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EDITORIAL

Minimal residual disease—a novel concept in uveal melanoma

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Uveal melanoma is the most common primary intraocular tumor in adults, with an incidence of 5.1 per million in the United States of America [1]. Although we are able to provide the majority of patients satisfactory local tumor control and eye retention rates using various radiotherapeutic and surgical techniques, up to almost 40% of patients will develop metastatic disease [2].

In the absence of clinically evident metastatic disease, current treatment options for uveal melanoma are limited at this time by inadequate diagnostic abilities.

Regarding primary ocular treatments, successful tumor control with local radiation reaches >90% [3]. In terms of systemic metastasis, imaging often can detect remote tumor once it reaches a certain size but our treatments have been ineffective [4, 5].

Recently, the concept of minimal residual disease (MRD) has been introduced to ocular oncology for vitreoretinal lymphoma by Stacey and Pulido [6]. Generally speaking, in the field of systemic oncology, MRD describes the concept of a small number of malignant cells that are impossible to image and remain viable in the patient following primary treatment of malignancy [7]. In time, these residual cells can proliferate and cause recurrent disease either at the original site or remotely leading to metastasis. In leukemia, MRD is common terminology and is further subclassified into undetectable MRD and detectable MRD. Detectable MRD is the lowest number of leukemic cells that can be found using present methods [8]. The reason that the MRD terminology is important is threefold. First, there is often misperception by patients that they are free of disease, especially after they reach 5-year follow-up. By stating that they have undetectable MRD, the patients realize that they still need to be followed. Second, MRD pushes the physician to develop methods to evaluate the for subclinical metastasis with even more sensitivity than the existing methods. Third, detection of MRD allows for earlier therapy aimed to control and, hopefully, eradicate the detectable MRD prior to overt disease recurrence.

The current model of uveal melanoma metastasis hypothesizes the existence of circulating tumor cells (CTC) in the blood of affected patients that are present early in the disease process [9]. These take residence in other organs, usually the liver, and can remain in a dormant state for years [9]. We therefore have to assume that in at least half of our patients, even after successful treatment of the primary melanoma in the eye, there is undetectable MRD outside of the eye.

At the present time, we are not able to prove that patients are free from disease after successful treatment of the primary tumor, so patients should be regarded as having undetectable MRD of uveal melanoma. To date, this includes all patients who have undergone local treatment of uveal melanoma—either by radiotherapy, surgery, or a combination of both—and are now under follow-up (Fig. 1). Just like MRD in other areas of oncology, using this terminology allows us to realize the limitations of our knowledge of the present and future evolution of the disease process.

One of the most promising advancements in oncology is the improvement in the detection of circulating tumor DNA (ctDNA) and CTCs in the affected patients' blood [10, 11]. Not only has this made a difference in detecting low levels

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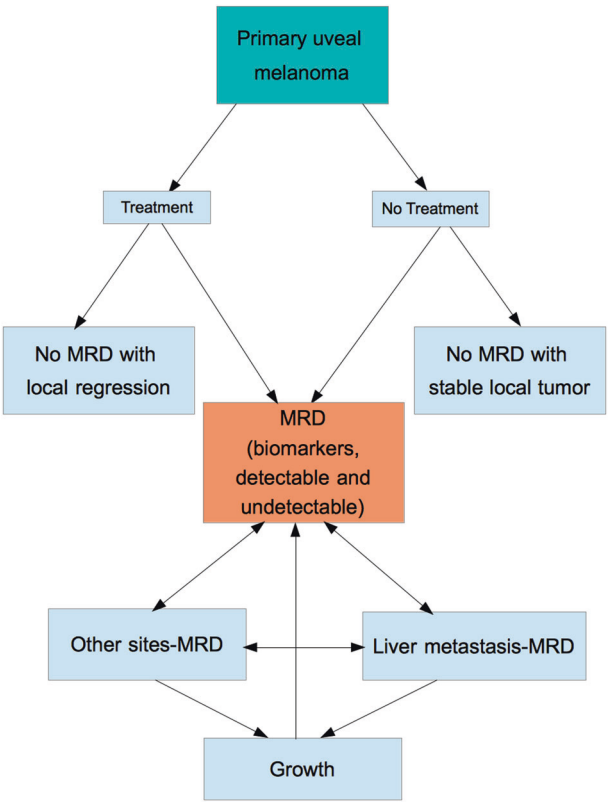

Fig. 1 Diagram depicting the concept of MRD in uveal melanoma. The main focus should be on reducing the number of patients with undetectable MRD.

of cancer cells in leukemia and lymphoma but it is also now being used in evaluating MRD in solid tumors as well [12]. A good example is breast cancer where CTCs (cells which entered the blood circulation) and disseminated tumor cells (CTCs that enter and persist at the distant site) can be detected [13]. This information can be used to refine the diagnostic and therapeutic follow-up to the benefit of the patient. In cutaneous melanoma, ctDNA and CTC are being investigated as prognostic indicators to assess tumor response and metastatic disease with regard to immune therapy and as a prognostic indicator for survival [14].

The presence of CTCs in blood samples of uveal melanoma patients was described several decades ago using standard microscopy and special staining techniques, however, modern molecular testing methods like PCR and mRNA expression studies allow for a more precise detection of the aforementioned markers [15, 16]. A number of studies have described the potential to assess the patients' risk to develop metastatic disease by detecting either CTCs or ctDNA in blood samples of patients with uveal melanoma though at the present time, the sensitivity and specificity are low [17, 18].

Advancements in these testing methods should, in the future, change our view on how we view uveal melanoma as a disease and sharpen the line between disease detectable by imaging, detectable MRD, and undetectable MRD in those cases where there are still residual malignant cells in the patient that cannot be detected by these testing methods.

In summary, the use of the MRD terminology in ocular oncology and specifically in the case of uveal melanoma will allow us to better instruct patients and better define the boundaries of our knowledge of disease burden for clinicians.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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