Uveal Melanomas

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Traditionally, it has been thought that metastatic spread in uveal melanoma (UM) and dissemination occurs prior to presentation and that treatment of the primary tumor does not change outcome. However, it seems as though small UM tumours can not only be lethal with high risk monosomy 3 mutations, treated at an earlier time point at a smaller stage seems to improve mortality outcomes.

uveal melanoma | monosomy 3 | metastatic risk

1. Introduction

The success of local control of primary uveal melanoma (UM) with radiotherapy or surgery is high (80–100%, depending on treatment modality) [1][2][3][4][5][6]. Recent advances in treatment regimens and the advent of intraocular laser therapies and drugs have increased the rates of eye- and vision retention [7][8][9][10][11]. Although certain treatments for metastatic UM, such as monoclonal antibody infusions or hepatic resections of isolated lesions, have shown some benefit [12][13][14][15][16][17][18][19][20][21], they are suitable for only select UM patients [22][23][24][25]. Clinical trials are underway for other treatments for patients with metastatic disease [26]; however, to date, the prognosis remains poor and the metastatic mortality rate associated with UM remains at 40–45% [27][28][29][30][31].

Prognostic parameters associated with an increased risk of developing metastatic UM are related to primary tumor characteristics, such as larger size, ciliary body involvement, extra-ocular extension and histologic features (e.g., epithelioid cell morphology, closed connective tissue loops, high mitotic count) [32][33][34]. In addition, chromosomal alterations, particularly loss of one copy of chromosome 3 (monosomy 3; M3) and gene mutations (e.g., in *BAP1, SF3B1* and *EIF1AX*) play a major role in determining metastatic risk in UM [35][36][37][38][39][40][41] [33]. At the Liverpool Ocular Oncology Centre (LOOC), metastatic risk is determined using the Liverpool Uveal Melanoma Prognosticator Online (LUMPO) algorithm that incorporates clinical, histological and genetic parameters, to provide an individualized approach to patient management [33]. This prognostic algorithm has been validated externally in multiple centers worldwide [42][43][44].

Many UM patients present with advanced ocular disease, with approximately 23% reporting that their tumor was initially missed when they presented with symptoms [45][46]. Previously, it had been considered that systemic tumor cell dissemination occurs prior to presentation, and hence that ocular treatment does not reduce the risk of metastatic disease and mortality. However, there are indications that earlier detection and treatment of smaller UM

are not only associated with better local outcomes but may also be associated with improved survival rates [47][48][49][50][51][52][53].

2. Small High-Risk Uveal Melanomas Have a Lower Mortality Rate

Due to the peak of metastatic mortality occurring 2 years after enucleation for UM [54], early hypotheses (Zimmerman–McLean–Foster) suggested that enucleation itself may increase the risk of metastatic disease by systemic dissemination of tumor cells [55]. If this study had been performed in the 1970s, proponents of the Zimmerman–McLean–Foster hypothesis might have attributed the higher mortality in patients with larger tumors to the treatment of such tumors by enucleation. This theory has been largely refuted by the COMS study with similar mortality rates for those undergoing enucleation or plaque brachytherapy [56][57]. It has therefore been assumed that hematogeneous dissemination of UM cells occurs long before the primary tumor has been diagnosed [58]. Tumor doubling time calculations support this hypothesis by suggesting that the metastatic dissemination precedes the initial diagnosis and treatment [59][60]. Other studies suggest that most UM patients have circulating tumor cells (CTC), whereby the genotypic and phenotypic profiles of the CTCs match the primary tumor [60][61]. As such, there is a prevailing dogma that treatment of the primary UM is undertaken only to preserve vision (and, if possible, the eye) but will not prevent metastatic disease. Alternate opinions propose, however, that by “stemming the metastatic flow” of UM cells into the bloodstream, this could result in a reduction in the subsequent CTC load, and consequently reduce metastatic risk [50][51][62]. That is, there may indeed be a window of opportunity for metastatic disease prevention by treating UM earlier, and this would be particularly relevant in small lethal M3-UM [53].

It is well established in UM that various clinical risk factors, including tumor size, are related to the risk of metastatic disease and subsequent mortality, with small incremental increases in primary tumor size significantly affecting outcomes [47][63][64]. It has been assumed that larger UM are innately more aggressive, as they have either high-risk genetic factors from the outset or have accumulated these factors over time, termed ‘crescendo malignancy’ [65]. On this basis, it is conventional practice in many ocular oncology centers to monitor small, indeterminate uveal melanocytic tumors for months (or even years) until growth is documented [66][67][68][69][70]. Weis et al. demonstrated that most of these indeterminate lesions are low-risk D3-UM [71]. Our current study supports these findings, with 73% of the small melanocytic tumors being D3; however, importantly, researchers demonstrate that over one quarter (i.e., 27%) of these small lesions are M3-UM, and therefore have a high metastatic risk. Furthermore, whilst most of these small UM are D3 at this stage, it is unclear what proportion could subsequently transform into higher-risk M3-UM, if left untreated. Certainly, there are reports of genetic heterogeneity within larger UM [65][72][73][74][75], which suggests that there is an evolutionary process of uveal melanocytic lesions from low to high genetic risk. In addition, researchers have previously demonstrated that asymptomatic patients with UM identified via the annual UK national diabetic retinopathy screening program have lower mortality than those detected via alternative routes [52]. Taking all of these data into account, which suggest that early detection and treatment of UM may enable the prolongation of life in patients, there could be justification for the consideration of earlier treatment in small uveal melanocytic tumors. If these lesions are monitored, adequate patient counselling and informed consent are vital.

Afshar et al. described a number of cases whereby patients were monitored for years by their optometrist or local ophthalmologist without being informed that there was a possibility that their ‘suspicious nevus’ was malignant; some of these patients were eventually found to have a lethal UM when biopsy was ultimately performed [76]. On the other hand, it is also important to emphasize here that researchers do not recommend treatment of all small, benign, melanocytic lesions; it can indeed be difficult to differentiate benign nevi from small melanomas. These are best assessed and treated by teams having the required expertise in ocular oncology so as to avoid unnecessary visual loss whilst not delaying treatment of life-threatening melanomas. For example, researchers were able to confirm malignancy in such small lesions by performing biopsy using skills and techniques that are now widely available.

At present, unfortunately, it is not possible using the available clinical imaging technologies to genetically subtype these small uveal melanocytic lesions. With the advent of artificial intelligence and its application in ophthalmology, however, this may change [77]. Consequently, at present, to determine the genetic status of the cells within an atypical uveal melanocytic lesion, intraocular biopsies must be performed. Our previous experience indicates that this procedure is safe in most patients and can be undertaken following radiotherapy [78][79].

In this analysis, researchers have attempted to control for lead time bias with previously published methods [80] requiring an estimate of sojourn time, which is the unobserved period of time during which the tumor is asymptomatic but detectable at screening, and thus it artificially increases the follow-up time. Sojourn time estimation is a difficult problem in general, particularly in UM, where often asymptomatic patients are detected at a routine screening visit [45]. Therefore, researchers have created a range of estimates, as suggested for other forms of cancer where sojourn time is undefined [80], in order to take this into account, as previously described [52]. Although these calculations come with their limitations, these corrected calculations have also supported a risk benefit of those small melanoma lesions treated at an earlier stage.

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