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Overview

Understanding the Revised Fourth Edition of the World Health Organization Classification of Tumours of the Central Nervous System (2016) for Clinical Decision-making: A Guide for Oncologists Managing Patients with Glioma

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Abstract

The recognition of specific molecular prognostic factors has altered the management of primary brain tumours over the past decade. These factors have allowed stratification of morphologically similar tumours into different prognostic groups and are now also being used to determine clinical trial eligibility. Many of these factors have been included in the revised fourth edition of the World Health Organization (WHO) Classification of Tumours of the Central Nervous System, released in May 2016. This revised edition places greater emphasis on molecular testing and, for certain tumour types, molecular testing is required for diagnosis. Many pathology departments have also adopted the four-tiered report format suggested in the Haarlem guidelines, and provide a final 'integrated diagnosis' incorporating a morphological diagnosis, the WHO grade and molecular findings. Pathologists need to perform and report these molecular tests in a timeframe that is relevant for clinical decision-making. Clinicians need to understand and incorporate these changes into their daily practice, as they have direct effects on both the type and intent of therapeutic interventions.

Key words: Classification; glioma; neuropathology

Statement of Search Strategies Used and Sources of Information

Literature searches were conducted using key word searches on PubMed for neuropathology, World Health Organization classification and Haarlem consensus guidelines. Reference lists of relevant journal articles found through that process were also reviewed and individual journal articles of relevance to each topic were obtained.

Introduction

The decade from 2007 to 2016 has been associated with major changes to neuro-oncology practice, including improved magnetic resonance imaging and metabolic imaging, aggressive strategies for gross total resection, targeted radiation therapy and increased utilisation of systemic therapies [1]. This has especially been evident for patients diagnosed with high-grade glioma, including anaplastic oligodendroglioma, anaplastic astrocytoma and glioblastoma. The median survival for patients with glioblastoma managed with curative intent has doubled from 9–12 months in 2005 to 18–24 months in 2014 [2–4] and selected elderly patients also benefit from combined modality therapy [5]. Based on clinical trial data, it is now anticipated that patients with anaplastic oligodendroglioma may survive

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beyond 15 years [6,7]. With improved outcomes, prognostic groups, defined by factors unknown in 2007, are now being identified for either treatment escalation or de-escalation [8].

This altered practice has contributed to neuro-oncology becoming a highly subspecialised clinical service, requiring multidisciplinary input for patient decision-making. However, given the relatively low incidence of malignant brain tumours (age-standardised rate 6.7 per 100 000 per year or 1.3% of all cancer diagnoses) [9], management at most centres is delivered by oncologists with major subspecialty expertise in other tumour streams.

Decision-making for high-grade glioma management over the past decade has been based on the histopathological subtype and grade (the latter based predominantly on tumour proliferation assessed by the mitotic count and the presence of pleomorphism, necrosis and/or microvascular proliferation), as defined by the 2007 World Health Organization (WHO) Classification of Tumours of the Central Nervous System, together with clinical features such as age, extent of resection and performance status. These pathological and clinical factors involve a significant degree of subjective assessment, although criteria based on the results of recent clinical trials have reduced some of the variability. For most patients, grading based on neuropathological criteria has generally provided a structure to guide prognosis. However, in the past 5 years a number of molecular prognostic factors have been identified and rapidly, but inconsistently, introduced into clinical practice to aid decision-making. These have identified different prognostic groups within tumours of the same histological grade and subtype, especially within anaplastic glioma, where a favourable subgroup can now be identified based on molecular factors [10]. The recognition of these molecular prognostic markers has now become a discriminating factor for clinical trial eligibility, not just prognostic stratification. However, this molecular testing has not been uniformly implemented, or may only be utilised at high volume centres where patients are enrolled into clinical trials requiring such testing for stratification. The awareness of molecular subtype may then also impact or influence other decision-making in those patients, both at the time of initial management or interpretation of response.

In this clinical environment, the release of a significantly revised pathological classification of brain tumours that incorporates relevant prognostic molecular factors by the WHO in May 2016 requires communication and clarification [11]. Consequences of this reclassification include a greater reliance on molecular findings, not previously included in standard neuropathological protocols, and the creation of new diagnostic criteria which, for certain tumour subtypes, direct treatment interventions with significantly altered intent. Many pathology departments have also adopted the four-tiered report format suggested in the Haarlem guidelines [12] and provide a final ‘integrated diagnosis’ incorporating a morphological diagnosis, the WHO grade and molecular findings. It is essential that clinicians understand and incorporate these changes into their daily practice, as they have direct effects on both the type and intent of therapeutic interventions.

Major Molecular Markers

The identification of driver mutations for glioma growth has led to a greater understanding of the pathways involved in gliomagenesis and a realisation that molecular parameters can be used to refine the classification of glioma into meaningful clinically relevant groups. A number of these molecular parameters have been incorporated in the revised fourth edition of the WHO Classification of Tumours of the Central Nervous System [11] and several glioma subtypes have been defined by the presence of one of four molecular markers (summarised in Table 1):

(i) point mutations in isocitrate dehydrogenase (IDH) 1 or 2;
(ii) loss of the whole arm of chromosomes 1p and 19q;
(iii) a K27M point mutation in histone H3;
(iv) a C11orf95-RELA gene fusion.

Table 1
Markers required for the World Health Organization (WHO) 2016 classification

Molecular test	Relevance
IDH1/IDH2 mutation	• Major early driver mutation for low-grade glioma. • Diagnostic, prognostic and predictive marker in astrocytic tumours. • With 1p19q co-deletion is required for diagnosis of oligodendroglioma. • Most common mutation (IDH1 R132H) identified by IHC; 10–15% of IDH-mutated tumours negative by IHC; require DNA sequencing of IDH1 codon 132 and IDH2 172 codon [13].
1p19q co-deletion	• Involves complete loss of both short arm of chromosome 1 and long arm of chromosome 19. • Occurs early in oligodendroglial tumour genesis. • Diagnostic, prognostic and predictive marker for oligodendroglioma. • Testing most commonly by FISH. Single nucleotide polymorphism array or polymerase chain reaction-based techniques are alternative methods [14].
H3 K27M mutation	• Detected through IHC. • Identifies the presence of a diffuse midline glioma, an aggressive contrast-enhancing WHO grade IV tumour most common in children and young adults, usually within the thalamus or brainstem regions. • Associated with poor outcome. • Management as per glioblastoma as no current specific targeted therapy [15].
C11orf95-RELA gene fusion	• Surrogate IHC marker to identify high-risk supratentorial RELA-fusion-positive ependymoma. • No specific targeted therapy [16].

IDH, isocitrate dehydrogenase; IHC, immunohistochemistry; FISH, fluorescent *in situ* hybridisation.

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