation) of eyes with tumour > 50% of the eye was similar to eyes with tumour > 2/3 of the eye. A tumour < 3 mm predicted excellent failure free probability, and therefore was the cut-off in the cT1 group in the 8th edition of the AJCC staging.

2. Distance of tumour from fovea AND optic nerve:

Tumour distance from the fovea and optic nerve correlated well with failure-free probability. Tumours > 1.5 mm from disc or fovea demonstrated a better failure-free probability, and therefore was the cut-off for distance from the fovea and disc between cT1a and cT1b.

3. Amount of subretinal fluid:

The amount of subretinal fluid (or retinal detachment) surrounding a tumour correlated well with the failure-free probability. Subretinal fluid > 3 mm from the tumour margin demonstrated a worse failure-free probability, and therefore was the cut-off in describing the features of a cT2 tumour.

4. Extent of vitreous seeds:

The distribution of vitreous and subretinal seeds had been presumed important, assuming that localized seeding (<3 mm from the tumour; Group C IIRC) could be treated by brachytherapy while seeding >3 mm would be prone to failure. The survey showed no significant difference between localized and distant seeding, so any seeding constitutes cT2b eyes.

5. Features of eyes at risk of extraocular disease (ie; Group E by IIRC):

Univariate analyses suggested that glaucoma, orbital cellulitis, and tumour touching lens predicted advanced disease. Still pending are multivariate analysis of this subset of data and correlation with death, metastasis, and high-risk pathology on primary enucleation.

6. *Diffused infiltrating retinoblastoma:*

The failure free survival of eyes with diffuse disease was similar to eyes with tumours > 3 mm (Murphree IIRC) and < 50% of the eye (Shields ICRB), therefore were not included in cT3.

References:

1 Mallipatna, A. C. *et al.* in *AJCC Cancer Staging Manual, 8th ed.* (eds Mahul B. Amin *et al.*) Ch. 68, 819-831 (Springer, 2017).

2 Murphree, A. in *Ophthalmic Oncology, Ophthalmology Clinics of North America* Vol. 18 (ed AD Singh) 41-53 (Elsevier Saunders, 2005).

3 Shields, C. L. & Shields, J. A. Basic understanding of current classification and management of retinoblastoma. *Current Opinion in Ophthalmology* **17**, 228 (2006).

4 Chantada, G. *et al.* A proposal for an international retinoblastoma staging system. *Pediatric blood & cancer* **47** (2006).