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**Recent advances in management of retinoblastoma: A review**

Chawla B *et al.* Recent advances in management of retinoblastoma

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**Abstract**

The management of retinoblastoma has evolved significantly over recent years. Current treatment options aim to preserve the globe as well as vision with minimum morbidity. High resolution imaging has improved tumor detection and is useful for prognosticating cases and monitoring response to treatment. Targeted chemotherapy such as intra-arterial and intra-vitreal chemotherapy has shown promising results and these routes are being increasingly employed world-wide for globe preservation. The advent of new radiotherapy techniques has led to improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. This review aims to highlight newer advancements in the field of diagnosis and management of retinoblastoma that have been introduced in recent times, with a special emphasis on globe-preserving therapy.

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**Key words**: Retinoblastoma; Recent advances; Chemotherapy; Radiotherapy

**Core tip:** The management of retinoblastoma has improved significantly over the past few decades. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The purpose of this article is to review the literature on various key developments in the field of retinoblastoma, with particular emphasis on globe-conserving treatment.

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**INTRODUCTION**

The diagnosis and management of retinoblastoma (RB) often presents as a challenge to the ophthalmologist. Recent advances have contributed towards improving the clinical outcome of the most common intraocular malignancy seen in children. Evolution in imaging techniques has facilitated accurate diagnosis and staging of RB. There has been a paradigm shift from enucleation towards conservative treatment modalities that aim at vision and globe salvage. The introduction of intra-arterial and intra-vitreal chemotherapy in recent times has shown encouraging results. The advent of newer radiotherapy techniques have led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. The purpose of this article is to review the literature on various key developments in the field of RB, with particular emphasis on globe-conserving therapies. A brief overview of these recent advances is highlighted below.

**IMAGING**

Imaging plays a key role in the diagnosis of RB. With the introduction of high-resolution three-dimensional (3D) FSE (Fast Spin Echo) Magnetic Resonance Imaging (MRI) and high resolution ultrasound, the diagnosis of RB is no longer a dilemma. Although CT scan is very useful in detecting calcification which can sometimes be missed on ultrasonography, it has been reported that high-resolution three-dimensional (3D) FSE (Fast Spin Echo) T2 weighted imaging with thin sections (0.4 mm) and high Signal to Noise Ratio (SNR) can also detect calcification[1].Gradient-echo T2 weighted MR imaging is also effective in detecting calcified structures[1]. Recently, it has been observed that the difference in ADC (Apparent Diffusion Co-efficient) values on diffusion-weighted MR imaging can be helpful in differentiating between viable and necrotic tumor[2].In addition, this modality can also be used to monitor the response of tumor to chemotherapy in cases of trilateral RB as well as in those eyes that are treated with globe salvaging therapies[2,3].The presence of vitreous haemorrhage can pose difficulty in delineating the tumor, which can be overcome by T1-weighted MR images without the use of gadolinium-based contrast material[4]. Apart from its diagnostic value, MRI is also an established imaging modality for staging of RB[5]. Contrast-enhanced T1-weighted MR imaging with fat saturation is recommended to rule out optic nerve involvement as well as extra scleral involvement[6].The sensitivity and specificity of MR imaging for depicting post-laminar optic nerve invasion has been reported to range from 50%-90%[4,5].A retrospective study by Song *et al*[7] in cases of unilateral RB concluded that focal strong enhancement and enlarged optic nerve on MR films had better correlation with optic nerve invasion than optic nerve enhancement, tumor size and tumor location[7].It is noteworthy that in some children, this enhancement can be due to aseptic cellutis or inflammation of soft tissues rather than true invasion[8]. A short course of systemic steroids and repeat MR imaging facilitates accurate staging in such cases and has been found to be useful in guiding further management[8].

Another application of imaging in RB is the use of high resolution ultrasound to detect the tumor in the fetus at its earliest stage[9].Investigators have used high resolution ultrasound at 37 wk of gestation to detect a 2-3 mm elevated lesion in a fetus at risk of heritable RB[9].Being a rapidly growing tumor, doubling time for RB is considered approximately 15 d[10].Therefore, it has been suggested that infants proven to carry the family's *RB1* mutant allele can be delivered a few weeks early, to optimize the chances of retaining good vision with minimally invasive therapy[11].

**CHEMOTHERAPY**

Although enucleation is accepted as the standard treatment for advanced tumors, local and site selective delivery of chemotherapeutic drugs has shown encouraging results in salvaging the globe as well as vision in many eyes otherwise destined for enucleation. These newer therapeutic approaches are discussed briefly.

***Super-selective Intra-arterial chemotherapy***

This novel approach has evolved rapidly over the last few years and has shown encouraging results in both early and advanced tumors[12,13].Being a site directed therapy, it has considerably fewer systemic side-effects in comparison to conventional intra-venous chemotherapy. Over the last few decades, the selectivity of the technique has improved from sites such as the internal carotid artery,supra-orbital artery and superficial temporal artery,to the currently used ophthalmic artery[14-18]. Melphalan is the drug of choice for intra-arterial chemotherapy and heparin (70 U/kg) is the anticoagulant used.There is no standardised dosing schedule, however, the conventional dose ranges from 3-5 mg per sitting[13,16,17]. Recently, Abramson *et al*[16]and Gobin *et al*[17]have recommended intra-arterial chemotherapy as a safe and effective treatment for advanced intra-ocular RB. Although intra-arterial chemotherapy has the advantage of fewer systemic side effects as compared to intravenous chemotherapy, some investigators consider melphalan as a more toxic agent than those drugs which are used for intravenous chemotherapy[19]. Exposure to fluoroscopy related radiation and ophthalmic artery occlusion are other concerns[19].It has been suggested that a selective ophthalmic artery angiogram instead of carotid angiogram can be used to minimise radiation exposure[13].Though not yet established as a primary treatment, intra-arterial chemotherapy has also been used as a first line treatment in less advanced cases of intraocular RB[12]. There are other investigators who consider it as a part of a multi-modal therapeutic approach[13,18].Intra-arterial chemotherapy has been reported to be associated with an overall success rate of 55%-100% in salvaging the globe, in addition to the advantage of very low systemic toxicity[12,13].Recently, Francis *et al*[20] have demonstrated that Carboplatin ± topotecan ophthalmic artery chemosurgery (OAC) can allow for prompt regression of tumors and can be curative as a single agent in combination with focal techniques, with ocular survival of 89.9% at two years. Furthermore, Carboplatin ± topotecan infusions have low hematologic and ocular toxicity and no statistically significant influence on electroretinogram responses, and can be used in conjunction with melphalan-containing OAC[20].It has been recommended that children, especially less than 6 mo of age at the start of treatment with carboplatin, should routinely undergo thorough long-term audiologic monitoring[21].Recently, a single-centre retrospective study has compared the relative incidence of new intraocular lesions after treatment with carboplatin through intravenous (systemic) and ophthalmic artery chemosurgery (OAC) in naïve eyes, or those with prior treatment (systemic chemotherapy/ external beam radiotherapy)[22].The incidence reported were 56%, 2.4% and 8% respectively[22]. The systemic chemotherapy treated patients had multiple new lesions within months of treatment, as compared to fewer new lesions in the OAC group[22]. It was noted that previously irradiated eyes showed delayed appearance of new lesions. The new lesions were more common at a younger age and usually located in the peripheral retina, which can be explained by the centrifugal development of retina[22].

***Intravitreal chemotherapy***

Another local route for drug delivery that has shown promising results in RB is intra-vitreal chemotherapy (IViC)[23,24].However, this route is recommended only as salvage therapy for recurrent or recalcitrant vitreous seeds and should not be considered as a primary treatment[19]. In a study by Munier *et al*[23] in RB cases with recalcitrant vitreous seeds, melphalan was injected intravitreally in a dose of 20-30 μg (0.1 mL of 0.2 mg/mL) using anti-reflux procedure, followed by triple freeze-thaw cryoapplication to sterilize the needle track[23]. The procedure was carried out every 7-10 d and was repeated upto eight injections if a response could be documented, until complete seed fragmentation was observed or complete response was achieved[23].Complete response was established if the seeds (1) completely disappeared (vitreous seeding regression type 0); or were converted into (2) refringent and/or calcified residues (vitreous seeding regression type I); (3) amorphous, often non-spherical, inactive residues (vitreous seeding regression type II); or (4) a combination of the last two (vitreous seeding regression type III)[23]. The authors recommended that IViC could be repeated if vitreous recurrence occurred[23]. In their study, a success rate of 84.14% at 2 years was achieved[23].A localised peripheral salt-and-pepper retinopathy at the injection site was the only complication noted in 10 eyes (43%)[23]. Another retrospective study on intra-vitreal chemotherapy by Shields *et al*[24] showed 100% (11/11) success rate with 1 to 4 cycles of monthly IViC (melphalan 20-30 μg) at 2 year follow-up[24].

***Sub-conjunctival /sub-tenon chemotherapy***

It has been observed that systemic chemotherapy alone may not be sufficient to treat Group C (eyes with focal vitreous or subretinal seeding and discrete retinal tumors of any size and location) and Group D (eyes with diffuse vitreous or subretinal seeding and/or massive, nondiscrete endophytic or exophytic disease) cases[25,26]. Local injections of chemo-therapeutic agents like sub-tenon or sub-conjunctival carboplatin have been used with varying degrees of success, usually as an adjuvant to systemic chemotherapy to avoid enucleation and external beam radiotherapy in cases of group C and group D retinoblastoma with vitreous/subretinal seeds. The Children’s Oncology Group recommends use of 20 mg sub-tenon carboplatin along with chemoreduction and focal consolidation for Group C and D tumors[27]. *Leng et al*[28]have reported a favourable outcome with the use of sub-conjunctival carboplatin in RB tumors that progressed despite ablative therapy[28].

**RADIATION THERAPY**

Despite the established role of radiotherapy (RT) in RB, treatment modalities were shifted to primary chemotherapy combined with local treatment options such photocoagulation, cryotherapy and thermotherapy[29,30].The high incidence of radiation induced growth deformities and second malignancies was attributed to external beam radiotherapy and RT was therefore reserved for tumours refractory to chemotherapy and local therapies. However, the assessments of risk by RT were based on outcomes of radiation delivery in the old era[31,32].In recent times, there has been substantial advancement in radiation therapy and the advent of newer radiotherapy techniques has led to greatly improved radiation delivery to the target and more conformal treatment plans with better normal tissue sparing. These newer radiotherapy techniques which include intensity modulated radiotherapy (IMRT), stereotactic radiotherapy (SRT) volumetric modulated arc therapy (VMAT), proton therapy, and helical tomotherapy (HT) provide highly accurate radiation delivery[33].

Proton beam therapy provides uniform dose coverage of the target and unlike photon beams, has no exit dose and distributes no energy beyond the target. These unique properties reduce the incidence of late effects of radiation. A study by Sethi *et al*[34] compared the risk of second malignancies in survivors of RB treated with photon and proton radiation therapy[34]. The observed 10 year cumulative incidence of RT induced second malignancies were significantly different in proton and photon modalities (*P* = 0.015)[34].However, proton therapy is expensive and is currently not widely available. In another study on the dosimetric comparison of various RT techniques by Eldebawy *et al*[33], it was concluded that inverse image guided radiotherapy using VMAT or HT provides superior conformity index and improved orbital bone and brain sparing[33].

Plaque Brachytherapy is commonly used for recurrent and residual disease after failure with chemotherapy and local therapy. The American Brachytherapy Society Ophthalmic Oncology Task Force (ABS-OOTF) recommends primary brachytherapy for unilateral anterior lesions[35]. Small tumours less than 15 mm in base and up to 10mm in thickness in the absence of vitreous seeding are eligible[35].The choice of radionuclide is decided according to local availability and intraocular dose distribution. I125 and Pd103 are used in North America, whereas I125 and Ru 106 are used in Europe. Dosimetry of plaques presents a unique challenge which is due to the steep dose gradient within the tumour and presence of critical structures within few millimetres of the radioactive source. However, the TG-129 reports that adoption of heterogeneous dose calculation methods in clinical practice would result in dose variation of > 10% and requires careful assessment[36].

**GUIDELINES FOR PATIENT FOLLOW-UP**

After completion of therapy, regular follow-up is extremely important in these children in order to detect any recurrence of tumor, new lesion, or metastatic disease. It is recommended to follow-up all affected cases till the age of 16 years and to conduct screening of unaffected relatives or mutation carriers till the age of five (reference: 2013 Copyright American Cancer Society) or seven years (reference: NHS England/ E04/S(HSS)/a, Copyright NHS Commissioning Board, 2013).

To summarize, the management of RB has evolved significantly over the last few years. Worldwide, there is an increasing trend towards preservation of globe and vision in RB affected children. Newer advancements in diagnostic and therapeutic modalities have resulted in improved treatment outcomes in these children. Familiarity with these diagnostic and treatment modalities is essential for optimum management.

**REFERENCES**

1 **Razek AA**, Elkhamary S. MRI of retinoblastoma. *Br J Radiol* 2011; **84**: 775-784 [PMID: 21849363 DOI: 10.1259/bjr/32022497]

2 **de Graaf P**, Pouwels PJ, Rodjan F, Moll AC, Imhof SM, Knol DL, Sanchez E, van der Valk P, Castelijns JA. Single-shot turbo spin-echo diffusion-weighted imaging for retinoblastoma: initial experience. *AJNR Am J Neuroradiol* 2012; **33**: 110-118 [PMID: 22033715 DOI: 10.3174/ajnr.A2729]

3 **Bonci GA**, Rosenblum MK, Gilheeney SW, Dunkel IJ, Holodny AI. Diffusion-weighted imaging to assess treatment response in a child with trilateral retinoblastoma. *Pediatr Radiol* 2013; **43**: 1231-1234 [PMID: 23478798 DOI: 10.1007/s00247-013-2662-9]

4 **Rauschecker AM**, Patel CV, Yeom KW, Eisenhut CA, Gawande RS, O'Brien JM, Ebrahimi KB, Daldrup-Link HE. High-resolution MR imaging of the orbit in patients with retinoblastoma. *Radiographics* 2012; **32**: 1307-1326 [PMID: 22977020 DOI: 10.1148/rg.325115176]

5 **Chawla B**, Sharma S, Sen S, Azad R, Bajaj MS, Kashyap S, Pushker N, Ghose S. Correlation between clinical features, magnetic resonance imaging, and histopathologic findings in retinoblastoma: a prospective study. *Ophthalmology* 2012; **119**: 850-856 [PMID: 22218144 DOI: 10.1016/j.ophtha.2011.09.037]

6 **Sirin S**, Schlamann M, Metz KA, Bornfeld N, Schweiger B, Holdt M, Schuendeln MM, Lohbeck S, Krasny A, Goericke SL. Diagnostic image quality of gadolinium-enhanced T1-weighted MRI with and without fat saturation in children with retinoblastoma. *Pediatr Radiol* 2013; **43**: 716-724 [PMID: 23314985 DOI: 10.1007/s00247-012-2576-y]

7 **Song KD**, Eo H, Kim JH, Yoo SY, Jeon TY. Can preoperative MR imaging predict optic nerve invasion of retinoblastoma? *Eur J Radiol* 2012; **81**: 4041-4045 [PMID: 23017191 DOI: 10.1016/j.ejrad.2012.03.034]

8 **Chawla B**, Duraipandi K, Sharma S. MRI in retinoblastoma with orbital cellulitis. *Ophthalmology* 2013; **120**: 1308-9.e1-4 [PMID: 23732058 DOI: 10.1016/j.ophtha.2013.01.008]

9 **Paquette LB**, Miller D, Jackson HA, Lee T, Randolph L, Murphree AL, Panigrahy A. In utero detection of retinoblastoma with fetal magnetic resonance and ultrasound: initial experience. *AJP Rep* 2012; **2**: 55-62 [PMID: 23946908 DOI: 10.1055/s-0032-1316465]

10 **Abramson DH**, Schefler AC, Beaverson KL, Rollins IS, Ruddat MS, Kelly CJ. Rapid growth of retinoblastoma in a premature twin. *Arch Ophthalmol* 2002; **120**: 1232-1233 [PMID: 12215105 DOI: 10.1001/archopht.120.9.1232]

11 **Bristowe A,** Staffieri S, Fink M. Managing fetuses at high risk of retinoblastoma: lesion detection on screening MRI. Presented at 2nd Asia-Pacific perinatal imaging (US and MRI) symposium. Vancouver and Whistler, 2014

12 **Abramson DH**, Marr BP, Brodie SE, Dunkel I, Palioura S, Gobin YP. Ophthalmic artery chemosurgery for less advanced intraocular retinoblastoma: five year review. *PLoS One* 2012; **7**: e34120 [PMID: 22545080 DOI: 10.1371/journal.pone.0034120.61]

13 **Thampi S**, Hetts SW, Cooke DL, Stewart PJ, Robbins E, Banerjee A, Dubois SG, Char D, Halbach V, Matthay K. Superselective intra-arterial melphalan therapy for newly diagnosed and refractory retinoblastoma: results from a single institution. *Clin Ophthalmol* 2013; **7**: 981-989 [PMID: 23818751 DOI: 10.2147/OPTH.S43398]

14 **Reese AB**, Hyman GA, Tapley ND, Forrest AW. The treatment of retinoblastoma by x-ray and triethylene melamine. *AMA Arch Ophthalmol* 1958; **60**: 897-906 [PMID: 13582334 DOI: 10.1001/archopht.1958.00940080917010]

15 **Kiribuchi M**. [Retrograde infusion of anti-cancer drugs to ophthalmic artery for intraocular malignant tumors]. *Nihon Ganka Gakkai Zasshi* 1966; **70**: 1829-1833 [PMID: 6009660]

16 **Abramson DH**, Dunkel IJ, Brodie SE, Kim JW, Gobin YP. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. *Ophthalmology* 2008; **115**: 1398-404, 1404.e1 [PMID: 18342944 DOI: 10.1016/j.ophtha.2007.12.014]

17 **Gobin YP**, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. *Arch Ophthalmol* 2011; **129**: 732-737 [PMID: 21320950 DOI: 10.1001/archophthalmol.2011.5]

18 **Suzuki S**, Kaneko A. Management of intraocular retinoblastoma and ocular prognosis. *Int J Clin Oncol* 2004; **9**: 1-6 [PMID: 15162819]

19 **Boughton B.** Intravitreal Chemotherapy for Retinoblastoma: Promising but Controversial. *Eyenet* 2013: 31-33. Available from: http://www.aao.org/publications/eyenet/201309/oncology.cfm

20 **Francis JH**, Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Jonna G, Abramson DH. Carboplatin +/- topotecan ophthalmic artery chemosurgery for intraocular retinoblastoma. *PLoS One* 2013; **8**: e72441 [PMID: 23991112 DOI: 10.1371/journal.pone.0072441]

21 **Qaddoumi I**, Bass JK, Wu J, Billups CA, Wozniak AW, Merchant TE, Haik BG, Wilson MW, Rodriguez-Galindo C. Carboplatin-associated ototoxicity in children with retinoblastoma. *J Clin Oncol* 2012; **30**: 1034-1041 [PMID: 22370329 DOI: 10.1200/JCO.2011.36.9744]

22 **Abramson DH**, Francis JH, Dunkel IJ, Marr BP, Brodie SE, Gobin YP. Ophthalmic artery chemosurgery for retinoblastoma prevents new intraocular tumors. *Ophthalmology* 2013; **120**: 560-565 [PMID: 23177361 DOI: 10.1016/j.ophtha.2012.08.023]

23 **Munier FL**, Gaillard MC, Balmer A, Soliman S, Podilsky G, Moulin AP, Beck-Popovic M. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. *Br J Ophthalmol* 2012; **96**: 1078-1083 [PMID: 22694968 DOI: 10.1136/bjophthalmol-2011-301450]

24 **Shields CL**, Manjandavida FP, Arepalli S, Kaliki S, Lally SE, Shields JA. Intravitreal melphalan for persistent or recurrent retinoblastoma vitreous seeds: preliminary results. *JAMA Ophthalmol* 2014; **132**: 319-325 [PMID: 24407202 DOI: 10.1001/jamaophthalmol.2013.7666]

25 **Friedman DL**, Himelstein B, Shields CL, Shields JA, Needle M, Miller D, Bunin GR, Meadows AT. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. *J Clin Oncol* 2000; **18**: 12-17 [PMID: 10623688]

26 **Chan HSL**, Heon E, Budning A. Improvement of the cure rate of intraocular retinoblastoma without significantly increasing toxicity with higher dose carboplatin teniposide in a cyclosporine multidrug reversal regimen. Presented at the 10th International Symposium on Retinoblastoma. Florida, 2001

27 **Shields CL**, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. *Curr Opin Ophthalmol* 2010; **21**: 203-212 [PMID: 20224400 DOI: 10.1097/ICU.0b013e328338676a]

28 **Leng T**, Cebulla CM, Schefler AC, Murray TG. Focal periocular carboplatin chemotherapy avoids systemic chemotherapy for unilateral, progressive retinoblastoma. *Retina* 2010; **30**: S66-S68 [PMID: 20419851 DOI: 10.1097/IAE.0b013e3181d34a8c]

29 **Shields CL**, Mashayekhi A, Cater J, Shelil A, Meadows AT, Shields JA. Chemoreduction for retinoblastoma. Analysis of tumor control and risks for recurrence in 457 tumors. *Am J Ophthalmol* 2004; **138**: 329-337 [PMID: 15364213 DOI: 10.1016/j.ajo.2004.04.032]

30 **Shields CL**, Meadows AT, Leahey AM, Shields JA. Continuing challenges in the management of retinoblastoma with chemotherapy. *Retina* 2004; **24**: 849-862 [PMID: 15579981 DOI: 10.1097/00006982-200412000-00003]

31 **Marees T**, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst* 2008; **100**: 1771-1779 [PMID: 19066271 DOI: 10.1093/jnci/djn394]

32 **Kleinerman RA**, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, Li FP, Fraumeni JF. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005; **23**: 2272-2279 [PMID: 15800318 DOI: 10.1200/JCO.2005.05.054]

33 **Eldebawy E**, Parker W, Abdel Rahman W, Freeman CR. Dosimetric study of current treatment options for radiotherapy in retinoblastoma. *Int J Radiat Oncol Biol Phys* 2012; **82**: e501-e505 [PMID: 22197231 DOI: 10.1016/j.ijrobp.2011.07.024]

34 **Sethi RV**, Shih HA, Yeap BY, Mouw KW, Petersen R, Kim DY, Munzenrider JE, Grabowski E, Rodriguez-Galindo C, Yock TI, Tarbell NJ, Marcus KJ, Mukai S, MacDonald SM. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer* 2014; **120**: 126-133 [PMID: 24122173 DOI: 10.1002/cncr.28387]

35 **American Brachytherapy Society - Ophthalmic Oncology Task Force.** The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy* 2014; **13**: 1-14 [PMID: 24373763 DOI: 10.1016/j.brachy.2013.11.008]

36 **Chiu-Tsao ST**, Astrahan MA, Finger PT, Followill DS, Meigooni AS, Melhus CS, Mourtada F, Napolitano ME, Nath R, Rivard MJ, Rogers DW, Thomson RM. Dosimetry of (125)I and (103)Pd COMS eye plaques for intraocular tumors: report of Task Group 129 by the AAPM and ABS. *Med Phys* 2012; **39**: 6161-6184 [PMID: 23039655 DOI: 10.1118/1.4749933]

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