

Review

Iris Melanoma: Management and Prognosis

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Abstract: Iris melanomas represent 2–5% of uveal melanomas. Iris melanomas vary in their size, shape, degree of pigmentation and clinical behavior. The main local clinical complications of iris melanomas are tumor vascularization, ectropion uvea, pupillary distortion, pigment dispersion, sector cataract, chronic uveitis, hyphema and glaucoma with irreversible optic nerve damage. The most effective treatment for iris nevus and melanoma remains debatable; treatment modalities have been proposed depending on the local status as well as the age and general condition of the patient. A melanocytic iris nevus is usually observed until documented progression is identified. In this case, radiotherapy or surgical resection is generally performed. Cataract, glaucoma and limbal stem cell deficiency are usually secondary to radiotherapy, while incomplete tumor excisions, which could lead to recurrence, hemorrhage, vitreous loss, dislocated lens, iridocyclitis, macular edema, retinal detachment, glaucoma and cataract, are related to surgical resection. In some cases, a combination of radiotherapy and surgery is used. Conservative treatment is an efficient alternative to enucleation and allows good local tumor control.

Keywords: iris melanoma; brachytherapy; proton beam therapy

1. Introduction and General Overview

Uveal melanoma is the most common primary intraocular tumor [1] and arises from the malignant proliferation of uveal melanocytes [2]. About 85% originate in the choroid, followed by the ciliary body (12–15%) and the iris (2–5%), which is the least common site for uveal melanoma [3–8]. McLaughlin et al. found the incidence of uveal melanomas to be about six cases per million people (6.8 for men and 5.3 for women) [9]. For iris melanoma, the incidence varies between 0.2 and 0.9 per million people [10]. The lowest value was found in Finland [11,12] and the highest was found in New Zealand [2,13]. There

is evidence in the literature that the incidence of iris melanoma has been increasing during the last few decades [14], which is likely related to the impact of solar radiation [2,11,12,14]. Reese states the average age of patients with malignant melanomas of the iris is 46 years; i.e., about 10 to 20 years younger than that of patients with malignant melanoma elsewhere in the uvea [15]. In different studies, the mean patient age varies between 45 and 65 (range 10–89 years) [1,8,14–18]. In 1992, Feldman et al. estimated the average patient with iris melanoma to be between 40 and 47 years of age, with few cases of patients below the age of 20 and with the risk of developing the disease increasing with age [3]. The corresponding age-adjusted incidence rates are 0.10 for men and 0.09 for women, while between 70–89 years of age, the age-specific incidence becomes higher in men (0.41) than in women (0.28) [14]. However, there is no statistically significant difference in incidence between genders in other age groups [14]. Prevalence does not seem to be different according to geographic location [13]. McLaughlin reported that iris melanomas are most frequently detected in white patients with a light-colored iris. These conditions were eight times less frequent in black people [9]. On the basis of 3680 cases analyzed in the United States, 96% of sufferers were estimated to be Caucasians, while African Americans were estimated to comprise 2% of the total, Hispanics 1% and Asians and others <1% [19]. An international, multicenter, Internet-assisted study in ophthalmic oncology demonstrated that, among 131 patients diagnosed from August 1990 to July 2010 with iris tumors, 125—the majority (95.4%)—were white [20]. A pre-existing nevus is the most common origin of iris melanoma, although de novo cases do occur [9]. In 2013, Shields et al. reported that 3% of iris nevus turns into melanoma at 5 years, 4% at 10 years and 11% at 20 years based on follow-up [19]. Epidemiological, physiological and genetic data suggest that high levels of solar ultraviolet B radiation can be involved in the pathogenesis of iris melanomas, although this evidence is controversial [9]. There is also evidence that a light-colored iris and skin color are risk factors for iris melanoma [9]. The loss of chromosome 3 and loss of chromosomal region 9p21, equivalent to tumor suppressor gene CDKN2A, also play a role in developing iris melanoma [18]. Moreover, studies show that chromosomal alterations observed in iris melanoma are different from posterior uveal melanoma [9].

Iris melanomas vary in their size, shape, degree of pigmentation and clinical behavior [15] and usually present as a solitary nodular tumor [7]. The variability of pigmentation (a sign of cellular heterogeneity) is more often associated with a malignant histology, fast progression and poor prognosis [8,15]. Pigmentation may change between being heavily diffuse, variable or amelanotic. The areas of origin—from the most to the least frequent—are the peripupillary iris, the midzone and the iris periphery [7]. They can extend to the anterior and/or the posterior chamber, commonly being limited by the lens [21]. In sequential order, the most affected quadrant is the inferior (between the positions of 5 and 7 o'clock), followed by the temporal, nasal and then superior quadrant [7]. Ten percent of all iris melanomas are diffuse iris melanoma (DIM). DIM appears as a flat, infiltrating tumor with possible seeding that progressively changes the iris coloration and rate of invasion to the angle, resulting in a secondary glaucoma that responds poorly to hypotensive eye drops, causing severe disc cupping and functional loss [21]. Tapioca melanoma, which is a particular form of DIM—named for its macroscopic resemblance to tapioca pudding—is characterized by the diffuse, circumferential, neoplastic involvement of the iris and anterior chamber angle and may involve the ciliary body causing glaucoma [21]. According to Shields, to correctly diagnose an iris melanoma, the lesion should replace the stroma of the iris, should be larger than 3 mm in diameter and 1 mm in thickness and should present at least three of the following five features: photographic evidence of growth, secondary cataract, glaucoma, conspicuous vascularity and iris ectropion [22]. Jakobiec and Silbert believe that ectropion uvea, vascularity, pupil distortion, involvement of the angle and glaucoma could be evident in other types of lesions (nevus or melanoma) [23]. They propose only the involvement of the ciliary body as the most indicative aspect of malignancy, while Shields is of the opinion that documented growth is the most important sign to diagnose iris melanoma [22].

After the evaluation of 1611 eyes, Shields et al. constructed an ABCDEF guide to remember the risk factors that are predictive of iris nevus growth to melanoma, where A is age (young), B is blood

(past episodes of hyphema), C is the clock hour (a tumor location from 4 o'clock to 9 o'clock), D is a diffuse configuration, E is ectropion and F is a feathery margin. These key clinical features help to identify iris melanoma at a time in which therapy could be life-saving [22]. The main local clinical complications of iris melanomas are tumor vascularization (in terms of sentinel episcleral vessel and posterior iris feeder vessel), ectropion uvea, pupillary distortion, pigment dispersion, sector cataract, chronic uveitis [19], hyphema and glaucoma with irreversible optic nerve damage [23]. The most common mechanism of elevated intraocular pressure (IOP) in patients with iris tumor is the invasion of the trabecular meshwork with outflow reduction, whereas the anterior displacement of the iris and lens and iris neovascularization, leading to angle closure, are the main mechanisms in choroidal melanoma [17]. Shields et al. demonstrated that an elevated IOP and iris root invasion are risks that are almost exclusively related to iris melanoma; in fact, increased IOP is encountered in approximately 7–30% of patients with iris melanoma and only 2% of those with choroidal melanoma [17]. Moreover, Shields et al. analyzed the clinical factors that are statistically associated with glaucoma: the seeding of melanoma into the anterior chamber angle, large tumor size, the tumor epicenter being at the iris root, a flat shape and a visual acuity less than 20/20 [17]. In general, the greater the clock hour involvement with angle seeds, the greater the IOP. In addition, in an eye with iris melanoma and glaucoma, the likelihood of metastasis increases considerably [17]. For a precise patient diagnosis, the following lesions in the iris need to be differentiated: congenital heterochromia, congenital ectropion iridis, Cogan–Reese syndrome (iridocorneal endothelial syndrome, which usually affects one eye of young to middle-aged women), siderosis, hemosiderosis, pigmentary glaucoma, melanocytolytic glaucoma [21], Koeppe or Busacca nodules characteristic of sarcoidosis, Lisch nodules in neurofibromatosis, iris nevi, iris cysts, iris metastases, leiomyoma, juvenile xanthogranuloma and ciliary body melanoma with anterior extension [7].

2. Imaging Studies

In order to monitor growth and to describe the dimensions of the basal and antero-posterior diameter, as well as the margins, of iris melanoma, there is agreement in the literature regarding the use of sequential photographs with a slit lamp and ultrasound biomicroscope, obviously before dilation. Ultrasound Bio Microscopy (UBM) is a high-resolution ultrasound technique that allows noninvasive in vivo imaging of structural details of the anterior ocular segment at near-light microscopic resolution and provides a detailed assessment of anterior segment structures, helping to differentiate solid iris lesions from iris cysts (acoustically empty), as well as to detect the involvement of the anterior chamber angle and ciliary body. Moreover, this examination can show a “lion’s paw” appearance, defined as a posterior extension of the iris delimited by the lens [24].

Anterior Segment Optical Coherence Tomography (AS-OCT) is a relatively new imaging technique, without direct contact with the eye, based on low-coherence interferometry, measuring the time delay and intensity of light back-reflected from tissue structures at various depths compared with a reference standard [25]. In the literature, AS-OCT is compared with UBM in imaging anterior segment lesions. Hau et al. suggest that Anterior Segment Optical Coherence Tomography can be used in minor iris tumors with a low degree of pigmentation, whereas UBM is suggested for tumors of the ciliary body and those with heavy pigmentation [26]. They also suggest that AS-OCT is better than UBM for imaging iris lesions measuring ≤ 2 mm at the base and 0.6 mm in elevation, whereas UBM is superior for lesions larger than 3 mm, heavily pigmented lesions and those with posterior or ciliary body invasion [26]. Fluorescein angiography, which is usually less performed in clinical practice for posterior uveal melanomas, is rarely helpful to establish diagnosis [7,22]. The vascular pattern of the tumor is irregular compared with the normal vascular pattern of the iris, and it can be hyperfluorescent inside and around the tumor. If fluorescein leakage is noted at a site that is distant from the tumor, occult or multifocal tumors should be suspected. In general, a disorganized vasculature showing a wide leakage of dye is suggestive of malignancy [7]. The use of computerized tomography and magnetic resonance imaging has also been described [27].

3. Tumor Staging and Histological Findings

The clinical and pathologic staging guidelines of the seventh edition of the American Joint Committee on Cancer–Union for International Cancer Control (AJCC-UICC) TNM system are derived from a multicenter retrospective evaluation of more than 8000 patients and document tumor size and extension, the presence of secondary glaucoma, regional lymph nodes and distant metastasis: T0—No evidence of primary tumor; T1—Tumor limited to the iris; T1a—Tumor limited to the iris (not more than three clock hours in size); T1b—Tumor limited to the iris (more than three clock hours in size); T1c—Tumor limited to the iris with secondary glaucoma; T2—Tumor confluent with or extending into the ciliary body, choroid or both; T2a—Tumor confluent with or extending into the ciliary body, choroid or both with secondary glaucoma; T3—Tumor confluent with or extending into the ciliary body, choroid or both with scleral extension; T3a—Tumor confluent with or extending into the ciliary body, choroid or both with scleral extension and secondary glaucoma; T4—Tumor with extraocular extension; T4a—Tumor with extrascleral extension <5 mm in diameter; T4b—Tumor with extrascleral extension >5 mm in diameter; NX—Regional lymph nodes cannot be assessed; N0—No regional lymph node metastasis; N1—Regional lymph node metastasis; MX—Distant metastasis cannot be assessed; M0—No distant metastasis; M1—Distant metastasis; M1a—Largest diameter of the largest metastasis (<3 cm); M1b—Largest diameter of the largest metastasis (3.1–8.0 cm); M1c—Largest diameter of the largest metastasis (>8 cm); GX—Grade cannot be assessed; G1—Spindle cell melanoma; G2—Mixed cell melanoma; and—G3 Epithelioid cell melanoma. The AJCC eighth edition classification for iris melanoma showed minimal changes compared with the seventh edition. The main differences are evident in categories T2 and T3. The more recent eighth edition differentiates category T2 with regards to invasion of the ciliary body only (T2a) and both the ciliary body and choroid (T2b). Moreover, it eliminates the T3a category because of the small number of iris melanomas that fall into this category. Categories T1 and T4 remained unchanged [28].

When there is a clinical suspicion of melanoma, fine-needle aspiration biopsy (FNAB) is recommended [10]. The most frequently used needles for ophthalmic FNAB are 25 to 30 gauge, because the likelihood of an insufficient sample increases with needles below 22 gauge and above 30 gauge [10]. In order to decrease the risk of a negative biopsy, Medina et al. recommended bending the needle tip to 90 degrees and entering the tumor tangentially rather than radially [10,29]. The sample is then retrieved using intraocular forceps that are specially designed for histological and immunohistochemical typing. Complications from iris biopsy such as persistent hyphema, prolonged hypotony, lens damage or endophthalmitis have been reported in less than 1% of cases [10]. Adequate results can be achieved in collaboration with an experienced surgeon and cytopathologist [10]. Iris melanomas usually have a blander morphology than choroidal and ciliary body melanomas and vary from completely amelanotic to densely pigmented. There are three histologic types of iris melanomas: spindle cell, mixed cell and epithelioid cell melanomas. Morphologically, spindle cells or epithelioid cells may be observed. The first have nuclei with linear interdigitation related to a chromatin strip, small nucleoli (spindle B cells) or with no evidence of nucleoli (spindle A cells). Epithelioid cells are larger, polygonal cells with an abundant, glassy cytoplasm, distinct cell border and a large, round nucleus with marginated coarse chromatin [30]. Mixed cell type melanomas have a variable number of both cell types. The mitotic activity of iris melanomas is usually low and varies from 1 to 3 mitoses per 20 high-power fields. Iris melanomas, as choroidal and ciliary body melanomas, are positive for S100 protein, HMB45 antigen, and melan-A [30]. In the literature, most reported iris melanomas are spindle cell melanomas, whereas diffuse iris tumors tend to be of the epithelioid cell type with a resultant higher risk of metastasis than circumscribed ones [30].

Numerous studies show that histology—in particular, the presence of epithelioid cells—gives a worse prognosis with a higher risk of metastasis [8]. In a retrospective non-comparative case series of patients diagnosed with iris melanoma from 1980–2000 from the University of Sydney, Conway et al. identified three features associated with an epithelioid component: rapid growth (<3 years), prominent tumor vessels and heterogeneous pigmentation. Their presence increases the likelihood of a more

malignant phenotype, although their absence does not rule out this possibility [8]. In this series, pupil distortion, ectropion uveae, sector cataract and anterior chamber angle involvement are not significantly associated with an epithelioid cell component [8].

4. Treatment and Management

4.1. Surgical Excision

As many primary iris lesions have a benign prognosis, many authors tend to manage smaller iris tumors (less than 3 mm basal diameter) in a conservative way [9]. However, the treatment of choice for growing lesions has typically been excision, while advances in microsurgical techniques and equipment have allowed more accurate tumor resection with fewer complications and less trauma to the eye. If the tumor is localized in the iris with no extension to the iris roots or seeding, Shields et al. suggested a partial lamellar scleroidectomy with a scleral flap incision to reduce postoperative astigmatism, and a wide limbal incision (five or more clock hours) to prevent cancer cells from touching surrounding tissues, according to the “no touch” technique; that is, without handling the tumor tissue directly [17]. It is essential to resect at least 1 to 2 mm of safety margins [17]. In cases of confined tumors with iris root invasion but with no seeding, a partial lamellar iridocyclectomy with a more posterior scleral flap, large incision and excision of the entire iris mass surrounded by the normal iris and ciliary body may be preferable [17]. Serious management problems arise when the seeding of the tumor occurs on the contiguous iris or in the angle, as well as at a distance on the lens or on the corneal endothelium [17]. When seeding from iris melanoma is diffuse, the ophthalmic surgeon is advised to perform enucleation after cytologically confirming the diagnosis (FNAB) or, in special circumstances, using plaque radiotherapy [17]. However, if the seeding is confined to a size of within one or two clock hours of the tumor, the careful removal of the whole mass and seeding is executed, usually followed by the insertion of a radioactive plaque to the resection site [17]. In the literature, complications following iris melanoma resection include hemorrhage, vitreous loss, dislocated lens, iridocyclitis, macular edema, secondary glaucoma, retinal detachment and cataract. The rate of vitreous loss, hemorrhage and macular edema is low [8]. Other disadvantages arise from the large opening of the iris, such as diplopia, photophobia, sensation of glare and cosmetic alteration of the iris. Although good visual acuity can be provided with spectacle correction, the best correction method remains the use of a toric, rigid gas-permeable contact lens; in particular, lenses including an artificial pupil [9].

Compared with radiotherapy, surgical resection shows advantages such as tumor removal, minimal cataract and a lack of radiotherapy-induced side effects [1]. The incidence of recurrence and metastases is similar for all procedures. In a comparison between radiotherapeutic and surgical treatment of iris melanoma, Yousef and Finger state that tumor resection presents a higher risk of complications (hemorrhage and endophthalmitis) than plaque radiotherapy, which is an external procedure [31].

Samira Khan et al. assert that smaller tumors (diameter <5 mm) are more likely to be managed by surgery alone and that larger tumors (diameter ≥5 mm) are more likely to be managed by radiotherapy [20].

4.2. Proton Beam and Plaque Radiotherapy

In cases of non-resectable iris melanoma, proton-beam radiotherapy offers excellent local tumor control [6,32,33], particularly in the diffuse form, and because of the scant alternatives, it offers an acceptable rate of complications, preserving visual function in most patients during follow-up [33] (Figure 1).

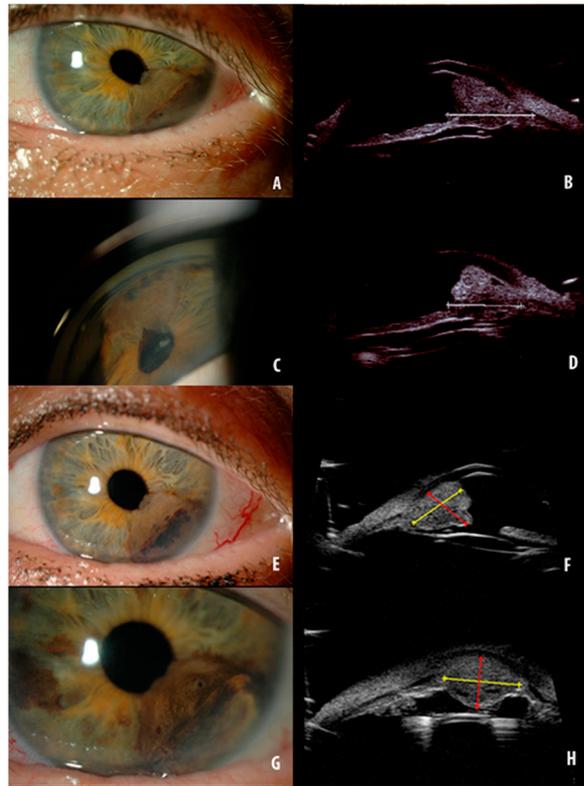


Figure 1. Iris melanoma before proton-beam therapy (A,C), Ultrasound Bio Microscopy (UBM) of iris melanoma before proton-beam therapy, with a size of 5.9×4.4 mm. (B,D). Iris melanoma 6 months after proton-beam therapy (E,G), UBM of iris melanoma 6 months after proton-beam therapy with a size of 5.3×4.1 mm (F,H).

Proton-beam therapy is a form of highly collimated external-beam radiotherapy that uses protons rather than X-rays. Proton beam therapy is characterized by precise dose delivery to the tumor through the cornea [33]. In plaque radiotherapy, a radioactive disc is sutured for a certain amount of time on the surface of the globe for the radiation of the iris melanoma through the cornea [4,31]; it can be delivered without prior resection or after the resection of a high degree of a malignant iris melanoma, or when tumor cells reach the margin of the resection specimen [17]. In a review of 17 studies comprising a total of 761 eyes, Popovic et al. compared outcomes following the radiotherapeutic and surgical management of iris melanoma, with a particular focus on common complications, local tumor recurrence and metastases [1]. They reported that more tumors are treated with radiotherapy (with proton-beam therapy at 49.4% and plaque radiotherapy at 31.4% of the total) compared to surgical excision (19.2%). Rates of local recurrence (with a range of 0–8%) and metastatic development (0–5%) are favorable after proton-beam therapy and plaque radiotherapy. They also showed that the most common complications were cataract (36–73%) and glaucoma (3–92%) [1]. The exact etiology of elevated IOP after treatment appears to be a combination of both tumor seeding into the angle and radiation effects on the angle structures (increased pigmentation with open configuration, angle closure and neovascularization in a minority of cases) [1]. Glaucoma filtration procedures should not be performed in this setting in the case of a possible iris melanoma, as they might lead to the seeding of the tumor cells and metastasis [4].

As opposed to choroidal melanoma [34,35], no radiation maculopathy, papillopathy, vitreous hemorrhage or corneoscleral necrosis or chronic degeneration are observed. According to Shields et al., no eyes require enucleation from complications of radiotherapy [4]. Proton-beam therapy and plaque radiotherapy are both able to treat all iris melanomas, even diffuse forms or those presenting angle seeding, and do not show side effects related to surgery [1]. Some centers prefer proton-beam

radiotherapy as a first-line treatment, even for small and circumscribed tumors that might be treated with surgical excision [1].

To summarize (as shown in Table 1), plaque radiotherapy and proton-beam radiotherapy show similar rates of recurrence and metastasis, but plaques are more widely diffuse and costs are considerably reduced [1]. Limbal stem cells or corneal epithelial/endothelial cell damage may occur after radiant or surgical treatments [1]. Proton-beam and plaque radiotherapy show rates of cataract and glaucoma development that are generally higher after treatment compared to surgical excision [1]. Finally, if radiotherapy is not possible because of diffusely growing or overly large tumors, enucleation may be required.

Table 1. Advantages and disadvantages of various strategies with possible complications.

Treatment	Indications	Advantages	Disadvantages	Complications
Surgical Excision	Small tumors, circumscribed in the iris with no seeding	Good local control, minimal cataract, no radiotherapy-induced side effects, comparable rates of recurrence and metastases, less expensive	Photophobia, double vision, sensation of glare, cosmetic deformity of the iris	Hemorrhage, vitreous loss, dislocated lens, iridocyclitis, macular edema, secondary glaucoma, retinal detachment and cataract
Plaque Radiotherapy	All iris melanomas, diffuse or with angle seeding	Good local control, no surgery complications, no radiation maculopathy, papillopathy, vitreous hemorrhage, corneoscleral necrosis	Corneal suffering	Cataract and glaucoma
Proton-Beam Therapy	All iris melanomas, diffuse or with angle seeding	Good local control, no surgery complications, no radiation maculopathy, papillopathy, vitreous hemorrhage, corneoscleral necrosis	Not available in all ocular oncology units	Cataract and glaucoma

5. Metastatic Spread

The prognosis of iris melanoma is generally better than that of other sites of uveal melanoma, although the rationale is not well defined. Most primary tumors are usually smaller than their posterior segment counterparts at the time of diagnosis and are benign, and this might be considered favorable in terms of survival [6]. Moreover, young adults seem to show a smaller melanoma basal dimension and a lower rate of tumor-related metastasis and death than older adults [29]. The mortality rate ranges from 0–11% according to the eventual presence of metastases, the cell type and the extension to the ciliary body; if the ciliary body is not involved, the rate is 0–3%. The metastatic rate related to cell type is 2.6% for the spindle cell type, 6.9% for the epithelioid cell type and 10.5% for the mixed cell type [36–38]. Ronés and Zimmerman found 1% metastasis at 5 years and 6% metastasis at 10 years, which was further corroborated by the results of a major ophthalmic oncology center, which reported over 3% metastasis at 5 years, 5% metastasis at 10 years and 10% metastasis at 20 years [39]. The predictive clinical risk factors for the development of metastasis are [38] an older patient age, the tumor infiltrating the iris root or angle, tumor seeding in the angle, secondary high intraocular pressure, extraocular extension and recurrence after surgical treatment. Although the overall metastasis rate is relatively low, prognosis and management decisions are highly dependent upon various risk factors in iris melanoma. In his study, Davidorf showed that iris melanoma is diagnosed when the volume is only an average of 55 mm³, while choroidal melanoma is usually diagnosed with a mean volume of 300 mm³. This disparity in tumor volume at diagnosis may explain the disparate rate of metastasis of only 3% with iris melanoma and approximately 15% for choroidal melanoma [40]. Other results from animal studies suggest that elevated intraocular pressure, biochemical properties, anatomic differences, tumor vascularization and host immune response may also be involved in the different rate of metastasis of the iris versus ciliary body and choroidal melanoma [17].

Although metastatic disease in circumscribed iris melanoma is rare, it is more frequently observed in DIM, likely because its epithelioid cells are poorly cohesive and lead to tumor dispersion on the iris and into the angle [17]. Its incidence has been reported to be approximately 13% at 6 years [22].

According to the TNM staging, the risk of mortality is not significantly different between pT0_pT1 and pT2_pT3_pT4, whereas the risk of mortality is eight times higher from grade G2 and G3 tumors than from grade GX and G1 tumors after adjusting for the effects of sex, age and grade [28].

6. Conclusions

In conclusion, a melanocytic iris nevus is usually observed until documented progression is identified. In this case, radiotherapy or surgical resection is generally performed. In some cases, a combination of radiotherapy and surgery is used. Conservative treatment is an efficient alternative to enucleation and allows good local tumor control. Since iris melanomas are visible when they are very small, they are diagnosed early and can be treated quickly. Therefore, a patient with this tumor has a better chance of survival than those with tumors of the posterior uvea.

Long-term follow-up studies indicate the mortality of iris tumors to be very low, while the mortality rates of choroidal and ciliary body tumors are 10 times greater. This might be secondary to the greater size and more malignant cytology of posterior tumors [37].

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