applied sciences

MDPI

Editorial

Ocular Melanoma: Current Concepts

Rosario Caltabiano [1,*] and Andrea Russo [2]

[1] Department G.F. Ingrassia–Section of Anatomic Pathology, University of Catania, Santa Sofia Street 87, 95123 Catania, Italy
[2] Department of Ophthalmology, University of Catania, Via Santa Sofia 78, 95123 Catania, Italy; andrearusso2000@hotmail.com
* Correspondence: rosario.caltabiano@unict.it; Tel.: +39-095-378-2003

1. Introduction

Uveal melanoma (UM) is the most frequent intraocular malignancy in adults, affecting the iris, choroid, and ciliary bodies [1,2]. UM is an indolent neoplasm, whose natural history is characterized by the onset of distant metastases, especially in the liver within 10–15 years from the diagnosis [1]. The choroid represents the most commonly affected site, followed by the ciliary bodies and the iris [1] Iris melanomas, despite their rarity, are characterized by a better prognosis than their choroidal and ciliary body counterparts, probably due to the fact that they are more visible and thus are often diagnosed early [3]. Histologically, UM may exhibit an epithelioid, spindled, or mixed morphology The epithelioid subtype is classically associated with a worse outcome than the spindled and mixed type UM [1]. This special issue contains five accepted manuscripts that provide readers with the "state of the art" concerning the current knowledge about this rare neoplasm. Multiple aspects of UM, including the histopathology, the genetic/prognostic features, the diagnostic approach, and the current treatment options, are discussed with emphasis on future research perspectives.

2. Prognostic Factors

As already recommended for other neoplasms including breast, brain. and colo–rectal cancers [4–7], some data with prognostic value must be included in the pathology report [1]: (i) tumor location, as choroidal tumors have a better prognosis than those involving the ciliary bodies; (ii) the presence of extra-ocular (scleral) extension; (iii) cell type; (iv) greatest thickness and largest basal diameter of the tumor; and (v) the loss of the immunohistochemical expression of BRCA1 associated protein-1 (BAP1), as this represents an easily identifiable surrogate for the presence of BAP-1 mutations, classically associated with higher metastatic risk [8]. In the last years, some new prognostic factors, detectable by immunohistochemistry, have been reported in UM [9–11]. In this regard, Broggi et al. reported recently the prognostic value of some autophagy-related proteins, including Beclin-1, on a series of 85 metastasizing and non-metastasizing UMs, showing that the high immunohistochemical expression of Beclin-1 correlated with better outcomes [12].

Similarly to other forms of cancer, the current interest of the scientific community in the discovery of new prognostic factors of UM corresponds to the need to identify specific subsets of patients with better prognosis in order to personalize the treatment options available [5].

3. Genetic Features

The current knowledge of the genetic landscape of UM shows that it is a molecularly distinct tumor, different from its cutaneous counterpart [1,2]. Two mutually exclusive driver mutations have been found in Guanine nucleotide-binding protein G, q polypeptide (GNAQ) (~55%) or Guanine nucleotide-binding protein G, and subunit alpha-11 (GNA11) in 55% and 40% of cases, respectively [1]. However, since these mutations have also been found in choroidal nevi, they have no diagnostic and prognostic value [1]. Conversely,

Citation: Caltabiano, R.; Russo, A. Ocular Melanoma: Current Concepts. *Appl. Sci.* **2021**, *11*, 5678. https://doi.org/10.3390/app11125678

Received: 1 June 2021
Accepted: 15 June 2021
Published: 19 June 2021

the monosomy of chromosome 3 and the gain of chromosome 6p have been traditionally associated with a worse and better outcome, respectively [1,9–12]. Unlike cutaneous melanomas, UMs rarely harbor V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) and kit mutations [1]. It has been demonstrated that the above-mentioned nuclear loss of BAP-1 protein is strongly associated with loss-of-function mutations of this gene, identified in about 80% of UMs with liver metastases [1,8].

4. Diagnosis and Treatment

UM usually remains clinically silent, being incidentally found on routine ophthalmic screening. However, this tumor may sometimes present as a retinal detachment, intraocular infections, and/or vitreous bleeding [10]. The diagnosis is mainly based on clinical evaluation and imaging techniques [13,14]; magnetic resonance imaging (MRI) is extremely useful not only for diagnostic confirmation but also for evaluating the extent of disease, and the potential response to neoadjuvant radiotherapy [13,14]. Surgical primary enucleation, plaque brachytherapy, and proton beam radiotherapy are the most accepted local treatments of UM [14]. However, as in the last decades, the radiotherapeutic approach has gained increasing importance as the first-choice treatment option [14]. The primary enucleation is currently reserved only for large-sized tumors and UM with optic nerve invasion or extraocular extension [14].

Author Contributions: R.C. and A.R. made a substantial, direct and intellectual contribution to the work, and approved it for publication. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Broggi, G.; Russo, A.; Reibaldi, M.; Russo, D.; Varricchio, S.; Bonfiglio, V.; Spatola, C.; Barbagallo, C.; Foti, P.V.; Avitabile, T.; et al. Histopathology and genetic biomarkers of choroidal melanoma. *Appl. Sci.* **2020**, *10*, 8081. [CrossRef]
2. Barbagallo, C.; Caltabiano, R.; Broggi, G.; Russo, A.; Puzzo, L.; Avitabile, T.; Longo, A.; Reibaldi, M.; Barbagallo, D.; Di Pietro, C.; et al. LncRNA LINC00518 acts as an oncogene in uveal melanoma by regulating an RNA-based network. *Cancers* **2020**, *12*, 3867. [CrossRef]
3. Russo, A.; Avitabile, T.; Reibaldi, M.; Bonfiglio, V.; Pignatelli, F.; Fallico, M.; Caltabiano, R.; Broggi, G.; Russo, D.; Varricchio, S.; et al. Iris melanoma: Management and prognosis. *Appl. Sci.* **2020**, *10*, 8766. [CrossRef]
4. Broggi, G.; Filetti, V.; Ieni, A.; Rapisarda, V.; Ledda, C.; Vitale, E.; Varricchio, S.; Russo, D.; Lombardo, C.; Tuccari, G.; et al. MacroH2A1 immunoexpression in breast cancer. *Front. Oncol.* **2020**, *10*, 1519. [CrossRef] [PubMed]
5. Broggi, G.; Salvatorelli, L. Bio-pathological markers in the diagnosis and therapy of cancer. *Cancers* **2020**, *12*, 3113. [CrossRef] [PubMed]
6. Broggi, G.; Salvatorelli, L.; Barbagallo, D.; Certo, F.; Altieri, R.; Tirrò, E.; Massimino, M.; Vigneri, P.; Guadagno, E.; Maugeri, G.; et al. Diagnostic utility of the immunohistochemical expression of serine and arginine rich splicing factor 1 (SRSF1) in the differential diagnosis of adult gliomas. *Cancers* **2021**, *13*, 2086. [CrossRef] [PubMed]
7. Brex, D.; Barbagallo, C.; Mirabella, F.; Caponnetto, A.; Battaglia, R.; Barbagallo, D.; Caltabiano, R.; Broggi, G.; Memeo, L.; Di Pietro, C.; et al. LINC00483 has a potential tumor-suppressor role in colorectal cancer through multiple molecular axes. *Front. Oncol.* **2021**, *10*, 614455. [CrossRef] [PubMed]
8. Stålhammar, G.; Grossniklaus, H.E. Intratumor heterogeneity in uveal melanoma BAP-1 Expression. *Cancers* **2021**, *13*, 1143. [CrossRef] [PubMed]
9. Russo, D.; Di Crescenzo, R.M.; Broggi, G.; Merolla, F.; Martino, F.; Varricchio, S.; Ilardi, G.; Borzillo, A.; Carandente, R.; Pignatiello, S.; et al. Expression of P16INK4a in uveal melanoma: New perspectives. *Front. Oncol.* **2020**, *10*, 562074. [CrossRef] [PubMed]
10. Broggi, G.; Musumeci, G.; Puzzo, L.; Russo, A.; Reibaldi, M.; Ragusa, M.; Longo, A.; Caltabiano, R. Immunohistochemical expression of ABCB5 as a potential prognostic factor in uveal melanoma. *Appl. Sci.* **2019**, *9*, 1316. [CrossRef]

11. Caltabiano, R.; Puzzo, L.; Barresi, V.; Ieni, A.; Loreto, C.; Musumeci, G.; Castrogiovanni, P.; Ragusa, M.; Foti, P.; Russo, A.; et al. ADAM 10 expression in primary uveal melanoma as prognostic factor for risk of metastasis. *Pathol. Res. Pract.* **2016**, *212*, 980–987. [CrossRef] [PubMed]
12. Broggi, G.; Ieni, A.; Russo, D.; Varricchio, S.; Puzzo, L.; Russo, A.; Reibaldi, M.; Longo, A.; Tuccari, G.; Staibano, S.; et al. The macro-autophagy-related protein beclin-1 immunohistochemical expression correlates with tumor cell type and clinical behavior of uveal melanoma. *Front. Oncol.* **2020**, *10*, 589849. [CrossRef] [PubMed]
13. Spatola, C.; Liardo, R.L.E.; Milazzotto, R.; Raffaele, L.; Salamone, V.; Basile, A.; Foti, P.V.; Palmucci, S.; Cirrone, G.A.P.; Cuttone, G.; et al. Radiotherapy of conjunctival melanoma: Role and challenges of brachytherapy, photon-beam and protontherapy. *Appl. Sci.* **2020**, *10*, 9071. [CrossRef]
14. Foti, P.V.; Inì, C.; Travali, M.; Farina, R.; Palmucci, S.; Spatola, C.; Liardo, R.L.E.; Milazzotto, R.; Raffaele, L.; Salamone, V.; et al. MR imaging–pathologic correlation of uveal melanomas undergoing secondary enucleation after proton beam radiotherapy. *Appl. Sci.* **2021**, *11*, 4310. [CrossRef]