Review Article

The Interdisciplinary Diagnosis and Treatment of Intraocular Tumors

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Summary

Background: Recent years have seen major changes in the diagnosis and treatment of solid intraocular tumors, mainly owing to an improved molecular biological understanding of their pathogenesis, new therapeutic approaches for the local treatment of tumors in children, and long-term follow-up observations in clinical trials.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed.

Results: Retinoblastoma is the most common type of primary intraocular tumor, with approximately 8000 new cases per year around the world, while malignant melanoma of the uvea is the most common primary intraocular tumor in adults, with approximately 7000 new cases per year around the world. Intraocular metastases of malignant tumors are ten times more common, in terms of incidence, than primary intraocular tumors and are therefore the most common intraocular tumors overall. Improved methods of intraocular biopsy, diagnostic imaging, and molecular genetic investigation have led to steady improvement in clinical and predictive diagnostic assessment. In the treatment of retinoblastoma, local techniques including brachytherapy and intra-arterial and intravitreal chemotherapy play a prominent role. Prognostic molecular-genetic testing now enables the highly selective identification of uveal melanomas that have a high potential to metastasize. Cutaneous and uveal melanomas differ both in their clinical behavior and in their basic biological features; to date, effective systemic treatment has been established for melanoma of the skin, but not for metastatic melanoma of the uvea. Intraocular metastases are common and often the initial manifestation of an extraocular tumor, particularly lung cancer.

Conclusion: Modern diagnostic and therapeutic concepts for intraocular tumors can only be implemented through the close interdisciplinary collaboration of ophthalmologists, oncologists, radiologists, radiotherapists, pathologists, and human geneticists.

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Almost all types of tissues can give rise to intraocular tumors. Moreover, nearly all malignant tumors elsewhere in the body can metastasize to the eye. This review is therefore restricted to description of the most commonly occurring intraocular tumors and their differential diagnoses. Recently developed methods for molecular genetic identification of risk groups have transformed the treatment strategies for these tumors and necessitate close interdisciplinary cooperation to implement modern treatment concepts. These strategies are presented here.

Retinoblastoma Diagnosis

Owing to the high numbers of patients in countries with rapid population growth, retinoblastoma is the world's most frequently occurring primary intraocular tumor (1). Retinoblastoma is usually detected before the age of 5 years, and the mean age at initial diagnosis is 18 months. Only very rarely is it first identified in adulthood. The cardinal symptoms in childhood are leukokoria and strabismus (*Figure 1*). The so-called Brückner test evaluates the pupillary reflex and has become a standard component of pediatric ocular screening. This test detects leukokoria at an early stage, enabling timely diagnosis of retinoblastoma, in addition to cataract and strabismus (2).

When it is detection of leukokoria that leads to the first diagnosis of retinoblastoma, the tumor has usually already reached an advanced stage. In the early stages, one finds whitish, flat tumors on the retina. In cases of genetic predisposition these may be multifocal or bilateral. Further growth can lead to subretinal and intravitreal spread (*Figure 2*), followed by infiltration of the optic nerve (*Figure 3*) and/or the choroid and by dissemination of tumor cells into the anterior chamber. Across the world, specialist centers use the International Classification of Retinoblastoma (*Table*) more frequently than the TNM (tumor, node, metastasis) classification. The former is better suited to development of treatment strategies independent of tumor stage.

Retinoblastoma as manifestation of a hereditary disposition to cancer

Retinoblastoma is caused by alterations in the tumor

Figure 1: Leukokoria in advanced retinoblastoma as seen in a typical family photograph

Figure 2: Image of the fundus in solitary unilateral retinoblastoma (left); macroscopic image of the exposed eyeball in advanced multifocal retinoblastoma with extensive vitreous body dissemination (right)

suppressor gene *RBI*. Most cases are sporadic rather than familial. Nevertheless, almost 50% of patients have hereditary retinoblastoma. Almost all patients with bilateral retinoblastoma and more than 10% of those with sporadic unilateral disease have a genetic predisposition (3). This predisposition can also be inherited from parents who do not themselves have retinoblastoma (incomplete penetration). The genetic origin of hereditary and non-hereditary retinoblastoma is explained in *eFigure 1*.

Around 5% of patients with hereditary retinoblastoma also develop an intracranial tumor (“trilateral retinoblastoma”). The risk of contracting other cancers (subsequent primary neoplasms, SPN) is elevated, particularly for sarcoma and cutaneous malignant melanoma. Exogenous cancerogenic factors, particularly radiotherapy, greatly increase the risk of SPN (4).

Genetic diagnosis in patients with retinoblastoma

Establishment of genetic origin of a patient’s retinoblastoma affects their treatment and follow-up and prompts screening of their relatives. In most patients with familial or bilateral retinoblastoma, the underlying alteration can be identified in DNA from a blood sample. Patients in whom additional abnormalities are found, particularly delayed motor development and facial dysmorphism (5), should undergo chromosome analysis.

In around 15% of patients with sporadic unilateral retinoblastoma, the genetic origin of the disease can be determined from blood DNA using conventional procedures. In contrast, genetic analysis of the tumor itself reveals the genetic origin of the retinoblastoma in almost all patients. For this reason, samples of the enucleated tumor should be sent for genetic testing. Various analytic procedures are required to cover the broad spectrum of possible alterations in the two *RBI* alleles of the tumor tissue. When the complete tumor genotype has been established, analysis of blood DNA can demonstrate or exclude hereditary retinoblastoma. This genetic differential diagnosis is not possible if only a blood sample is available. In tumors without mutation of *RBI*, analysis for amplification of the *MYCN* oncogene is necessary.

Treatment

In recent years the treatment of retinoblastoma has evolved more than that of almost all other tumors. Percutaneous radiotherapy considerably increases the risk of a second tumor in patients with bilateral retinoblastoma. The life expectancy of patients with hereditary disease is significantly reduced by percutaneous radiotherapy (6), so this form of treatment finds no place in current strategies for the management of retinoblastoma.

In contrast to almost all other malignant tumors of childhood, no prospective randomized studies of the treatment of retinoblastoma have been published. Nevertheless, there is a broad consensus that group A and B tumors should be treated with local procedures such as laser coagulation, cryotherapy, and brachytherapy. The best treatment for group C and D tumors is either systemic chemotherapy, as a rule six cycles of vincristine, etoposide, and carboplatin (possibly in combination with thermochemotherapy), or local intra-arterial or intravitreal chemotherapy (7).

Intra-arterial chemotherapy (IAC) involves highly selective injection of 3–5 mg melphalan into the ophthalmic artery. By this means a study group in New York succeeded in preserving 85% of a series of (prognostically unfavorable) non-pretreated group D eyes over a mean follow-up period of 34 months. The principal complications of this treatment were transient leukopenia and local adverse effects such as erythema and madarosis. The severe local complications comprised phthisis of the affected eye, suprachoroidal hemorrhage, vitreous body hemorrhage, optic nerve palsy, and papillary edema. However, three of the 103

patients in this series developed metastases. For this reason, together with the local complication rate, IAC is controversial. A randomized study of this form of treatment seems essential (8).

The therapeutic armamentarium was extended considerably by the combination of local procedures with intravitreal and intra-arterial chemotherapy (9). The results of a pioneering Japanese study group showed remission of vitreous body dissemination in 68% of 264 eyes treated with intravitreal chemotherapy (total number of injections: 1067) between 1990 and 2011 (10). Only in one eye was there a circumscribed nodular subconjunctival metastasis. After a mean follow-up period of more than 5 years (maximum 138 months), 47% of the eyes had vision of 0.4 or better.

The survival rate of children with retinoblastoma is over 97% in countries with highly developed healthcare systems but under 25% elsewhere. Creation of corresponding structures in these countries represents a particular challenge (11).

Uveal melanoma

Prevalence, incidence, and clinical characteristics

Malignant melanoma of the uvea is the most commonly occurring primary intraocular tumor in adults. Among persons with light-colored skin the incidence is ca. 0.6–0.7 per 100 000 inhabitants, around 10 times higher than in the darker-skinned population. Onset is typically in the sixth decade of life. Patients with the rare dysplastic nevus syndrome (DNS), also known as FAMM syndrome (FAMM, familial atypical multiple mole melanoma), and carriers of an oncogenic mutation of the *BAP1* gene have an elevated risk of malignant melanoma of the uvea. No other associations with systemic diseases, particularly dermatologic conditions, are known. The initial symptoms depend largely on the position of the tumor. Peripheral tumors may go unnoticed for a period of months or even years, not coming to attention until the onset of symptoms such as lens displacement, secondary glaucoma, or visual field defects. Tumors of the posterior pole of the eye (Figure 4) have an early effect on the patient's sight because of their proximity to the macula.

Around half of all patients with melanoma of the choroid or ciliary body die from metastases of the primary tumor. The death rate has remained unchanged since the earliest studies on this topic (12, 13). It is assumed that the patients already have micrometastases at the time of diagnosis and that these are not influenced by the primary treatment. The tumors are divided into those with loss of chromosome 3 (monosomy 3) and a very high risk of metastasis and those without monosomy 3 and a good prognosis (14, 15) (eFigure 2). Activating mutations in the *GNAQ* gene or the paralog *GNA11* gene are found in 90% of uveal melanomas (16, 17).

Treatment

The principal eye-preserving treatments are radiotherapy and surgical excision. Brachytherapy with

Figure 3: Histological section through the posterior pole of the eye and the optic nerve in advanced retinoblastoma with infiltration of the nerve behind the lamina cribrosa

either β -plaques (106 Ru) or γ -plaques (125 J) and percutaneous irradiation with protons are established standard treatments worldwide. Brachytherapy necessitates surgical implantation of a radioactive applicator and presents decisive advantages with regard to the sparing of extraocular structures including the ocular adnexa. Moreover, β -applicators display steep dose reduction with increasing distance from the source, allowing high-dose treatment of small and medium-sized tumors while largely sparing neighboring structures. Proton radiotherapy at appropriate energy levels (60–70 MeV) is characterized by very steep dose drop-off laterally and at the furthest extent of the irradiation, which may be advantageous in the case of tumors adjacent to the papilla or fovea. In tumors less than 6–7 mm thick, 5-year local tumor control rates of over 95% can be achieved with both forms of irradiation. The prospective randomized Collaborative Ocular Melanoma Study (COMS) showed that brachytherapy does not change the individual risk of metastasis. The visual prognosis depends crucially on the site and size of the tumor, with planar tumors in the area of the equator offering the best prospects of a favorable outcome. A review on this topic was published by Damato in 2012 (18). One serious weakness of the research into eye-preserving irradiation of ocular melanomas, however, is the almost complete lack of randomized clinical

TABLE

International Classification of Retinoblastoma (ICRB; simplified)

Group	Findings
A	Tumor thickness <3 mm
B	Tumor thickness >3 mm; located within the temporal arcade
C	Localized vitreous body or subretinal metastasis
D	Diffuse vitreous body or subretinal metastasis
E	Massive tumor with no chance of preserving the eye

Figure 4: Dark pigmented melanoma of the choroid at the posterior pole with surrounding planar exudative retinal detachment

Figure 5: Extensive bilateral metastases of breast cancer with typical leopard-skin pigmentation. RE, right eye; LE, left eye

studies on the functional outcome of the different irradiation techniques.

For large intraocular melanomas (>8 mm thick) surgical resection, either transscleral from external or transretinal, represents the best option with regard to preservation of the affected eye and its function (19). The limits of surgical resection are essentially defined by the tumor's basal diameter (not exceeding 15 mm) and location (outside the temporal arcade). Surgical resection avoids the long-term complications of radiotherapy related to the degeneration of a large necrotic tumor within the eye (so-called toxic tumor syndrome). One study showed that after an average follow-up of 32.3 months the eye itself was preserved in 89% of cases and 13.4% of patients retained sufficient vision for reading (0.5 or better) (19).

Treatment for metastasized uveal melanoma

Around 50% of patients with uveal melanoma develop metastases, with median survival ranging from 4 to 15 months (20). To date no adjuvant treatment capable of improving the prognosis for patients with metastases has emerged. For this reason, participation in clinical

trials represents the recommended treatment strategy, even in the first line. Although uveal and cutaneous melanomas differ biologically, studies of the former have mostly used substances administered to patients with the latter. The remission rates for all published studies of the effects of classical chemotherapy are close to zero. On grounds of its favorable tolerance profile, gemcitabine/treosulfan is a potential alternative treatment for patients who cannot take part in a clinical trial or are not eligible for local treatment in the liver (21).

Metastases of uveal melanoma are exceptionally hepatotropic. Liver dysfunction can be assumed to be the principal cause of death in stage IV. Intensification of the liver dose to increase the effect is therefore a long-established strategy to delay death. Frequently used for this purpose are high-dose melphalan, fotemustin, and cisplatin-based transarterial chemoembolization (TACE) (22–24). Owing to the small case numbers, however, the benefit of these approaches cannot be quantified with confidence. Nevertheless, in view of its good tolerance and the frequent reports of extended periods of disease stability, intra-arterial chemotherapy is thought to be the treatment of choice for patients in whom liver metastases are the predominant issue.

In contrast to cutaneous melanoma, immunomodulatory treatment with checkpoint inhibitors of *PDI*, *PD-L1*, or *CTLA4* as monotherapy shows no benefit in patients with uveal melanoma (25). In uveal melanoma, unlike cutaneous melanoma, the signal pathway of mitogen-activated protein kinase is activated not by mutations in the *BRAF* or *NRAS* gene, but by alteration of *GNAQ/GNA11* (26).

Intraocular metastases

Prevalence, incidence, and clinical characteristics

Examination of eyes donated for research demonstrated the presence of intraocular metastases in 12.6% of patients who died of a metastasizing tumor (27). The risk of metastases in the eye is particularly high in patients who have metastases in more than one organ system. The preferential sites of intraocular metastases are the choroid and (less often) the ciliary body. Metastases to the iris are infrequent, and intraretinal or intravitreal metastases are found even more rarely. An overview is provided by Konstantinidis et al. (28).

The subjective symptoms of intraocular metastases are the same as for other adult intraocular tumors. In over half of the cases the primary tumor is breast cancer; in another quarter, bronchial carcinoma. All other primaries are found relatively uncommonly. They include, in order of frequency (29):

- Tumors of the gastrointestinal tract (circa 4%)
- Prostate cancer (circa 2%)
- Cutaneous melanoma (circa 2%)
- Renal cell cancer (circa 2%)

Choroid metastases manifest clinically either as planar subretinal masses, pigmented or unpigmented,

Key messages

- Worldwide, retinoblastoma is the most commonly occurring primary intraocular tumor while intraocular metastases are thought to be the most prevalent tumors of the eye overall.
- Integration of the Brückner test into the childhood ocular monitoring program presents a real opportunity to improve the early detection of retinoblastoma.
- Local procedures such as laser or cryotreatment, brachytherapy, and intra-arterial or intravitreal chemotherapy are preferentially used in the eye-preserving treatment of retinoblastoma.
- Malignant melanomas of the skin and of the uvea are completely different biological entities, so the treatment strategies for metastasizing cutaneous melanoma cannot be applied to uveal melanoma.
- Intraocular metastases are common and not infrequently overlooked. Proper early diagnostic work-up often enables identification of a primary tumor and avoids blindness in the advanced stages of generalized tumor disease.

with poorly defined borders or as amelanotic biconvex masses. They are often multifocal and bilateral, which is important in narrowing down the potential diagnoses for a given lesion (*Figure 5*). In individual cases it may be impossible to clinically differentiate choroid metastasis from, for example, cavernous hemangioma of the choroid or amelanotic choroidal melanoma. Modern biopsy techniques have greatly improved differential diagnosis in this area. Clinically and with conventional histopathological methods, intraocular metastases of cutaneous melanoma cannot be distinguished from primary uveal melanoma. However, molecular genetic processing of tumor samples permit clear-cut assignment based on the distinct differences in mutation profile between cutaneous and uveal melanomas (30). This differentiation is clinically important, because, as mentioned above, the two clinical treatment pathways diverge widely. Intraocular metastases of lung cancer are the first sign of a previously undetected primary tumor much more frequently than is found for other malignancies (31).

In one third of patients with choroid metastases no primary tumor has yet been detected at the time of initial ophthalmological diagnosis, and in around one third of this group the primary is bronchial carcinoma. Before the introduction of intraocular biopsy, in 17% of patients the primary could not be diagnosed with confidence despite a systematic search for tumors. These patients had a distinctly worse survival rate than the group as a whole (32).

Treatment and prognosis

Percutaneous radiotherapy is the method most commonly used in eye-preserving treatment of intraocular metastases, with a remission rate of 94% (28). Owing to the limited life expectancy, the potential long-term complications such as radiogenic optic neuropathy or cataract are usually not an issue. Local radiotherapy can be considered for solitary metastases, provided the posterior pole is unaffected and further metastases are unlikely. Systemic chemotherapy may bring about

dramatic remission of intraocular metastases, particularly when the primary is breast cancer (29), so in particular cases one can consider awaiting the results of systemic chemotherapy before starting percutaneous radiotherapy. The treatment plan for the individual patient should be determined in an interdisciplinary tumor conference.

Conflict of interest statement

Prof. Bornfeld has received consultancy fees from Allergan and Alimera and payments for lectures from Novartis and Bayer.

Prof. Bauer has received consultancy payments from Bayer, Novartis, and Pfizer.

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References

1. Kivela T: The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009; 93: 1129–31.
2. Gräf M: [Early detection of ocular disorders in children]. *Dtsch Arztebl Int* 2007; 104: 724–9.
3. Lohmann DR, Gallie BL: Retinoblastoma. In: Adam MP, Ardinger HH, Pagon RA, et al. (eds.): *GeneReviews*®. Seattle (WA): University of Washington, Seattle 1994–2017.
4. Temming P, Arendt M, Viehmann A, et al.: Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: a report from the German reference center. *Pediatr Blood Cancer* 2017; 64: 71–80.
5. Mitter D, Ullmann R, Muradyan A, et al.: Genotype-phenotype correlations in patients with retinoblastoma and interstitial 13q deletions. *Eur J Hum Genet* 2011; 19: 947–58.
6. Temming P, Arendt M, Viehmann A, et al.: How eye-preserving therapy affects long-term overall survival in heritable retinoblastoma survivors. *J Clin Oncol* 2016; 34: 3183–8.
7. Abramson DH, Shields CL, Munier FL, Chantada GL: Treatment of retinoblastoma in 2015: agreement and disagreement. *JAMA Ophthalmol* 2015; 133: 1341–7.

8. Yousef YA, Soliman SE, Astudillo PP, et al.: Intra-arterial chemotherapy for retinoblastoma: a systematic review. *JAMA Ophthalmol* 2016; doi: 10.1001/jamaophthalmol.2016.0244 [Epub ahead of print].
9. Biewald E, Holdt M, Bornfeld N: Neue Therapiestrategien beim Retinoblastom: Nichtsystemische Chemotherapie. *Ophthalmologe* 2014; 111: 379–82.
10. Suzuki S, Aihara Y, Fujiwara M, Sano S, Kaneko A: Intravitreal injection of melphalan for intraocular retinoblastoma. *Jpn J Ophthalmol* 2015; 59: 164–72.
11. Hill JA, Kimani K, White A, et al.: Achieving optimal cancer outcomes in East Africa through multidisciplinary partnership: a case study of the Kenyan National Retinoblastoma Strategy Group. *Global Health* 2016; 12: 23.
12. Kivela T, Kujala E: Long-term risk of melanoma-related mortality after uveal melanoma. *JAMA Ophthalmol* 2016; 134: 238–9.
13. Kujala E, Makitie T, Kivela T: Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci* 2003; 44: 4651–9.
14. Prescher G, Bornfeld N, Becher R: Nonrandom chromosomal abnormalities in primary uveal melanoma. *J Natl Cancer Inst* 1990; 82: 1765–9.
15. Thomas S, Putter C, Weber S, Bornfeld N, Lohmann DR, Zeschnigk M: Prognostic significance of chromosome 3 alterations determined by microsatellite analysis in uveal melanoma: a long-term follow-up study. *Br J Cancer* 2012; 106: 1171–6.
16. van Raamsdonk CD, Bezrookove V, Green G, et al.: Frequent somatic mutations of GNAQ in uveal melanoma and blue naevi. *Nature* 2009; 457: 599–602.
17. van Raamsdonk CD, Griewank KG, Crosby MB, et al.: Mutations in GNA11 in uveal melanoma. *N Engl J Med* 2010; 363: 2191–9.
18. Damato B: Progress in the management of patients with uveal melanoma. The 2012 Ashton Lecture. *Eye (Lond)* 2012; 26: 1157–72.
19. Biewald E, Lautner H, Gok M, et al.: Endoresection of large uveal melanomas: clinical results in a consecutive series of 200 cases. *Br J Ophthalmol* 2017; 101: 204–8.
20. Augsburger JJ, Correa ZM, Shaikh AH: Effectiveness of treatments for metastatic uveal melanoma. *Am J Ophthalmol* 2009; 148: 119–27.
21. Schmittel AH, Schmidt-Hieber M, Bechrakis NE, et al.: A randomized phase II trial of gemcitabine plus treosulfan versus treosulfan alone in patients with metastatic uveal melanoma. *J Clin Oncol* 2006; 24: 8018.
22. Heusner TA, Antoch G, Wittkowski-Sterczewski A, et al.: Transarterial hepatic chemoperfusion of uveal melanoma metastases: survival and response to treatment. *Rofo* 2011; 183: 1151–60.
23. Leyvraz S, Piperno-Neumann S, Suci 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* 2014; 25: 742–6.
24. Noter SL, Rothbarth J, Pijl ME, et al.: Isolated hepatic perfusion with high-dose melphalan for the treatment of uveal melanoma metastases confined to the liver. *Melanoma Res* 2004; 14: 67–72.
25. Algazi AP, Tsai KK, Shoushtari AN, et al.: Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer* 2016; 122: 3344–53.
26. Zuidervaart W, van Nieuwpoort F, Stark M, et al.: Activation of the MAPK pathway is a common event in uveal melanomas although it rarely occurs through mutation of BRAF or RAS. *Br J Cancer* 2005; 92: 2032–8.
27. Eliassi-Rad B, Albert DM, Green WR: Frequency of ocular metastases in patients dying of cancer in eye bank populations. *Br J Ophthalmol* 1996; 80: 125–8.
28. Konstantinidis L, Damato B: Intraocular metastases—a review. *Asia Pac J Ophthalmol (Phila)* 2017; 6: 208–14.
29. Arepalli S, Kaliki S, Shields CL: Choroidal metastases: origin, features, and therapy. *Indian J Ophthalmol* 2015; 63: 122–7.
30. Griewank KG, Schilling B, Scholz SL, et al.: Oncogene status as a diagnostic tool in ocular and cutaneous melanoma. *Eur J Cancer* 2016; 57: 112–7.
31. Shah SU, Mashayekhi A, Shields CL, et al.: Uveal metastasis from lung cancer clinical features, Treatment, and outcome in 194 patients. *Ophthalmology* 2014; 121: 352–7.
32. Shields CL, Shields JA, Gross NE, Schwartz GP, Lally SE: Survey of 520 eyes with uveal metastases. *Ophthalmology* 1997; 104: 1265–76.

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Genetic pathogenesis of hereditary and nonhereditary retinoblastoma

Genetic mutations in the retinoblastoma gene (*RB*) are responsible for the development of retinoblastoma.

a) Patients with hereditary retinoblastoma are heterozygous for a pathogenetically altered allele (*rb*) that they have received via the germline (first mutation). Tumor development is triggered by a genetic alteration of the other allele in a cell of the developing retina (second mutation). The patients can pass on the altered (*rb*) or unaltered allele (*RB*) to their offspring, each with a probability of 50%.

b) In patients with somatic mutation mosaic, the first pathogenetic alteration has occurred in the embryonal phase. If the mutant sector with the altered allele (*RB rb*) includes cells of the developing retina, a second mutation can lead to development of a tumor focus. The risk of transmission to offspring depends on the extent to which the mutant sector also contains germline cells.

c) Patients with nonhereditary retinoblastoma are homozygous for unaltered alleles of the retinoblastoma gene (*RB RB*). The alterations in the two alleles of this gene (first and second mutations), thought to be the precondition for development of a tumor focus, occur at a late stage.

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eFIGURE 2

Different gene mutation patterns in uveal melanomas with monosomy 3 and disomy 3

The development of most uveal melanomas is triggered by mutations in one of the two paralog oncogenes *GNAQ* or *GNA11*.

Above: In tumors with monosomy 3 there ensue, due to two mutation events, loss of chromosome 3 (chr. 3) and deactivation of the remaining allele of the *BAP1* gene.

Below: Tumors with preservation of both chromosomes 3 show mutations in either translation initiation factor *EIF1AX* or the *SF3B1* gene, which codes for a splice factor.

Center: One occasionally finds tumors with monosomy 3 and *BAP1* gene mutation, which may have arisen through transformation from tumor cells with a disomy 3 gene mutation pattern.