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Discussion of Uveal Melanoma Metastasis - Using Novel Biomarkers for Improved Tracking & Treatment

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ABSTRACT

Uveal Melanoma is the most common primary intraocular cancer and it affects thousands of individuals on an annual basis. Although uveal melanoma is rarer than other cancers it is very aggressive and can be extremely deadly, since in nearly half of all uveal melanoma cases the cancer ends up spreading to other parts of the body. With such a large chance of metastasis occurring in uveal melanoma cases, it is essential to discover effective ways to track the metastasis of uveal melanoma and treat the patients before the cancer has spread too far in the body. This paper first explains what uveal melanoma is and how it occurs and progresses throughout the body. Then, it discusses some novel biomarkers introduced by recent studies and highlights the way these biomarkers can offer a means of improved prognostication as well as help guide more effective personalized treatments for uveal melanoma patients.

Introduction

What is uveal melanoma?

Before delving deeper and discussing the use of novel biomarkers for uveal melanoma diagnosis it is necessary to understand what uveal melanoma actually is and where it even stems. For starters, uveal melanoma can be characterized as a type of cancer. In the United States, uveal melanoma accounts for around 3 to 5 percent of all melanomas and results in around 1500 to 2000 cases on an annual basis. On a broader scale, uveal melanoma results in around 7000 cases globally each year. This makes it one of the most common types of primary intraocular malignancies. Now, uveal melanoma is a non-cutaneous melanoma. So, instead of occurring on the surface of the skin, it arises from melanocytes (which are cells that produce a pigment called melanin) within the uveal tract of the eye. It is important to note that uveal melanoma is asymptomatic (which means it lacks symptoms and signs) and due to this many patients, who develop it end up visiting the hospital quite late. Some symptoms of uveal melanoma that have been observed in previous cases are a dark spot on the iris, blurry vision, a difference in the shape or size of the pupil, and the appearance of floaters (which are small shapes that drift across your field of vision). Uveal melanoma can also lead to vision loss if it gets very large or occurs in a very critical part of the eye.

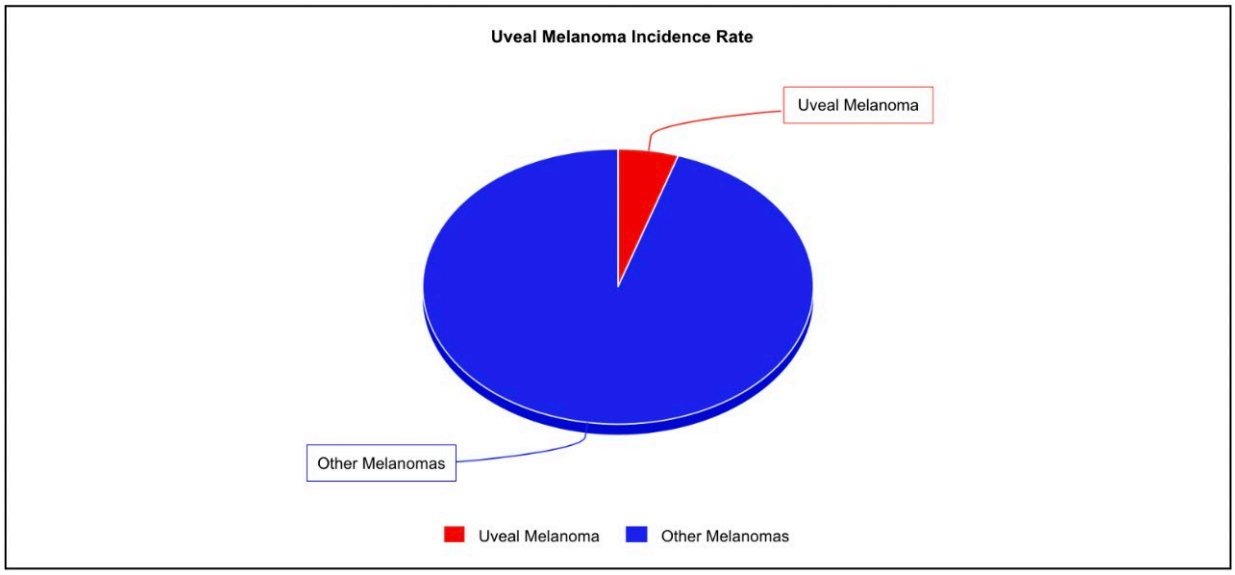

Figure 1: A graphical depiction of the incidence rate of uveal melanoma in comparison to other melanomas.

Where does Uveal Melanoma Start?

As in the name, uveal melanoma is the melanoma of the uvea. It starts in the melanocytes within the uveal tract of the eye. The uveal tract is the vascular middle layer located between the sclera and retina of the eye. It is made of three main parts and these are the iris, the ciliary body, and the choroid. The iris circles around the pupil and it can be described as the colored part in the frontal portion of the eye behind the cornea. The ciliary body is located right behind the iris and it includes muscles that allow the shape of our lens to change so that we can view objects from varying distances, and finally the choroid is a thin layer of blood vessels that helps supply nutrients to the internal parts of the eye.

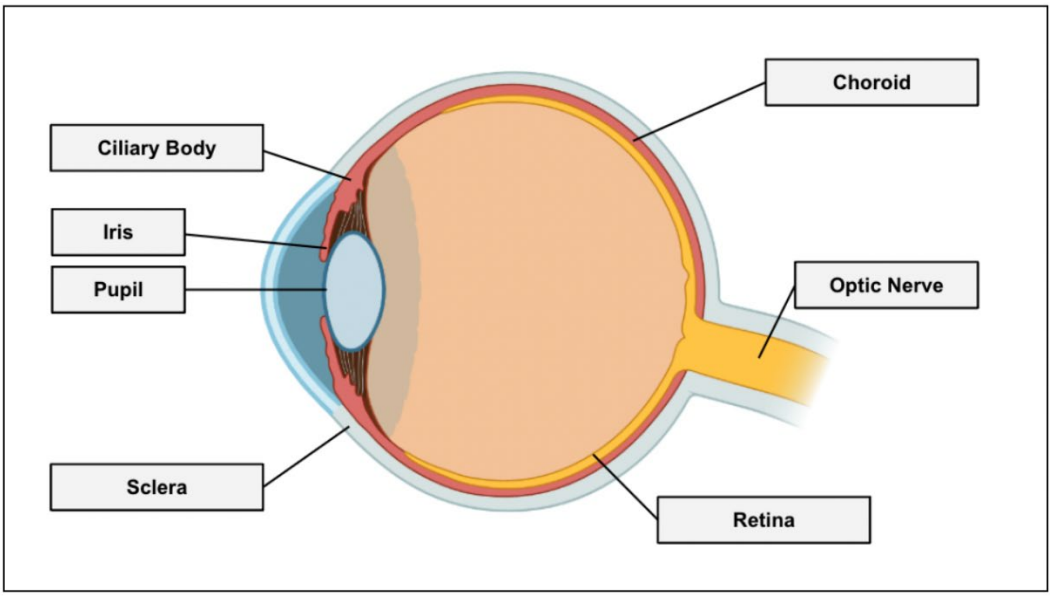

Figure 2: A more visual depiction with labeled parts of the eye.

Uveal melanoma can occur in any three of these parts of the eye and the place where it occurs does make a difference. Uveal melanoma in the iris is characterized by a small tumor that develops and grows at a relatively slower rate and it is not as likely to metastasize or spread across to other parts of the body. On the other hand, uveal melanoma of the ciliary body or the choroid is characterized by tumors of a larger size, and melanoma in these parts of the eye is much more likely to spread across the body.

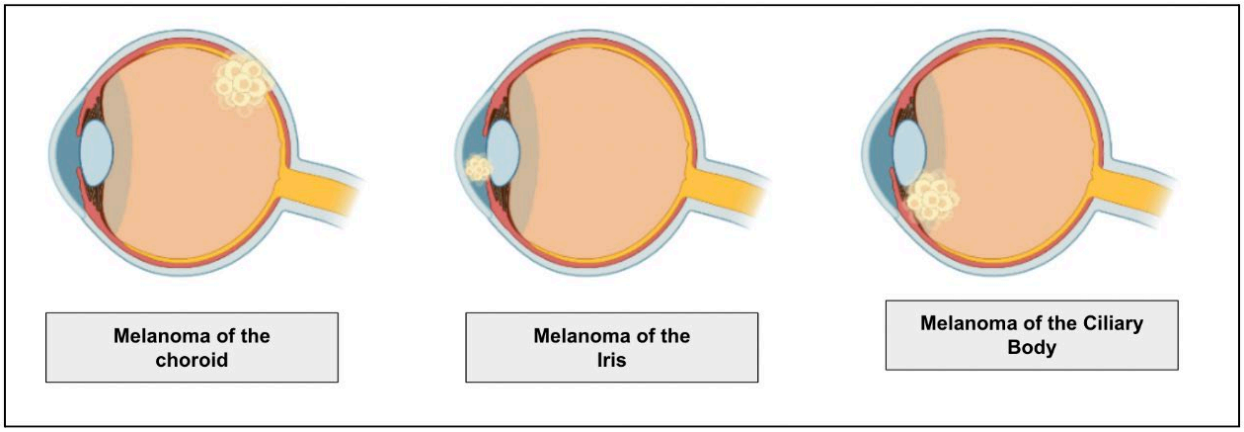

Figure 3: The three different locations of uveal melanoma.

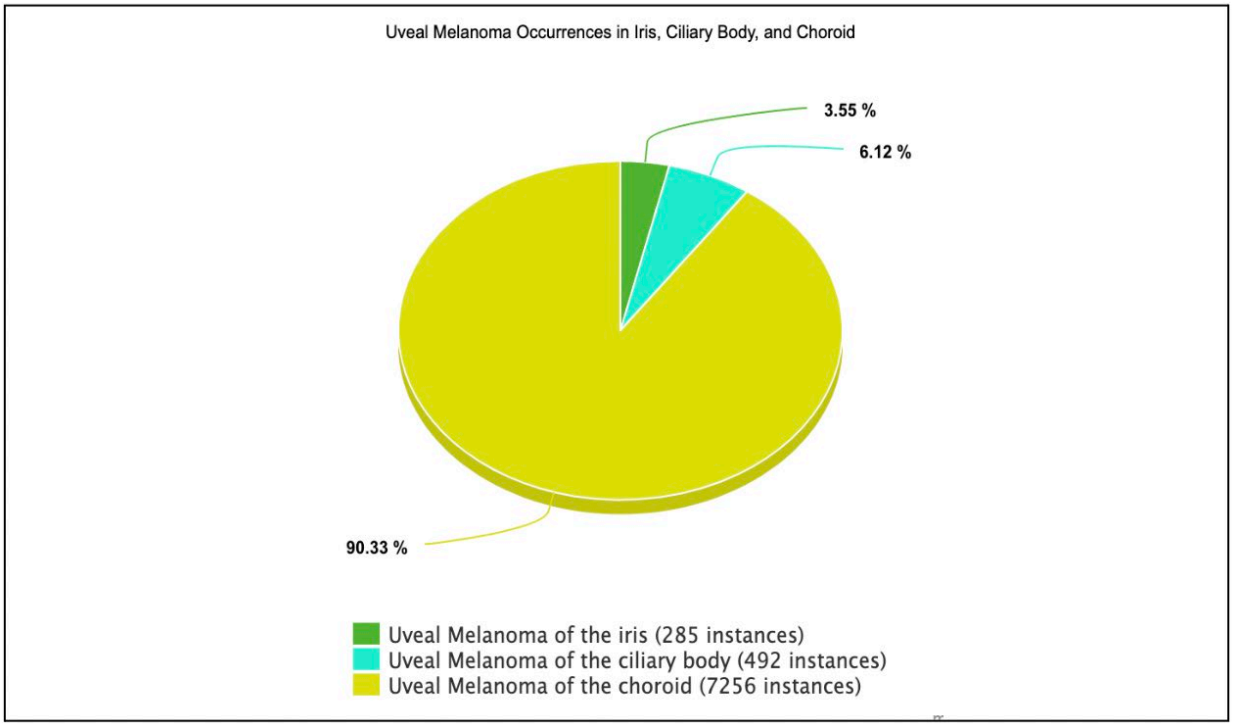

Figure 4: A graphical depiction of the number of uveal melanoma cases in each of the three parts of the uvea (Data sourced from Carol L. Shields, et al).

Shields et al conducted a study in which they consolidated the reports of 8033 patients who had uveal melanoma and used them to determine the most common location of uveal melanoma. Based on the report, there were 285 instances showing uveal melanoma located in the iris, 492 showing it located in the ciliary body, and lastly, 7256 showing

it located in the choroid. Hence, the choroid proved to be the most common location for uveal melanoma. As aforementioned, uveal melanoma of the ciliary body and choroid tends to metastasize (spread to other parts of the body) and this makes it even more dangerous.

Metastasis in uveal melanoma

Considering the tendency of the uveal melanoma to spread, there are a lot of efforts placed towards detecting and predicting the spread because if detected early, it can be treated at the roots and the patient can have higher chances of being saved. Metastasis is a key part of why uveal melanoma is so dangerous so here's a walk through the process of metastasis and how it happens with uveal melanoma because this background will help us understand why an improved tracking can be very beneficial. Metastasis is a complex biological process in which cancer cells go from a primary tumor (through the bloodstream or lymph system) and establish secondary tumors in distant organs and tissues. Uveal melanoma has a propensity to spread through the bloodstream (hematogenous spread), which can lead to the formation of metastatic tumors in distant organs. Metastasis significantly contributes to the morbidity and mortality associated with cancer and uveal melanoma. In fact, it is a leading cause of death after the diagnosis of uveal melanoma. Most patients who have uveal melanoma end up facing metastasis(Carvajal et al., 2017). So, metastasis is pretty common with uveal melanoma and in about 80% of cases, uveal melanoma has metastasized and spread to the liver, which makes the liver the most common site of spread (Kim & Choi, 2021).

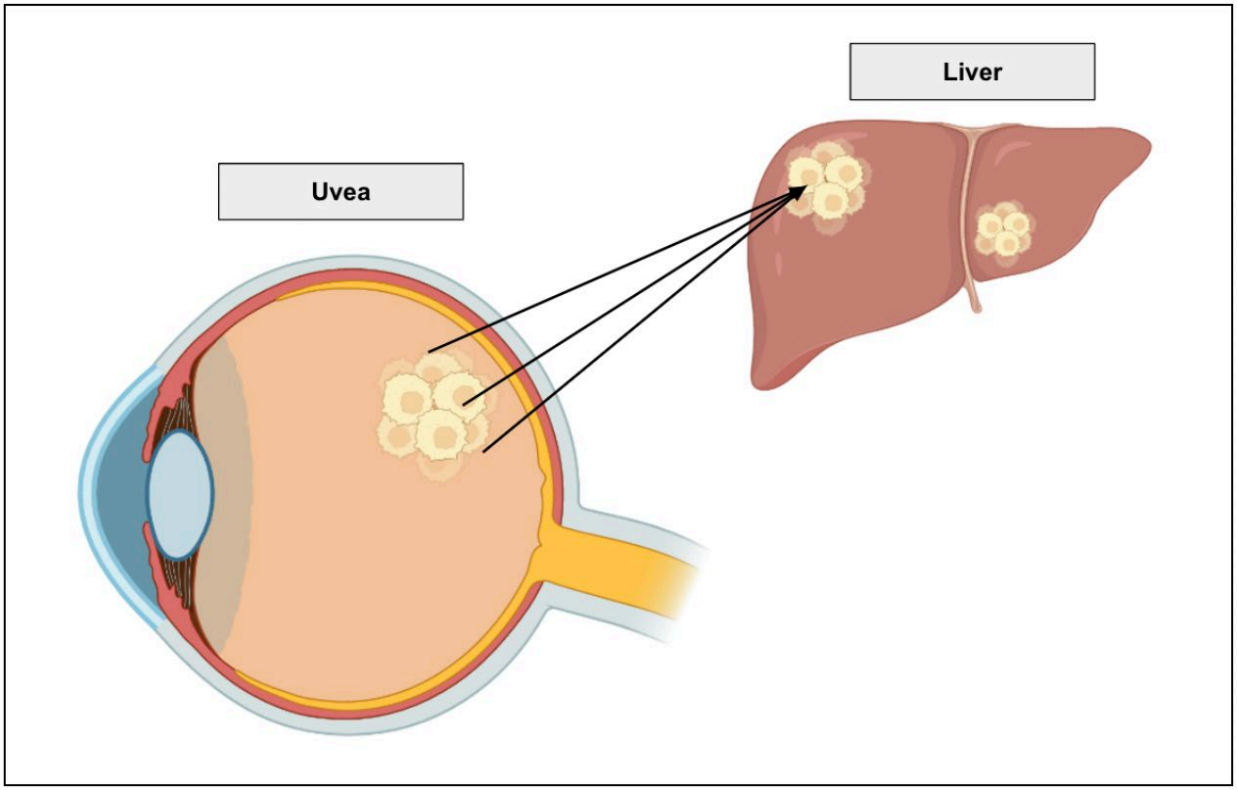

Figure 5: This is a depiction of the spread of uveal melanoma from the uvea to the liver. (An example of metastasis)

Apart from the liver, there are also other sites of metastasis and these include the lungs, bones, and skin. Metastasis is oftentimes quite challenging to predict and detect. This is because its occurrence truly varies from patient to patient. Sometimes it can happen right after the melanoma is discovered while other times it can occur years

after the initial diagnosis of the melanoma. In uveal melanoma, metastasis occurs from the eye to other parts of the body primarily through the bloodstream and it occurs in different stages. The stages of uveal melanoma typically follow a similar pattern to the spread of other melanomas and they are categorized by the size of the tumor and how far in the body it has spread.

State 0	Stage 1	Stage 2	Stage 3	Stage 4
Melanoma is confined to the topmost layer of the uvea. It has not spread yet.	The tumor is still within the uvea and metastasis still has not occurred.	The tumor grows and becomes bigger in size. There is a possibility of it starting to spread to locations and tissues near the uveal tract.	Metastasis begins to occur more evidently. The tumor spreads to tissues and organs near the uveal tract, however, it has still not made its way to distant locations yet.	This is the last stage. In this stage, metastasis has occurred in full form and the tumor has made its way to tissues and organs further in the body like the liver, bones, and lungs.

Figure 6: Staging Uveal Melanoma - Staging systems have some variation in their format and the one defined in this paper has been derived from the Ohio State University staging system.

As uveal melanoma metastasizes and progresses in stages, the prognosis becomes worse. Metastasis is a big hurdle for effectively managing uveal melanoma and despite the advancements made in technology and cancer research over the years, the risk of metastasis still lingers. Initially, uveal melanoma tumors show minimal signs of metastasizing but in the end, almost 50 percent of primary uveal melanoma tumors metastasize. (Woodman, 2012). With such a large amount of uveal melanoma cases going into metastasis, it is necessary to put efforts into researching ways to better track the uveal melanoma in the body. One way to help track metastasis is through the use of biomarkers.

Using Biomarkers

Biomarkers are molecular or cellular characteristics, and they can be utilized to pinpoint the current status/progression of a disease. By placing efforts in discovering new biomarkers, the metastasis of uveal melanoma tumors can be better tracked and this creates chances for more patients to be saved. Biomarkers can serve extremely beneficial purposes because not only can they help predict the likelihood of metastasis, but they can also help guide treatment decisions. Recently, several studies have been able to identify biomarkers that can help predict metastasis of melanoma from the uveal tract.

Novel Biomarkers for Predicting Metastasis

Liquid Biopsy

Liquid biopsy is a relatively new technique, and it has been able to detect cancer-specific biomarkers from blood samples. Before explaining the biomarkers associated with it, here's a brief description of how liquid biopsy works. In liquid biopsy, a blood sample is collected and screened to identify and analyze the spread of cancer cells from

tumors. It is based on the concept that in patients who have metastatic cancer, cancer tumors will release fragments and particles in the bloodstream.

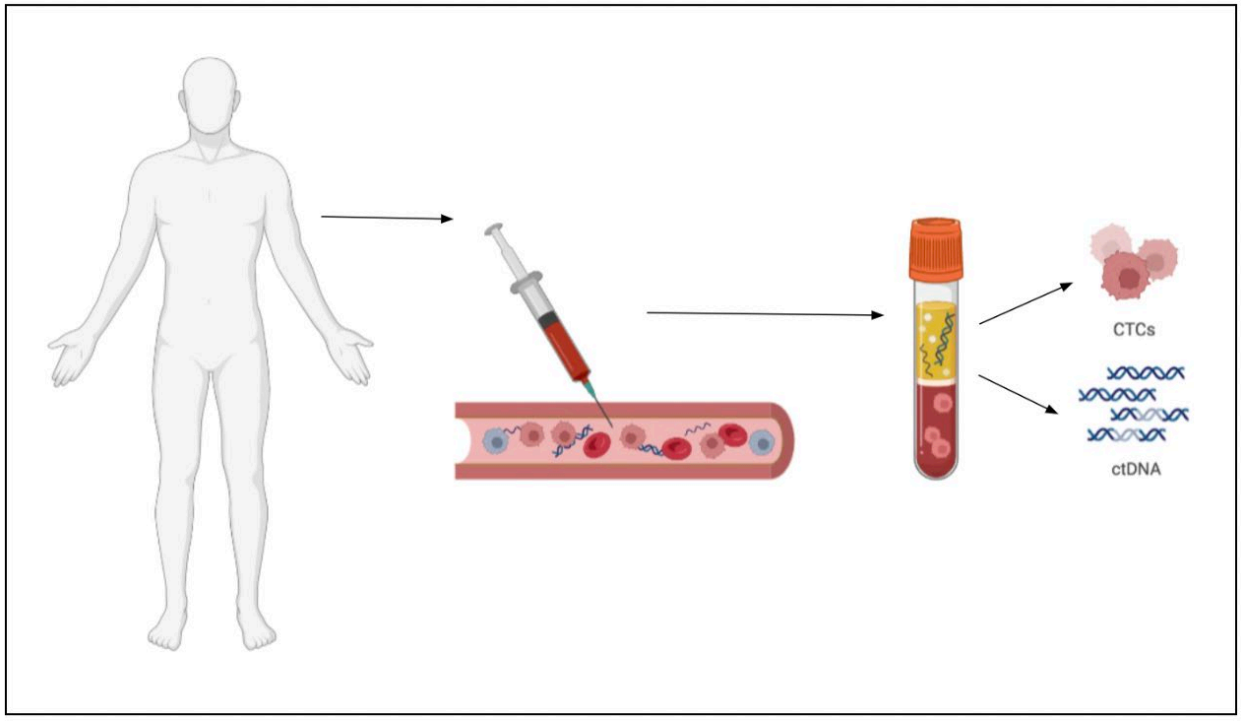

Figure 7: Here is a basic sequential view of how liquid biopsy works. First, a blood sample is collected from the human body and then analysis is performed on the sample.

Liquid Biopsy and Biomarkers

The article "Circulating tumor DNA tracking through driver mutations as a liquid biopsy-based biomarker for uveal melanoma" highlights a study conducted by a group of scientists that reveals some new liquid biopsy-based biomarkers. The scientists of this study focused on examining mutated circulating tumor DNA(ctDNA) and were able to observe a strong relation between the presence of GNAQ and GNA11(which are gene mutations) in relation to metastatic uveal melanoma. Their findings showcased that the GNAQ and GNA11 genes are actually found in many uveal melanoma cases and can serve as an early signal of the further development of uveal melanoma. More specifically, they showcase the initial development of the melanoma in around 90% of all uveal melanoma cases (Bustamante et al., 2021.)

Furthermore, the study also took a look at the relationship between circulating tumor cells (CTCs) and ctDNA after treatment. From this examination the researchers were able to discover that the presence of CTCs and ctDNA after treatment is in fact associated with worse survival outcomes and a possibility of the diseases occurring again in the near future. Through liquid biopsy, the scientists were able to identify and pinpoint these gene mutations in ctDNA and through such biomarkers, tracking the extent of metastasis and overall prognostication of uveal melanoma can become significantly easier.

Another group of scientists (Field et al., 2019) conducted a study to further understand the role of BAP1 (which is a gene) and they were able to figure out that BAP1 can serve as a biomarker. For some context, the BAP1 gene is typically known for suppressing the growth of tumors and keeping in check the growth of cells. In the study, the scientists analyzed circulating tumor DNA (ctDNA) obtained from blood samples and compared it to corresponding tumor tissue samples. The results of the study demonstrated a pretty high correlation between BAP1 muta-

tions detected in tumor tissue and ctDNA. What this means is that liquid biopsy has the potential to accurately identify BAP1 mutations in uveal melanoma patients and that the “loss of BAP1 expression or BAP1 gene mutations” is actually a genetic alteration observed in metastatic uveal melanoma. This serves as another example of biomarkers being discovered in liquid biopsy and this biomarker can help detect the extent of uveal melanoma metastasis along with helping identify potential treatments.

Proteomics

Proteomics, in simple words, can be described as a term for how proteomes (which are groups of proteins) function inside the body and in cells. Although proteomics is not as relatively new of a technique as liquid biopsy, it has brought about some novel biomarkers for uveal melanoma as well. Using proteomics, clinicians and scientists can analyze patterns of proteins in tumor tissues and pinpoint the specific proteins correlated with a higher risk of metastasis in uveal melanoma patients.

Proteomics and Biomarkers

The article “Proteomics of Primary Uveal Melanoma: Insights into Metastasis and Protein Biomarkers” highlights the efforts of a group of researchers in using a quantitative proteomic analysis and mass spectrometry to discover any correlation between tissues of metastatic and non-metastatic patients. While comparing the two types of tissues, the researchers found that the proteins BAP31 and MART-1 show high correlations with the metastatic tissues and this goes to show how they can serve as indicators and help predict/detect the metastasis of uveal melanoma.

Use of Biomarkers to Guide Personalized Treatment Decisions

Liquid biopsy-based biomarkers can help clinicians monitor the prognostication of uveal melanoma by taking note of the changes and genetic mutations that occur over time. As supplemented by the aforementioned studies and even by other published articles such as "Liquid biopsy for uveal melanoma: current insights and future perspectives", liquid biopsy can “identify the emergence of resistant clones or the acquisition of new mutations during treatment”. The identification and detection of these changes in circulating tumor DNA(ctDNA) can demonstrate the resistance being met by the treatment and the further growth of metastasis. Overall, the newly discovered biomarkers from liquid biopsy and proteomics provide researchers, clinicians, and scientists an avenue for monitoring the progression of uveal melanoma. Changes in these biomarkers can serve as an indication of progression and allow for adjustments needed to give patients a treatment that results in maximal success. Due to this, these biomarkers can play a very important role in guiding personalized treatment decisions for uveal melanoma patients. For instance, using such biomarkers, clinicians can track the start and even extent of spread of melanoma in the body. Based on a more accurate record of where the melanoma is and how it is spreading, clinicians will be able to better determine the treatment options for the patient alongside developing an effective timeline that they can follow to prevent the cancer from spreading to distant sites of the patient’s body.

Methodology

This review was created by searching keywords and synthesizing information from published peer-reviewed papers and articles found in medical journals, Google Scholar, and databases such as PubMed from the National Library of Medicine. Based on the different studies and data from these articles, this paper consolidated their findings and pro-

vided insight into how techniques like liquid biopsy and proteomics have showcased new biomarkers that can potentially set the stage for an improved diagnosis and treatment of metastatic uveal melanoma.

Discussion of Future

As aforementioned, the information presented in this paper was derived through conducting a literature review of various other papers and articles that are currently published. Considering these biomarkers are quite novel discoveries and techniques like liquid biopsy are still relatively new, so the amount of published papers and studies are limited. This paper discussed how these biomarkers point towards a better tracking of metastatic uveal melanoma and can help guide personalized treatment, however further studies are necessary for a more comprehensive evaluation of these biomarkers and their shortcomings. It is my sincere hope that these biomarkers are further researched, and they begin to be more commonly used for uveal melanoma prognostication and diagnosis.

Conclusion

Although rare, uveal Melanoma is one of the most aggressive and deadliest cancers. It affects thousands of individuals on an annual basis and possesses a high propensity of metastasis. As uveal melanoma metastasizes and progresses in stages, the danger increases and the possibility of survival decreases. With such a high risk of metastasis it is essential to have efficient tracking mechanisms in place for patients with uveal melanoma. Fortunately, recently discovered biomarkers such as the presence of GNAQ and GNA11, BAP1 gene mutations, and the proteins BAP31 and MART-1 can serve as early indicators of uveal melanoma. They can not only help improve its tracking, but also work towards guiding more personalized treatments in the near future. However, further research and studies are needed for a more complex evaluation of these biomarkers.

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