American Brain Tumor Association Webinar Transcript

New Global Classification of Brain Tumors

>> Welcome to the American brain tumor Association to free education webinar series. The key for participating in today's webinar. Today's webinar is on how New Global Classification of Brain Tumors. The webinar will be presented by Dr. Kenneth Aldape. Please note that all lines are muted. If you have a question you would like to ask please type it into the question box on the right-hand side of your screen. Questions will be answered at the end of the presentation. Over the next few days you will have an email -- receive an email asking you to share feedback. Please take a few minutes to share your feedback - it is important to us. Today's webinar is being recorded. Register participants will receive the webinar recording link in a following about –a follow-up email when it is available. Let's pause to begin our webinar recording.

>> The American Brain Tumor Association is pleased to welcome back to our webinar series. Our webinar today will discuss new global classification of brain tumors, improve diagnosis and treatment. My name is Emily Lippet, program manager here at the American brain tumor Association. I am delighted to introduce to you our speaker today Dr. Kenneth. Aldape. Dr. Kenneth is from the Princess Margaret Cancer Ctr., Toronto General Hospital and also the professor of the Department of Pathology at the University of Toronto. He is a neuro-pathologist with an interest in translational research and molecular approaches for brain tumor classification. He recently spoke at ABTA's Patient & Family Conference this past July on the World Health Organization reclassification of brain tumors. Thank you for joining us you may now begin your presentation.

>> Thank you so much. Thank you all for being here. I would like to talk a little bit today about the updates in the classification of brain tumors that has been coordinated with the World Health Organization (WHO). I will be presenting basic concepts as to the need of the classification and key elements that define the update which will help define brain tumors accurately for precision care. The classification of central nervous system tumors has been updated in 2016. I'll talk about the rationale and the concepts of the overall approach that was used. I will also present examples that highlight or illustrate some of the changes and types of changes in the classification.

>> On this slide we see the book covers of a variety of World Health Organization classification and update classification in brain tumors. The first edition on the left was in 1979. It was the pioneer. How and overall approach toward the tumor classification. And the WHO was interested in this to help standardize things across the world. This was followed up by second edition in 1993. And in 2000 and also in 2007. More recently in 2016 is the cover of the new update. As you can see, there is a variety of images on this cover to represent some of the different facets of classification which include the gross morphology imaging, the histology, chemistry and some of the molecular features.

>>Here is a high-level summary of some of the changes in the 2016 WHO classification update. I will not go into great detail. The first point in the table which says formulating a concept of how CNS diagnosis are structured in the molecular era. It is the overarching principle used to help guide the development of the 2016 classification. We are more and more able to learn about the molecular features of these tumors, we're more able to incorporate how -- tumors are classified.

>> Here are some of the key highlights. Some of the molecular alterations have been identified. One of them is the concept of co-deletion of chromosomes 1P 19Q or called 1P/19Q co-deletion. The second is mutations in the enzyme IDH. These two molecular changes have been identified as a fundamental importance change in gliomas, which includes the astrocytomas and olgiodendrogliomas.

>> And other mutation in a gene called INI1 has been found to be present in another tumor type. A rare pediatric tumor type called ATRT. Some other features that have been noted in the past 5 to 10 years include the notion of a medulloblastoma as having specific subtypes. On the microscope it looks like medulloblastoma, can actually represent four different diseases that can be resolved only through molecular analysis. Similar features occur with another brain tumor type, apendamoma [sp] where a molecular analysis shows that tumors that look identical under the microscope, actually have differential features based on molecular markers. Which may have clinical implications.

Going back to the previous addition of the update in 2007 some of these molecular markers are mentioned in the text of the blue book. They are not incorporated into the definition of these tumors. The major change in the new update 2016 is that we have reinforced the importance of these markers by putting them into the actual definition of some of these entities. In part to encourage the use of them universally when possible. Also to really help us define on a precision medicine basis of these tumors. Some of which can look the same in the microscope that have different micro features. Potentially differences in responses to therapy.

>> I will show you a picture here of a figure that was published on 100 years ago by a well-known neurosurgeon, Harvey Cushing [sp]. His pictures shown on the upper left. What is interesting about this figure is how many of the terms are still in use. For example, you will see on the lower right oligiodendroglioma and again on the lower portion you'll see an ependyma and other places talk about astrocytoma, etc. The point I would like to emphasize is many of the terms used have been around for a long time. They remain very useful in the update does not replace these terms it simply adds to them by using specific biomarkers that have been defined as being clinically relevant based on study.

>> I will provide an example of that change from 2007 to 2016 by showing this definition. This is direct from the 2007 WHO classification which every entity in the WHO has a definition. That definition is one to two sentences that is to the best of our ability to define the key elements of each of the entities. In this particular example this is oligiodendroglioma. The definition as you can read is based on where it is located. What kind of patient it is and in this case adults. It talks about the morphology cells representing oligiodendroglioma. You will notice after that it says and often harboring deletions of chromosomal 1p and 19Q. There is a subtle issue that the concept in 2007 which is it is defined based on how it looks under the microscope. The concept is it is associated with 1p and 19q co-deletion. The concept here is that the 1P 19 co- deletion is associated with oligiodendroglioma in 2007 but not defined by that molecular marker.

>>Here we will show you how we can test for 1p 19 q co-deletion in tumors. That is using a molecular method called fish or fluorescence hybridization. Here you can see an example. On panel A you have a fish result showing many of these cells two red dots and only one green dot, which indicates deletion of one arm of the chromosome associated with 1p 19q co-deletion.

>> One reason why we would want to help use molecular markers in helping to define entities is that morphology, the study of how the tumor looks under the microscope, although I can get us far it is standard practice among pathologist to classify tumors. It is subjective. There are specific cases that may have features difficult to discern. Because of that there can be diagnostic discordance in certain types of tumors.

>> There are some tumors that are difficult to classify in either group – says a paper from Dr. Coombs shows looking at grade 2 and grade3 diffuse gliomas that the concordance rate among pathologist may not be as good as we hoped. Based on the fact that there can be some subjectivity in morphologic diagnosis, there is a need to use molecular features to help close the gap so we can increase the concordance and increase the standardization of how we classify these tumors.

>> That is really the point I wanted to make on this slide. Molecular markers can improve observer concordance and standardization of classification. As I mentioned there are many morphologic features that have a basis in biologic findings. Oligiodendroglioma is often associated with 1P 19q co-deletion. It makes sense to connect those two and the morphology of oligiodendroglioma.

>> There are some markers that do not have such a relationship to biomarkers. Even so, they can illuminate clinically relevant distinctions within an entity. We would talk a little bit about that. That is IDH mutation status.

>> Lower grade gliomas, grade 2 and 3 diffuse gliomas, can have the presence or absence of the mutation status. Although they look similar under the microscope, the fundamental nature to determine biology is so important clinically that it was felt by the consensus of neuro-pathologists involved in the classification, which I was one, that the IDH mutation should be included in the definition. To separate those tumors that are IDH mutant from those that are not. It is also true that new technologies and genomics established the relevance of key markers in brain tumors. In other words it is possible that markers under investigation today, once we gain more experience and if clinical relevance is shown, it could be incorporated in a future update of the classification.

>>I will show you an example of how and I will not go into great detail. An example of how some molecular analyses have been used to justify the fundamental importance of IDH mutation in 1p and 19q to co-deletion. Really the classification of gliomas. I will not go into great detail but here is some data from an international initiative. It was a NIH sponsored and funded study which put together a number of different platforms. Will not go into great detail. I have listed them for your interest. The bottom line is for about 280 or 290 tumors of lower-grade glioma, in most of these tumors they were profiled using many of these platforms. Also an integrated analysis was performed on 254 tumors from this group. The major question being asked is if we can integrate all of these things together what is it telling us about some molecular markers we are using? What are the relevance of these markers? This slide is showing a high-level genomic analysis. The major concept is that three major subtypes you can see on the clustering analysis, because you can see group. Here and here. These groups corresponded to the presence of IDH mutation and also the presence or absence of 1p/19q co-deletion.

>> That information is summarized here. Starting with 280 tumors, grade 2 and 3 of lower-grade gliomas. The first cut or for separation between the two tumors was not how they looked under the microscope or whether they were astrocytomas or oligiodendroglioma. The first major cut was whether or not they had an IDH mutation or not. If they were IDH mutant a second cut could be seen in the genomic analyses.

>>Whether or not they had not. This gives us three major subgroups of diffuse lower grade gliomas. This is published a little over a year ago in the New England Journal of Medicine. I will point out a couple of things. That is that the IDH wild type gliomas which are a minority nonetheless can, at times, have some of the molecular features suggested of higher grade such as glioblastoma. As we talked about, 1p/19q co-deletion these are associated with the ones where several Mac associated with astrocytoma. And other point that was a finding from these studies is that the into the near pathologist knows as mixed oligioastrocytoma that is a tumor that features intermediate features between oligodendroglioma and astrocytoma, had no molecular correlate. In other words, tumors that were profiled by TCGA with a diagnosis of oligioastrocytoma had no distinctive molecular feature to distinguish them from either oligodendroglioma and astrocytoma. Based on that result there has been a movement. I have just illustrated a recent paper that provides a statement to that effect. Really indicative of the fact that this particular morphology does not have a molecular basis and therefore it has been deemphasized in the WHO 2016 update for classification of brain tumors. In large part based on this finding.

>> This leads us to a question that was put to the panel. It decided how to update the WHO in 2016 that is the overall question of how went to appropriate new molecular findings into the classification, like in medulloblastoma and ependymoma occur almost on a weekly or monthly basis in the literature. That makes it was very interesting and also adds to the question when is a part it practical to incorporate that molecular finding into a WHO definition? Balanced with the need to incorporate new data is the companion need to maintain consistency and a standardization. One needs to have a stopping point where one can incorporate changes so it can be accepted and studied by the community. Equally important is whether or not the molecular changes you found our clinically relevant because the classification is, above all, something that is to be used clinically and is important. There is also a need to ensure that the classification system is accessible unworkable to all. Molecular markers that are proposed really should be something that could be generalized across centers. We began this process in the summer of 2014. As I showed you we ended up with the publication in 2016.

>>On this slide I would like to point out that into these need to do fine as specifically and narrowly as possible to optimize the reproducibility. We do not want entities that are hard to reproduce, across centers and pathologist. We want to minimize diagnostic discordance, so things are standardized. Another concept that has been emphasized is what we call the layering of a diagnosis. Incorporating the fact that not only is there morphologic data under the microscope but molecular data. So we can layer these different kinds of information into a diagnostic report and integrate them. As we've talked about determination should be made for each tumor entity. Or i'm not ready for prime time so maybe you should be suggested not needed for the definition.

>> Some of the other features in the 2016 update for the WHO is that in many cases there are tumors that occur in children that although look similar and the microscope to tumors that occurred in adults but have a different molecular background. Oligodendrogliomas is one example. Those that occur in children do not have the 1p/19q co-deletion. They do not have the IDH mutation either. Even though they look similar under the microscope to the adult tumors, they are not the same molecularly. Since tumors behave according to the genes altered in the tumors, in many cases pediatric tumors should be separated from adult tumors. So we do not lump them together that are biologically not similar. Other features that weren't part -- important in the classification was codified by pathologists and by other experts in related disciplines such as medical oncologist, neurologist, near surgeons, etc. This was done to ensure the clinical relevance and clinical translation of some of these changes. As I mentioned, there is a need to incorporate this molecular testing and user reporting formats that are compatible with both the used of morphology and molecular analysis.

>>Here is an example of the layered diagnosis or layer diagnostic format that could be used. We are using it at our institution to integrate and incorporate all of the information that's relevant. Typically when a pathologist receives a case the initial material will be slides. Sections are cut from the tumor and sections are stained with ANDA. Based on that an initial classification is made.

>> For example, astrocytoma or olgiodendroglioma – that's the cell type for example and a grade is also assigned – grade 1, grade 2, grade 3…etc. the potential clinical behavior of that entity. This is the tried-and-true method of classification. Added to these layers are relevant molecular information. Once the molecular information is obtained on a particular sample that can now be integrated into the first layer which incorporates all the tissue-based data. Here are some examples of some potential integrated diagnoses of medulloblastoma. We will see later that there are some subtext of medulloblastoma. The richer grade is present. These are some examples of potential more information that can be present. The concept of the layered diagnosis goes along with incorporation of molecular analysis added to morphology to come up with an integrated diagnoses.

>>In this particular slide we talk about whether the marker actually defines that entity or is a highly correlated with that entity? Everything questions of what do we do when testing for the markers is not available, but we still need to make a diagnosis. For example, we talked about oligodendroglioma. There may be cases where the tissue is too small to do a test or the test may not be available at that particular center, so a variety of things can happen. The WHO needs to make sure that there is still a way to classify these tumors. The second issue is what to do when the molecular marker result is somehow at odds with the histological reports. We talked about it being of several issues with 1p/19q but what happens if there is a tumor that looks like but will not be, deleted. We need to have a way to put these things that do not quite fit into a diagnostic category. Here are some examples of how some issues are dealt with. In this particular example of the pediatric tumor is so ingrained with a particular mutation or set of mutations. Either one of these mutations have to be present to make the diagnosis. Here is an example of a layered diagnosis with the typical tumor where the INI one was mutated.

>> That's why I say no markers no entity. If it has the marker it can be a certain tumor but what if it doesn't? What if it does not have either one of these changes quick it was felt in that instance that we would back off from a specific diagnosis. For example, it looks like interrogatory tumor but it does not have the molecular -- molecular analysis required. This being example of how we would deal with a situation. It looks like a a TRT but it does not have the required molecular change. Either because it was tested and it was not present or for whatever reason it was not tested. We talked about other examples where testing is highly recommended for tumors that look like. One can imagine three scenarios. Acute testing could be performed I would be found to become deleted. It could be just a profound not to become deleted or for whatever reason testing may not be performed enough to give an example. We will have ways to make a diagnosis no matter what scenario is happening with a particular case. Here is an example of a code deleted [Indiscernible] where this would be the classification of its present but what about if it is not present? We may back off and give it a diagnoses of [Indiscernible] finally, and other proposed way of dealing with this is the so-called MLS category. -- In OS -- not otherwise specified classification. There is this category for the into the. -- Entity. Here are some of the possible scenarios. Where the histology and molecular -- we know there are some good [Indiscernible]. In the upper left is the [Indiscernible] which is known to be commonly mutated. It is usually not code deleted.

>> Here is an example of the several Mac that has the associated molecular abnormalities that would be easily calcified. We talked about the [Indiscernible] code deleted tumors but then we have to have all of these other possibilities that look like [Indiscernible] but yet have some of the other possibilities. I will not go into detail but here are some propose ways to classify these tumors. Again, we have talked about the NOS concept a pathologist can still classify these tumors as NOS or [Indiscernible].

>> I'm going to go over the next few slides quickly to make sure we cover everything. The concept here is what are the standards for testing? To keep insisting the WHO cannot mandate standards for testing. Specific ways things are tested can be different. The job of the WHO is to provide a guide for how these tumors are to be classified. To illustrate an example on how we use some of these markers we practice it turns out that I DH one when it does mutated the most common mutation occurs on code 182. That changes in amino acid from our 2H. Silcock are 130 2H. It turns out we need a and abiding marker that this mutant [Indiscernible] this is a helpful a diagnostic tool. It indicates that there is a mutation present. Here you can see the section of the brain with [Indiscernible]. Here it reinforces the concept that most mutations are [Indiscernible]. For the 10 to 15% of cases that are not antibody [Indiscernible]. We will then go on to sequence. We have talked here about testing that can be done by fish. Here are the possibilities of [Indiscernible] testing. Practically speaking the possibility on the right does it occur. Here are some of the ways we can think about these tumors.

>> Talked a little bit about the childhood tumor that has an appearance under the microscope. It has been found by middle clear analysis there are four roots of these tumors. They are qualified here. These are based on molecular analyses. I will not go into detail but this provides some rationale for why we might want to subtype these into four. Some of the Coleman molecular changes associated with each. Here is some additional data. At the provide some justification for why one would want to separate [Indiscernible] into one of the subgroups based on the clinical behavior. It gets even more detailed as more data is obtained and more questions are asked. Things become more complicated as usually happens. The only have they subdivided [Indiscernible] they have only looked at one group. They found based on the subset [Indiscernible] I will not go into great to deal but to give you a flavor that more and more we are finding additional ways to classify these tumors. This reemphasizes that [Indiscernible] may be important.

>> Ependyma is another type of tumor in the brain that comes from the lining of the ventricles of the brain. Here is some pictures. Although many of these look the same it is clear that they have different features. I have shown three major compartments. Some features can differ even though they look similar in the microscope some clinical features can differ based on location. Here is an example of that where in this particular paper they divided in several Mac into cerebral or superstore you. You can see here that this particular marker of effusion is present only in this compartment. Again showing the relationship of the location with the molecular lesion. Even though these tumors can look similar under the microscope it is clear that the basis can differ. Based on that the WHO has defined into the OC 11 or 95 that occur in the [Indiscernible] [Indiscernible - low volume] these tumors were very recently found that they can add changes in dose it is possible that may be incorporated into a eventual [Indiscernible] in the future. This is a high-level view of some of these changes showing the differences [Indiscernible - low volume]

>> This is finishing up to review. Here is some of the entities now in the WHO classification. In 2007 we just had [Indiscernible] and now we have flavors. The [Indiscernible] we talked about. You can have me tenants while -- we have talked about the Temple Loma where we have incorporated this new fusion. Then we talked about [Indiscernible] stoma. The final diagnosis is a integration of these two kinds of [Indiscernible]. Some people have asked me and other pathologist as to whether or not color analysis will render mythology irrelevant and I think the answer is no. Molecular analysis will help fill in gaps but morphologies still has a important role. The word pathologist classifies [Indiscernible]. Here is [Indiscernible] of patients based on morphology alone showing a great effect of mythology. It still has a very important role in what we're doing. We're trying to supplement that to help us and to help this gap. This group of patients that have lived a very long time, how do they differ from patients that have a much [Indiscernible]. How can we more precisely define these tumors in addition to mythology? I will not into great detail but we have conducted a survey of experts in the field by surveying the largest society of mythology. We asked them about their enthusiasm. Here is a breakdown of specialties. [Indiscernible] [Indiscernible - low volume]

>> You can see here that the vast majority, over 80%, felt the answer was yes. This is reassuring and supports some of the changes. To summarize the WHO opted and CMS has been done in 2016. Is not a static thing. There was a 2016 update but changes occur daily. More updates will be happening and needed in the future as we try to get to this goal of into five -- individualized precision medicine. We also need to accommodate the classification system. At some level will must have a two-tier system. The concept is to really interact with our colleagues and patients to ensure the ape dates and changes we make are clinically meaningful and important. With that thank you for your attention and I would be happy to go further with any questions that may come up.

>> Thank you. We will now take questions. If you have a question you would like to ask please type and submit it using the question box in the webinar control panel on the right-hand side of your screen. Our first question is can tumors be classified without a biopsy? Expect the answer is no. A tumor, to be classified, really requires a tissue sample.

>>That is either a biopsy or some sample of a tumor to be examined by a pathologist. There are circumstances where a biopsy may not be indicated for a variety of reasons. So there are some cases where a biopsy may not be performed. Diagnosis may be presumed based on the clinical features. The short answer is no a cannot be formally classified. More complex answer is they are rare cases where there is a presumed diagnosis.

>> Our next question asks, how have prognoses improved in the -- brain tumor patients with the new WHO classification system?

>> I think what we can say is the predicted prognosis of patients with the new WHO can be more accurately defined. That is [Indiscernible] we talked about the two main types on a molecular level. Those idea to me and those that are not. It turns out that I DH me patients have a better prognosis and patients whose tumors are not jaded. While the classification does not improve the diagnosis it improves the certification into more refined prognostic groups. The second example is some of the markers are predict. They help predict responses to particular therapies. The use of 1P 19 Q can help determine the appropriateness of alkylating chemotherapy for patients. In that way it can refine the classifications to get the most benefit from that particular therapy. That precision oncology precision medicine approach I think is mostly benefit of the molecular analysis.

>> Our next question asks are there specific genetic test names that need to be done to get its conclusive profile of molecular bio -- biomarkers for particular types? They also asked what type of genetic labs are qualified to test.

>> Many hospitals have the capability to do many of the test's I have talked about in this presentation. In particular I DH expectation. We talked about how 1P 19 two can be tested. That one is most commonly used. There are other methods that can be as equally as good. Again [Indiscernible] cannot dictate what method is used but every hospital that does analysis really has a certain set of standards that it must fulfill to do clinical tests. Usually Ibn showed to be an excellent test. If secretiveness can change the ways than the particular hospital usually has a method to do it. There are other tests I have shown me that may not be as widespread. That are in between the research and clinical use. We hope with the WHO 2016 update it encourages people to incorporate many of these. I would encourage patients who have specific questions to contact their physician about the relevance of a particular test.

>> This question ties to the previous question and asks how do I approach my healthcare team if I would like to get molecular testing done on my tumor? What are good questions to ask them?

>> That is a great question. It is important to know that there are some tumors were it is felt by the community -- medical community that the analysis is important. There are other tumors were we may not yet have a molecular test that is clinically relevant. I would encourage our their clinical molecular tests that would be relevant to that particular tumor type it may not be relevant for a particular tumor type one might have but there may be another type where it is highly relevant. I would definitely encourage that conversation to occur to ensure that each tumor is being diagnosed appropriately.

>> Thank you. Our next questions -- question asked if all reports can be used to determine a tumors classification according to the new WHO classification system?

>> That is a good question. For the most part the answer depends on a case-by-case basis on what is on the report. For example, if the pathology report has specific tumor types and somewhere in the report it talks about what the I DH status is then that can easily be reformulated into the integrated diagnosis. It depends on the individual pathology report as to whether it can be direct retranslated into the new classification so it would depend on the report and whether the molecular analysis was performed. Assuming it is then the one should be able to translate the old information into the new WHO 20 WHO 2016 classification.

>> Our last question asks, D go back and test again after a recurrence of a tumor? Is it necessary to test all tumor locations in a motive -- multifocal tumor?

>> Those are two very good questions. The answer is if -- we may go back and retest if there is a question in the procedure to confirm there has not been a change. We believe for the most part some of the markers we test for our fairly stable on average. Is not 100% but for the most part they are stable. There may be instances where it does not need to be retested. However, if there is a question based on the clinical features and how it looks under the microscope, sometimes we test to confirm sometimes we don't it depends on the individual circumstance it is a very active area of study right now. How the molecular features of a tumor may differ based on the location. What we are finding is some of the major markers we have talked about are very stable and do not vary among different sites. However, there are some secondary taste -- changes that may differ based on the location. That is not ready for clinical use that is an area of act investigation.

>> That is all the time we have for today. Thank you for joining us and thank you to the doctor for his want -- wonderful presentation. Besides our free educational webinars we have verity of programs to help connect patients and caregivers with information and resources to help support them in their brain tumor journey. As well as publications and reports sourced -- resources for healthcare professionals. For more information visit the website or call the Caroline staffed by caring professionals at 1-800-886-2282. Let's pause for a moment to conclude our webinar, -- recording. We invite you want to continue to check back at our website as we tend previously. -- Mentioned previously. A library of free on-demand webinars that feature renowned expert addressing a wide range of brain tumor topics.

>> Our next webinar will be on metastatic brain tumors and what patients need to know. This is on Wednesday, November 9 from 1 PM to 2 PM central standard time. A metastatic brain tumor also known as brings a test of these or secondary brain tumor is cancer that begins elsewhere in the body that -- and spreads to the brain. As many as one third of patients with primary lung breast and colon and skin cancers may develop rain metastases. Join Dr. Michael Lynn associate professor at Johns Hopkins University as he prevents key information about the signs and symptoms of a brain metastases. To help webinar participants to understand who are at highest risk. He will also focus on the latest cutting edge therapies.

Webinar participants will have the opportunity to ask the doctor questions in an interactive question and answer session. To register please visit our website at -- click on the brain tumor information and upcoming webinars. This concludes our webinar. They give for joining us and please be sure to complete the evaluation survey you will receive. You may now disconnect.