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The anatomy of neuroepithelial tumours

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Many neurological conditions conceal specific anatomical patterns. Their study contributes to the understanding of disease biology and to tailored diagnostics and therapy. Neuroepithelial tumours exhibit distinct anatomical phenotypes and spatiotemporal dynamics that differ from those of other brain tumours. Brain metastases display a preference for the cortico-subcortical boundaries of watershed areas and have a predominantly spherical growth. Primary CNS lymphomas localize to the white matter and generally invade along fibre tracts. In neuroepithelial tumours, topographic probability mapping and unsupervised topological clustering have identified an inherent radial anatomy and adherence to ventriculopial configurations of specific hierarchical orders. Spatiotemporal probability and multivariate survival analyses have identified a temporal and prognostic sequence underlying the anatomical phenotypes of neuroepithelial tumours. Gradual neuroepithelial de-differentiation and declining prognosis follow (i) an expansion into higher order radial units; (ii) a subventricular spread; and (iii) the presence of mesenchymal patterns (expansion along white matter tracts, leptomeningeal or perivascular invasion, CSF spread). While different pathophysiological hypotheses have been proposed, the cellular and molecular mechanisms dictating this anatomical behaviour remain largely unknown. Here we adopt an ontogenetic approach towards the understanding of neuroepithelial tumour anatomy. Contemporary perception of histo- and morphogenetic processes during neurodevelopment permit us to conceptualize the architecture of the brain into hierarchically organized radial units. The anatomical phenotypes in neuroepithelial tumours and their temporal and prognostic sequences share remarkable similarities with the ontogenetic organization of the brain and the anatomical specifications that occur during neurodevelopment. This macroscopic coherence is reinforced by cellular and molecular observations that the initiation of various neuroepithelial tumours, their intratumoural hierarchy and tumour progression are associated with the aberrant reactivation of surprisingly normal ontogenetic programs. Generalizable topological phenotypes could provide the basis for an anatomical refinement of the current classification of neuroepithelial tumours. In addition, we have proposed a staging system for adult-type diffuse gliomas that is based on the prognostically critical steps along the sequence of anatomical tumour progression. Considering the parallels in anatomical behaviour between different neuroepithelial tumours, analogous staging systems may be implemented for other neuroepithelial tumour types and subtypes. Both the anatomical stage of a neuroepithelial tumour and the spatial configuration of its hosting radial unit harbour the potential to stratify treatment decisions at diagnosis and during follow-up. More data on specific neuroepithelial tumour types and subtypes are needed to increase the anatomical granularity in their classification and to determine the clinical impact of stage-adapted and anatomically tailored therapy and surveillance.

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Introduction

In 2019, more than 347 000 patients worldwide were diagnosed with a primary neoplasm of the CNS, causing over 240 000 deaths and 8 600 000 disability-adjusted life years.[1] The term 'primary CNS neoplasms' refers to a heterogeneous group of primary intracranial and intraspinal tumours, including neoplasms with osseous, meningeal or haematolymphoid differentiation.[2] The more specific term 'neuroepithelial tumours' is confined to neoplasms of neuroepithelial differentiation and includes neuronal, astrocytic, oligodendroglial, ependymal and primitive neuroectodermal tumours. The classification of neuroepithelial tumours underlies a high-paced evolution driven by progressive insight into tumour biology.[3-13] While it was traditionally based on histological features only, significant advances in understanding the molecular landscape of neuroepithelial tumours have reshaped their categorization.[3-13] The most recent edition of the World Health Organization Classification of Tumours of the Central Nervous System (WHO CNS5) strengthened the role of molecular biomarkers in determining tumour type and grade.[2] In addition, the WHO CNS5 annotates individual tumour subtypes with spatial information, e.g. diffuse midline H3 K27-altered versus diffuse hemispheric H3 G34-mutant glioma, central versus extraventricular neurocytoma, or supratentorial versus posterior fossa versus spinal ependymoma.[2] Considering the anatomical complexity of the brain, however, the anatomical dimension may hold much more potential in the classification of neuroepithelial tumours.

In addition to complementing classification through the identification of generalizable anatomical patterns in neuroepithelial tumours, insight into the anatomical sequence of neuroepithelial tumour progression might serve as a basis for tumour staging. There is no established staging system for neuroepithelial tumours. Age, general and neurological performance, extent of resection and O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation are established prognostic factors in subsets of gliomas.[14,15] Classic tumour staging systems, such as TNM staging for solid tumours or Ann Arbor staging for lymphoma, however, are rooted in an understanding of the anatomical sequence of tumour progression and its correlation with prognosis.[16] Insight into such a sequence in neuroepithelial tumours could provide the basis for a staging system to inform patient-specific treatment and surveillance decisions.

Here we consolidate evidence on specific anatomical patterns and sequences identified in neuroepithelial tumours and discuss possible pathophysiological mechanisms. In addition, we outline the clinical potential of a higher anatomical granularity in the classification of neuroepithelial tumours, an anatomical staging system for neuroepithelial tumours and an anatomical tailoring of therapy and surveillance.

Archetypical anatomy in neurological diseases and brain tumours

Neurological diseases of various aetiologies are characterized by distinct neuroanatomical phenotypes. Examples include the selective affection of the cornu ammonis and cerebellar Purkinje cell layer in hypoxic conditions,[17-19] the selectivity for limbic structures in autoimmune encephalitis[20] or the entity-specific atrophy patterns with neurodegenerative diseases.[21,22] Both the anatomical pattern and its sequence of progression are determined by the interplay between disease-intrinsic affinity, i.e. tropism (from the Greek *tropos* for 'a turn, growth towards') and tissue-selective vulnerability, i.e. pathoclisis (from the Greek *pathos* for 'disease and -clisis for predisposition'). Thus, topographic probability and spatiotemporal dynamics provide insight into disease biology.

The anatomical phenotype in brain metastases is determined by the brain's arterial angioarchitecture, with the highest tumour probability at the cortical-subcortical boundary of cerebral and cerebellar watershed areas.[23-27] The specific patterns vary by primary tumour.[26-29] The growth of brain metastases is predominantly spherical with displacement and little invasion of neuroepithelial tissue.[26]

The anatomical phenotype in primary CNS lymphomas is determined by the white matter architecture. The cortex is characteristically spared, early disease has a predilection for the subcortical white matter with orientation along U-fibres, while more advanced lymphomas demonstrate extensive white matter involvement dominated by patterning along the major fibre tracts, e.g. corpus callosum or corticospinal tract.[25-27,30] The predominant growth pattern in primary CNS lymphomas is invasion along white matter tracts.[26]

The anatomical patterns and spatiotemporal dynamics of neuroepithelial tumours differ fundamentally from those of brain metastases or primary CNS lymphomas.

Anatomical phenotypes and sequences in neuroepithelial tumours

In 1938 and 1940, H. J. Scherer[31,32] concluded in his pioneering works *Structural development in gliomas* and *The forms of growth in gliomas and their practical significance* that neuroepithelial tumours do not behave stochastically, but adhere to certain anatomical patterns. Scherer[31,32] further proposed that gliomas follow specific rules in their spatial evolution, but that these rules differ depending on the 'aggressiveness' of the tumours.

More recently, topographic probability mapping and unsupervised topological clustering identified an inherent radial anatomy in neuroepithelial tumours and adherence to specific ventriculopial configurations.[25-27] In contrast to brain metastases or primary CNS lymphomas, neuroepithelial tumours revealed comparable tumour probabilities along the ventriculopial axis, irrespective of their WHO grade or anatomical extent along other axes.[26] An unsupervised clustering of the interstructural relationships in neuroepithelial tumours through non-negative matrix factorization identified generalizable topological patterns, which all shared a radial anatomy.[27] The ventriculopial configurations were deciphered into radial units of different hierarchical orders with sharp intergyral and supragyral boundaries.[26,27,33] The radial units differed in their topographic probabilities for neuroepithelial tumours in general, and in their histological and molecular profiles.[25,26] Progression

of neuroepithelial tumours to higher order radial units was associated with neuroepithelial de-differentiation and declining prognosis.[25,26,33]

In contrast to the predominant spherical displacing growth of brain metastases or the invasion of primary CNS lymphomas along white matter tracts, spatiotemporal probability analyses revealed that the growth patterns in neuroepithelial tumours are related to their degree of differentiation.[26] Well-differentiated lower grade neuroepithelial tumours exhibited either no growth, local displacing behaviour or a radial expansion along the ventriculopial axis.[26] In higher grade neuroepithelial tumours with a lower degree of differentiation, a radial spatiotemporal dynamic along the ventriculopial axis predominated, but along with occasional subependymal or leptomeningeal spread.[26]

Multivariate survival analysis identified the anatomical phenotype of neuroepithelial tumours as an independent prognostic factor across histological and molecular tumour types.[26,27] However, only specific anatomical features have an inherent prognostic relevance.[26,27] These include, with ascending hazard ratio: (i) the expansion into higher order radial units; (ii) the presence of subventricular spread; and (iii) the presence of a mesenchymal CNS pattern (expansion along white matter tracts, leptomeningeal or perivascular invasion, CSF spread).[26,27] In contrast, the anatomical localization itself, the extension of the tumour along the radial ventriculopial axis or the presence of a contact with the ventricle harbour no independent prognostic significance.[26,27]

The cellular and molecular mechanisms that dictate the observed anatomical behaviour of neuroepithelial tumours remain largely unknown. Yet, the specific topographic and topological patterns along with their temporal and prognostic sequences allow for indirect pathophysiological inferences.

Traditionally, it has been assumed that neuroepithelial tumours grow along white matter tracts.[31,32,34] This idea was fuelled by the observations of butterfly glioblastomas, i.e. glioblastomas extending across the corpus callosum.[35] *Ex vivo* and *in vivo* analyses support the ability of glioblastoma cells to migrate along myelin and defined underlying molecular mechanisms.[36-39] However, an invasion of the corpus callosum is only found in 6.2% of all glioblastomas, despite affection of the adjacent lobar white matter sector in 92.4% and the lateral ventricle ependyma in 92.3%.[26] The internal capsule, another large and anatomically clearly identifiable white matter bundle located in anatomical proximity to the lobar white matter sector, is affected in only 1.0% of glioblastomas.[26] Both the infiltration of the corpus callosum or the internal capsule are independently associated with a very poor prognosis in glioblastomas.[26,40,41] Affection of either structure is exceptionally rare in lower grade gliomas.[25,26] In addition, if neuroepithelial tumours would preferentially orient along white matter tracts, they were expected to demonstrate early transsulcal patterns due to a spread along the subcortical U-fibres.[25-27] In contrast to primary CNS lymphomas, this is not a dominant anatomical feature of neuroepithelial tumours.[25-27] Spatiotemporal probability analyses in neuroepithelial tumours also did not identify a general macroscopic extension along white matter tracts, except for isolated cases of glioblastoma. Collectively, white matter patterns in neuroepithelial tumours do occur, but are rare, linked to a high degree of de-differentiation and constitute an independent negative prognostic factor.[26,37,42-45]

While neoangiogenesis assumes a critical role during neuroepithelial tumorigenesis,[46,47] it has also been hypothesized that neuroepithelial tumours orient their growth along the brain's arterial and venous structures.[31,32] Various studies illustrate the capability of glioblastoma cells to invade along perivascular spaces and describe potential molecular drivers.[48-52] While perivascular invasion is a histological feature sometimes encountered with glioblastoma, it is rarely seen with lower grade neuroepithelial tumours.[31,32] The MRI based topographic probability maps and the higher order topological clusters in neuroepithelial tumours are inconsistent with both the arterial or venous anatomy of the brain.[25-27] Vascular anatomical patterns in neuroepithelial tumours are associated with a high degree of neoplastic de-differentiation.[26] Consequently, perivascular invasion, akin to growth along white matter tracts, is likely an anatomical feature relatively restricted to neuroepithelial tumours with a high degree of de-differentiation.

Thus, eight decades after Scherer's original publications, contemporary evidence validates his assessment that neuroepithelial tumours adhere to specific anatomical patterns, and that the rules of spatial evolution change with the degree of tumour de-differentiation. In the following, we adopt an ontogenetic approach towards the understanding of neuroepithelial tumour anatomy based on the current perception of the brain's neurodevelopmental architecture.

Ontogenetic architecture of the human brain

Contemporary understanding of histo- and morphogenetic processes during neurodevelopment permit to conceptualize the architecture of the brain into hierarchically organized radial ontogenetic units (Fig. 1).[53-55] The neural tube forms from the neural plate, which results in a radial orientation of the single layered neuroepithelium, thereby defining a natural coordinate system of the developing brain with a radial (ventriculopial) axis and a transverse plane (rostro-caudal and/or dorso-ventral).[53] According to Rakic's radial units hypothesis, radial ontogenetic units persist throughout life, evolving from the radially oriented, single-layered neuroepithelium of the neural tube to 3D neuro-glial complexes that extend from the ventricular to the pial surface in the mature brain.[55-57] The proliferative centre at the ventricle, the cellular output of which is translated by radial fibres to the expanding cortex, determines the identity of a radial unit, thereby forming a proto-map of the cortex.[55,57,58] Brain growth and morphogenesis are paralleled by a progressive arealization along the transverse plane, which results in a nested hierarchy of radial ontogenetic units.[53] This arealization is coordinated through the concerted activity of patterning centres, which release diffusible morphogens.[56,59,60] Based on a threshold phenomenon, periventricular stem and progenitor cells integrate morphogen gradients and translate them into sharp borders of gene expression to establish the spatial identity of a radial ontogenetic unit.[60] Possible target genes control cytoskeleton dynamics, allowing cell repulsion, attraction and migration.[60] Rostrocaudal arealization is exemplified by the progression of a three-vesicular to a five-vesicular stage and the formation of prosomeres, mesomeres and rhombomeres.[53,56] Along the dorsoventral dimension there is a division into pallium and subpallium, the former being further subdivided into dorsal, medial and lateral divisions, while the latter separates into a lateral, medial and caudal ganglionic eminence.[53,56] The eventual formation of cerebral gyri and subgyral divisions or cerebellar lobules and foliae are continued expressions of the tangential arealization of the brain.[55-57]

Histologically, ventricular radial glia cells (vRGC) are the determining cell type of the brain's radial organization, serving as both stem cells and radial migration scaffolds (Fig. 2A). vRGC are derived

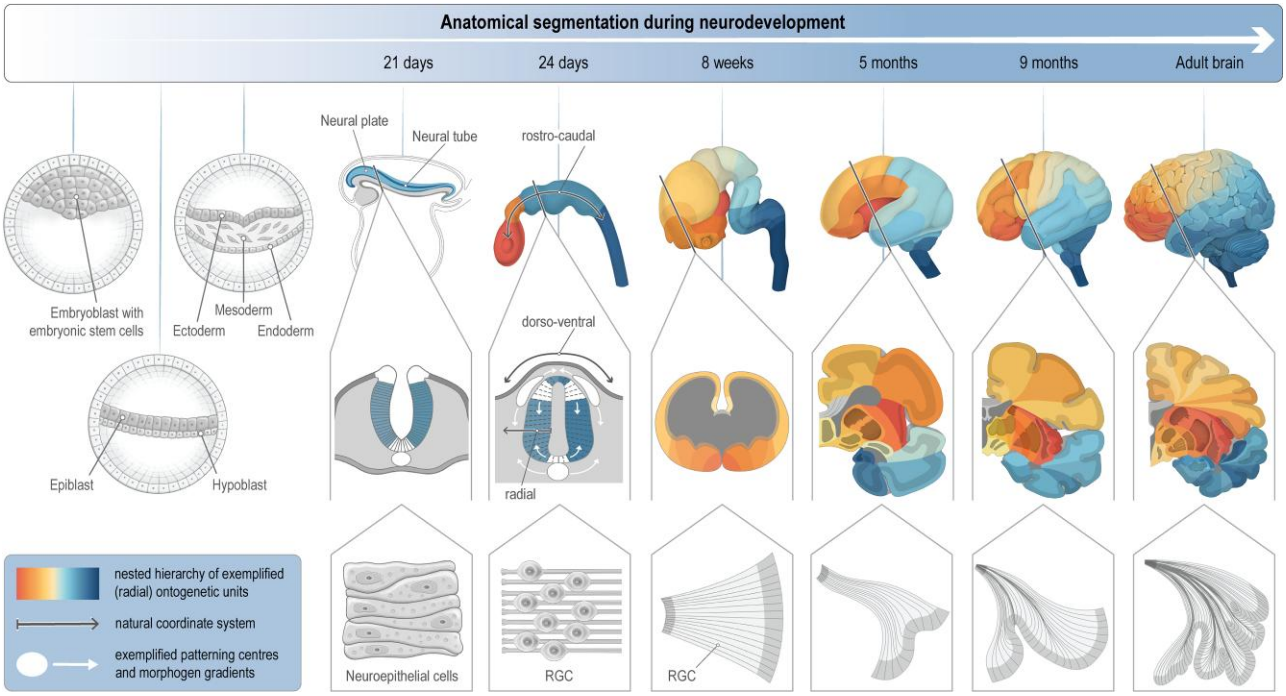

Figure 1 Ontogenetic architecture of the human brain. Directed by the concerted activity of morphogen-releasing patterning centres (white), brain growth during ontogeny is paralleled by progressive arealization along the natural coordinate system's (black arrows) transverse plane (rostro-caudal and dorso-ventral). This results in progressive anatomical segmentation and a developmental hierarchy of the brain composed of nested radial ontogenetic units. The ventriculopial configuration of radial glia cells (RGC) determines the anatomy of radial ontogenetic units and is subject to progressive distortion during morphogenesis (*bottom row*). Concept and design by Kevin Akeret, illustrations by Lucille Solomon.

from neuroepithelial cells and appear with the start of neurogliogenesis.[61-63] They have cell bodies situated near the ventricle, one fibre that extends to the ventricle and a second fibre that extends to the pia.[61-63] vRGC serve as direct and indirect stem cells for neurons, astrocytes, oligodendrocytes and ependymal cells.[61-71] They divide symmetrically, for self-renewal and maintenance of the progenitor pool, and asymmetrically, giving rise to more committed progeny.[71,72] The ventricular zone is the site of symmetric division of vRGC. Asymmetric vRGC division occurs in the outer subventricular zone deriving progenitor cells, such as intermediate precursor cells,[73] short neural progenitors[74,75] or outer radial glia cells (oRGC).[76,77] Neuron and glia cell production in the outer subventricular zone also means that their migration begins there. Instead of following the trajectory of a single vRGC fibre from the ventricular zone, they follow a relay of fibres that originate from oRGC.[78] Thus, vRGC give rise to a radial unit composed of clonally related directly and indirectly derived neurons, astrocytes, oligodendrocytes and ependymal cells, which are organized along the radial ventriculopial scaffold of the vRGC and corresponding oRGC.[61-70] The spatial identity of these clonal radial units is determined by the integration of morphogen gradients.[60] They constitute the smallest element in the ontogenetic concept of a radially organized brain. The nested grouping of these radial elements along the transverse axis reflects the ontogenetic hierarchy.

There is a direct link between the spatial configuration of ontogenetic radial units and the surface anatomy of the brain, since vRGC are also believed to direct brain morphogenesis, including cortical gyration and sulcation (Fig. 2B).[61-63,67] The tangential expansion of the brain surface area is driven by the number of symmetric self-renewing proliferations of vRGC or subventricular progenitor cells.[55,78,79] While the symmetric proliferation of vRGC in the ventricular zone leads to additional radial units, new fibres from the outer subventricular zone result in a fan-like expansion of the radial scaffold.[76,80,81] Gyrus formation correlates with the proliferation in the outer subventricular zone, and hence a high subventricular-to-ventricular zone and progenitor-to-ventricular-radial-glia cell ratio.[80,82-84] Cerebral fissures and sulci are characterized by an inverse relationship.[80,82-84]

The morpho- and histogenetic processes in the cerebellum resemble those in the cerebrum, albeit with relevant peculiarities.[85-88] The cerebellum develops bilaterally from the alar rhombencephalic neuroepithelium.[53,85,88] As a correlate to cerebral vRGC, neuroepithelial cells develop into radial glia cells (RGC) of the cerebellar ventricular zone with preserved contact to the fourth ventricle and the pial surface of the cerebellar anlage.[88-90] Bergmann glia cells arise from cerebellar ventricular zone RGC through the retraction of the ventricular process, relocation of the cell body towards the cerebellar cortex into the later Purkinje cell layer, and retention of the pial process that traverses the eventual molecular layer.[86,88,90-92] Bergmann glia cells constitute the cerebellar correlate to cerebral oRCG, both sharing common genetic expression profiles.[86] Like their cerebral counterparts, cerebellar RGC and Bergmann glia cells serve as stem cells, migration scaffolds and shape cerebellar lobulation and foliation.[87,88,93-97] They are the origin of cerebellar astrocytes and oligodendrocytes, Purkinje neurons, and interneurons (Golgi, stellate and basket cells).[85,88,98] This results in radial ontogenetic units of cerebellar neuro- and gliogenesis comparable to those in the cerebrum. A particularity is the development of the granule neurons, the most numerous neurons in the entire brain.[85,88,98,99] Towards the end of the embryonic period, a specific germinal region develops from the subventricular zone of the rhombic lip, adjacent to the lateral recess of the fourth ventricle.[85,88,98,99] Stem cells from this primary proliferative zone subsequently migrate tangentially to the surface of the cerebellum and form the external granular layer as a secondary

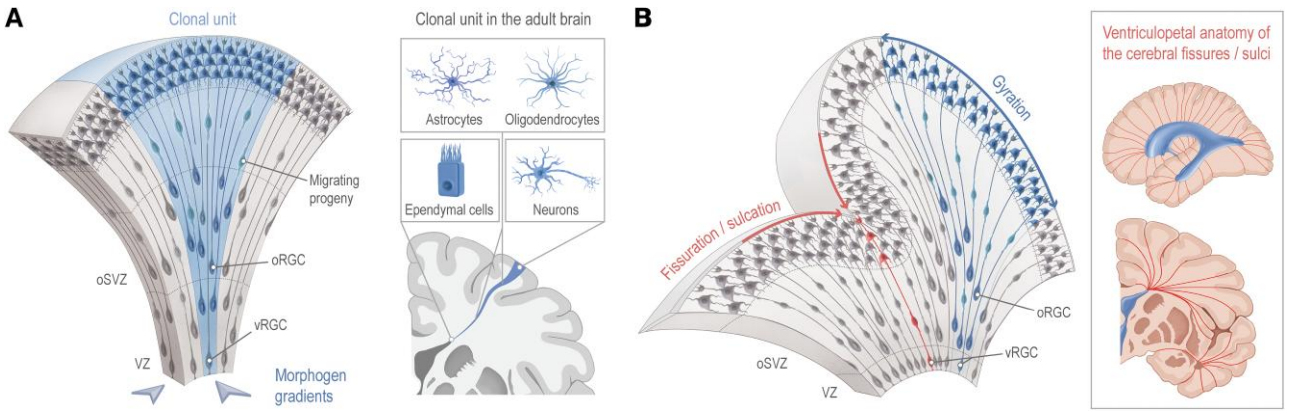

Figure 2 Radial glia cells in brain histo- and morphogenesis. (**A**) Concept of clonal radial units. Radial glia cells (RGC) serve as stem cells and radial migration scaffolds. RGC give rise to clonally related neurons, astrocytes, oligodendrocytes, and ependymal cells, which orient along their ventriculopial fibres. Ventricular radial glia cells (vRGC) are located in the ventricular zone (VZ). Outer radial glia cells (oRGC) are located in the outer subventricular zone (oSVZ) and constitute more committed progenitor cells resulting in a fanning of the radial glia scaffold. By the integration of morphogen gradients, periventricular proliferative centres define the spatial identity of the entire corresponding radial ontogenetic unit containing clonally related neurons, astrocytes, oligodendrocytes, and ependymal cells. (**B**) Role of RGC in brain morphogenesis. The anatomy of tangential pallial expansion depends on the ratio of self-renewing symmetric divisions of RGC between the VZ (i.e. vRGC) and oSVZ (i.e. oRGC). Dominant oRGC fibres from the oSVZ result in a fan-like pallial expansion and hence gyration. Fissures and sulci derive from a dominance of vRGC. Concept and design by Kevin Akeret, illustrations by Lucille Solomon.

proliferative zone.[85,88,98,99] In humans, the external granular layer appears at the end of the embryonic period and persists for several months to a few years after birth.[85,88,98,99] Here, cell proliferation continues, giving rise to the granule neuron precursors, which migrate ventriculopetally along the processes of Bergmann glia cells to their final location, the internal granular layer.[85,88,98,99]

The anatomical phenotypes and sequences seen in neuroepithelial tumours share remarkable similarities with the ontogenetic architecture and developmental program of the brain.[25-27]

Ontogenetic concept of neuroepithelial tumour anatomy

The initiation of various neuroepithelial tumours, their intratumoural hierarchy and tumour progression are associated with the aberrant reactivation of surprisingly normal ontogenetic programs.[100-105] Many transcription factors with well-characterized roles in lineage progression during neuroglial development have been identified as specific oncogenes or tumour suppressor genes, e.g. ASCL1 in adult-type diffuse gliomas or ATOH1 in medulloblastoma.[106,107] Controversy remains about the cells of origin of different neuroepithelial tumours. Collectively, there is experimental evidence that neuroepithelial tumours could arise from any cell along the entire spectrum of neuroglial differentiation, although with various resistance to neoplastic transformation: neural stem cells, such as RGC or their adult progeny subventricular astrocyte-like neural stem cells;[108-114] intermediate progenitor cells, such as oligodendrocyte precursor cells,[115-119] or granule neuron precursors in the cerebellum;[120,121] and mature cells, such as astrocytes or even neurons.[118,122-130] The degree of maturity of the cells correlates with their resistance to neoplastic transformation.[130] In addition, both intertumour and intratumour transcriptome heterogeneity in glioblastoma and medulloblastoma were shown to map along the neurodevelopmental spectrum from mature-like (e.g. neuron-like) to progenitor-like (e.g. neural progenitor-like) to mesenchymal-like cells.[105,119,131-133] A high degree of aberrant neuroepithelial differentiation is associated with good prognosis, while the poorest prognosis is associated with neuroepithelial tumours of a dominant mesenchymal-like phenotype.[119,134]

There are distinct similarities between the brain's radial ontogenetic organization and the anatomical patterns observed in neuroepithelial tumours of various types and subtypes (exemplified in Supplementary Fig. 1A–G).[26,27,135] On a population level, this is supported by the results of topographic probability mapping and unsupervised topological clustering, which identified an inherent radial anatomy and adherence to specific ventriculopial configurations.[25-27] The radial anatomy of neuroepithelial tumours located in the cerebral lobes may be only represented as a discreet tail of MRI signal alteration connecting a more superficial overt tumour mass to the ventricle (Supplementary Fig. 1A, left, example of a WHO grade 3 astrocytoma).[25,26] The MRI appearance of this radial tail resembles the transmantle sign sometimes observed with focal cortical dysplasia (Supplementary Fig. 1H).[136,137] Both trajectories may be determined by RGC, which could serve as scaffolds for migrating neoplastic cells, and along which migration is impaired in focal cortical dysplasia. In the cerebellum, the ontogenetic units of the ipsilateral hemisphere and half of the vermis converge in the lateral recess of the fourth ventricle (Supplementary Fig. 1G).[98] This is consistent with the original location of the cerebellar anlagen during neurodevelopment, which arise bilaterally from the rostral portions of the rhombencephalic alar plates and subsequently merge in the midline.[98] Despite the difficulty in assessing the anatomy of neuroepithelial tumours in the cerebellum given the close spatial relationships, there is a consistency in the association with one of the lateral recesses.[25-27]

The anatomical phenotypes in neuroepithelial tumours adhere to a temporal and prognostic sequence, which is associated to the degree of differentiation and displays inverse parallels to the anatomical specification during neurodevelopment (Fig. 3).[26,27] Spatiotemporal probability and multivariate survival analyses identified that gradual neuroepithelial de-differentiation and declining prognosis followed the sequence of (i) an expansion into higher order radial units; (ii) a subventricular spread; and (iii) the presence of mesenchymal patterns (expansion along white matter tracts, leptomeningeal or perivascular invasion, CSF spread).[26,27]

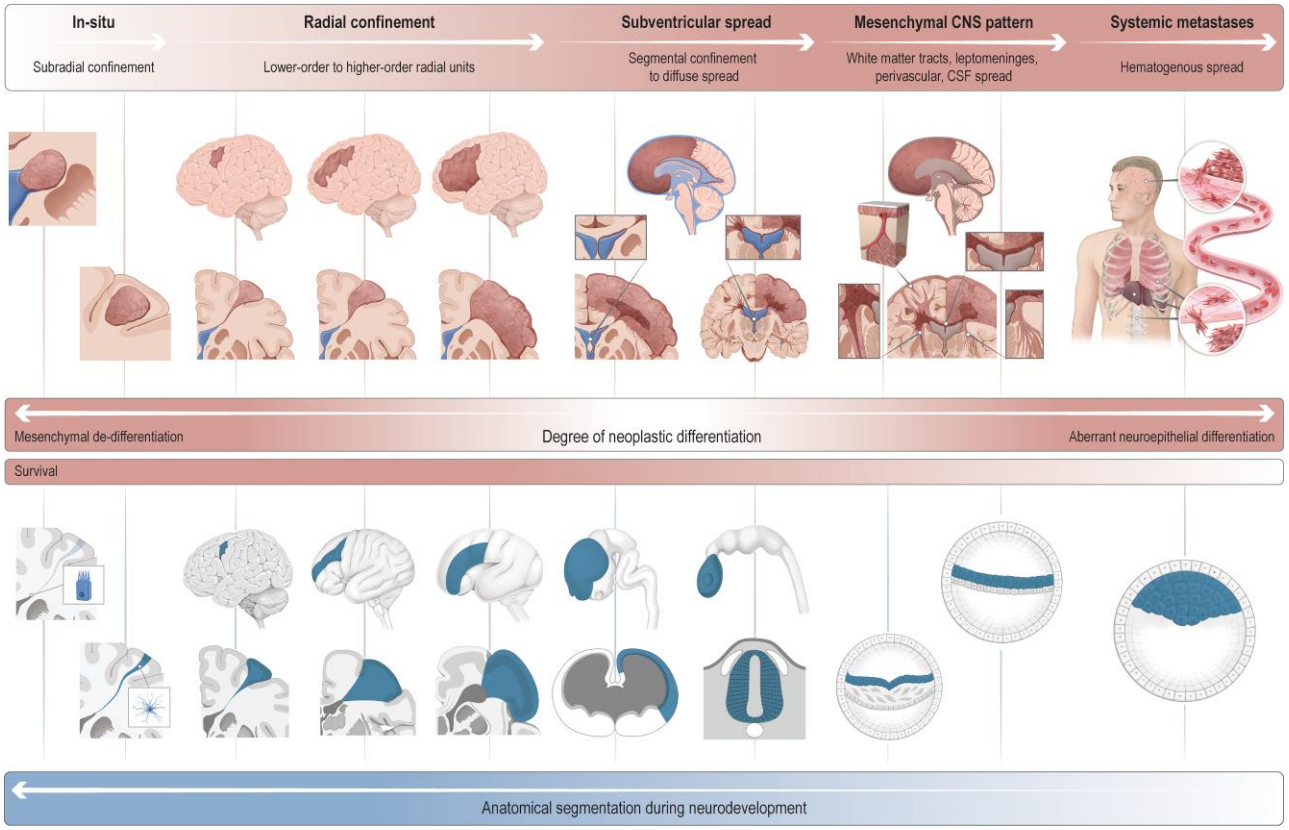

Figure 3 Temporal and prognostic sequence in neuroepithelial tumour anatomy. Red: The temporal and prognostic sequence identified behind the anatomical phenotypes in neuroepithelial tumours and its association to the degree of neoplastic differentiation. Blue: Illustration of the inverse parallels to the progressive arealization of the neural tube into tangentially nested radial units during neurodevelopment. Concept and design by Kevin Akeret, illustrations by Lucille Solomon.

Supplementary Fig. 2 exemplifies this anatomical sequence across different types and subtypes of neuroepithelial tumours. Neoplastic cells with a high degree of aberrant neuroepithelial differentiation may confine to subradial lineage-specific locations within affected radial units (*in situ*)[26,27]: neuronal differentiation may be associated with a specificity for cortical locations; ependymal differentiation might predispose to periventricular locations; neoplastic cells with aberrant astrocytic or oligodendrocytic differentiation may populate along the entire radial unit. Especially if they originate from mature cells,[118,122-130] neoplastic neuroepithelial cells may already arise at the respective anatomical sites. If they arise from periventricular progenitor or stem cells,[108-110] however, well-differentiated neoplastic cells may make use of the ontogenetic migration scaffolds to home to their designated sites. Reminiscent of their roles during ontogeny, RGC may in these cases serve as both, cell of origin, and migration scaffold for neuroepithelial tumours.[113,114,138,139] The site of overt tumour mass does therefore not necessarily correspond to the site of tumour origin, but they share the same ontogenetic unit. With progressive neuroepithelial de-differentiation, there is radial expansion of the tumour to the entire extent of the hosting ontogenetic unit, followed by gradual transverse expansion into radial units of higher hierarchical order.[25-27] This may manifest as an initially barely discernible tail from the superficially localized tumour to the ventricle, which becomes more prominent as encroachment on higher order ontogenetic units progresses.[25-27] More advanced neuroepithelial de-differentiation is reflected in a subventricular tumour spread, which corresponds to an extension to yet higher order ontogenetic units, including subcallosal extension to contralateral homologous sites.[25-27] De-differentiation to a mesenchymal phenotype is anatomically reflected in an expansion along white matter fibre tracts, invasion of the perivascular spaces and leptomeninges or CSF metastases.[26,140] Ultimately, de-differentiation might even enable systemic (non-CNS) metastases, which requires neoplastic intravasation, intravascular survival and peripheral extravasation.[141,142] The low degree of neuroepithelial differentiation with granule neuron precursors as the cell of origin of medulloblastomas may explain the high frequency of CSF dissemination and the occasional observation of systemic metastases.[26,27,143,144]

Collectively, this indicates that the anatomical phenotype of a specific neuroepithelial tumour may be framed by the spatial configuration of the hosting ontogenetic unit and further modelled by the tumours lineages and degree of neuroepithelial differentiation. The ontogenetic link between tumour differentiation, the anatomical tumour phenotype and prognosis provides potential for further anatomical refinement of the classification of brain tumours and for an anatomical staging system.

Anatomical classification and staging of neuroepithelial tumours

The identification of generalizable topological phenotypes in neuroepithelial tumours and their association with distinct molecular, histological and clinical features render anatomical tumour classes a promising extension of the current elements of

neuroepithelial tumour classification.[27] The WHO CNS5 is dominated by histological and molecular tumour profiling,[2] the quality of which depends on the representativeness of tissue samples.[14] Although serial biopsies reduce the risk of sampling bias,[145,146] intratumoural heterogeneity and the low relative number of stem-like tumour cells carries the inherent risk that bulk sequencing of tissue samples does not capture the cells that cause a tumour to progress or recur after therapy.[14] Modern neuroimaging provides detailed information on the anatomy of a neuroepithelial tumour at the time of diagnosis, which represents the tumour in its macroscopic entirety. Complementing the current classification of neuroepithelial tumours by an anatomical dimension has the potential to increase its robustness. However, large scale studies will be necessary to increase the granularity of anatomical tumour classes and to determine their impact on prognosis and response to therapy.

Staging systems, e.g. TNM staging in solid tumours or Ann Arbor staging in lymphoma, serve to estimate individual prognosis and to tailor patient-specific therapy and surveillance.[16,147] The anatomical extent of a tumour determines the appropriateness of surgical interventions, guides resection margins, or justifies the removal of an entire anatomical segment, a whole organ, or lymph drainage sites.[16,147] In addition, the indication for radiotherapy and/or systemic therapy and the specific field of irradiation are adapted to the tumour stage.[16,147] Tumour restaging during follow-up, e.g. rTNM, serves to readjust therapy and surveillance to the individual spatiotemporal tumour behaviour.[16,147] Ultimately, tumour staging also improves the comparability of clinical research results.[16] The principles of tumour staging may also be applicable to neuroepithelial tumours.

Classic tumour staging adheres to a general scheme (Fig. 4)[16]: 'Stage I' tumours represent a localized neoplasia, which is usually surgically removable; 'Stage II' characterizes early; and 'Stage III' late locally advanced tumours. The concrete stratification between Stages II and III depends on the tumour type. 'Stage IV' is generally reserved for metastasized cancer. Sometimes carcinoma *in situ*, i.e. neoplastic cells growing in their normal place, are referred to as 'Stage 0'. Thus, the basis of every staging system is an understanding of the natural sequence of anatomical tumour progression and its relationship to the degree of histological de-differentiation and prognosis.[16]

Based on the prognostically most critical steps within the presented anatomical sequence of neuroepithelial tumour progression, a staging system for adult-type diffuse gliomas has been proposed (Fig. 4).[26] Anatomical Stage I (AS1) groups *in situ* and radially confined tumour phenotypes. Anatomical Stage II (AS2) is defined by a transverse subventricular tumour spread (segmental confinement or diffuse). Anatomical Stage III (AS3) clusters tumours with mesenchymal CNS patterns (expansion along white matter tracts, leptomeningeal or perivascular invasion, CSF spread) or systemic metastases. Given the rarity of systemic metastases from adult-type diffuse gliomas and the poor prognosis associated with AS3 tumours, the distinction of a classic Stage IV was deemed of limited consequence. The validation of this staging system for adult-type diffuse gliomas in an independent cohort obtained from the same centre confirmed distinct survival differences for AS1-3 across tumour subtypes.[26]

To assess the generalizability of the proposed staging system to other neuroepithelial tumours and to evaluate the value of distinguishing between *in situ* tumours (classic Stage 0) and different hierarchies within radial units, larger multicentre cohorts are needed. Both the anatomical classification and the staging of neuroepithelial tumours harbour the potential to further stratify treatment decisions at diagnosis and during follow-up.[26]

Anatomical tailoring of neuroepithelial tumour therapy and surveillance

The diagnosis of a neuroepithelial tumour is generally made on the basis of MRI. MRI does not yet allow to predict the underlying histopathology and molecular characteristics with certainty but provides all necessary information for anatomical phenotyping.[14,25-27,148-150] The initial surgical intervention serves to specify the diagnosis by obtaining tissue, which defines subsequent individual therapy.[14,148-150] Whenever possible, the initial surgical intervention also serves as first treatment through maximum safe resection.[14,148-150] Both the surgical strategies for biopsy and microsurgical resection might benefit from stage-adaptation and anatomical tailoring.

If, due to the clinical condition of the patient or the anatomical localization of the tumour, microsurgical resection does not appear safe, diagnostic specification is sought via biopsy.[14,148-150] These are usually performed openly or stereotactically,[145,146] while the benefits of liquid biopsies, i.e. detection of cell-free tumour DNA in blood or CSF, are controversial.[151] Although often multiple samples are taken, these reflect only a small and potentially unrepresentative proportion of the tumour, resulting in the risk of sampling bias and misdirection of subsequent therapy.[152,153] Histopathological and molecular diagnostics are aimed at the tumour cell population with the highest degree of neuroepithelial de-differentiation and associated stem-like tumour cells. An ontogenetic conceptualization of the spatiotemporal behaviour of neuroepithelial tumours could provide valuable guidance in choosing the most appropriate biopsy strategy to capture this target cell population. In tumours with subventricular spread (AS2), the subventricular zone should be included in the sampling strategy whenever possible. In tumours with mesenchymal CNS patterns (AS3), separate biopsies of the different mesenchymal representations should be taken. If there is evidence of perivascular or leptomeningeal invasion, or the anatomical phenotype suggests CSF spread, attempting a liquid CSF biopsy prior to stereotactic or open biopsy may be appropriate. While still speculative, tailoring the biopsy strategy to the anatomical tumour stage and the brain's ontogenetic architecture could therefore maximize the prognostic and therapeutic significance of histopathological and molecular results.

If the clinical condition of the patient and the localization of the tumour so allow, initial surgery is performed with therapeutic intent and the goal to achieve maximum safe resection, defined by the tumour mass visible on MRI.[14,148-150] Additional intraoperative methods, such as ultrasound or 5-aminolevulinic acid guided surgery, contribute to the definition of the extent of resection.[154-156] Both the anatomical stage of a neuroepithelial tumour and the spatial configuration of its hosting radial unit could inform patient-specific surgical strategies.[26,27] For *in situ* and radially confined tumours (AS1), the entire corresponding radial unit should represent the surgical target volume. The rationale is that neuroepithelial tumours can be maintained by any stem-like tumour cell within the affected ontogenetic unit, even cells distant from the tumour mass.[103,157-160] In cases, where such a radical surgical approach is functionally not justifiable, the remnant of the radial unit should be integrated into the radiation target volume whenever possible.[26] Instead of a therapeutic surgical approach, patient with AS2 or AS3 tumours might benefit more from an anatomically tailored biopsy,

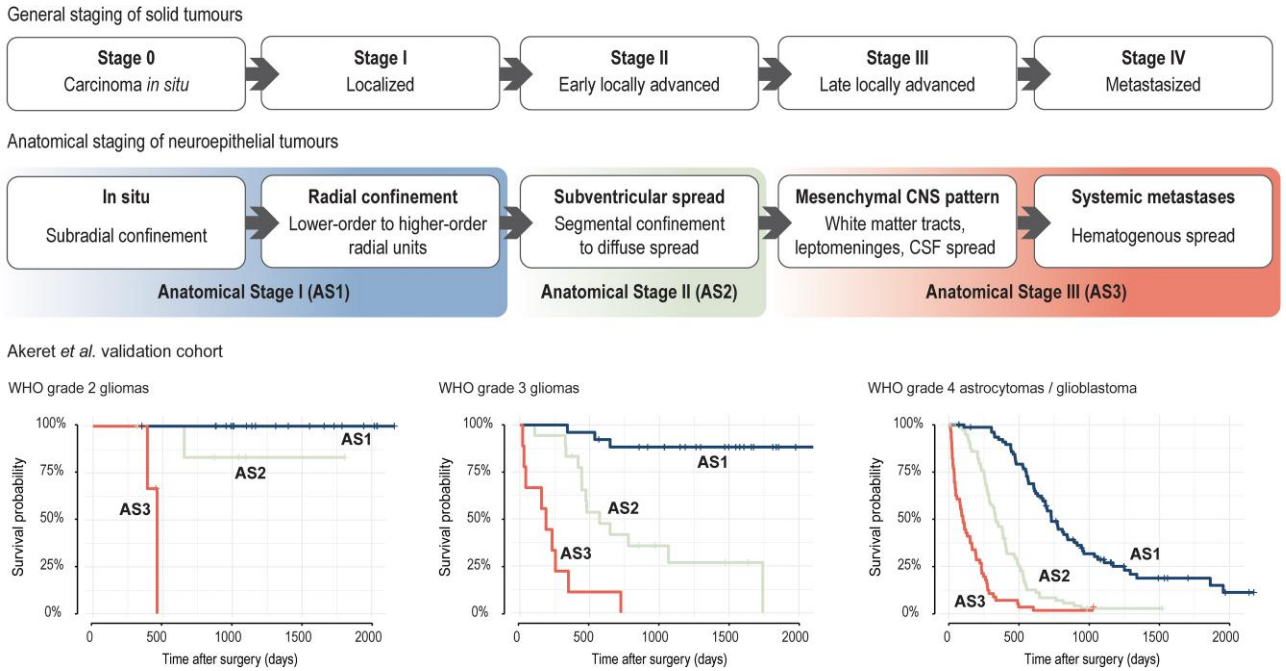

Figure 4 Anatomical staging of neuroepithelial tumours. *Top:* Scheme underlying the general staging of solid tumours. *Middle:* Prognostic sequence underlying the anatomical phenotypes in neuroepithelial tumours and the corresponding Anatomical Staging (AS) proposed for adult-type diffuse gliomas.[26] *Bottom:* The Kaplan-Meier curves reproduced from an external validation of the staging system[26] demonstrating the survival probability of AS 1–3 WHO grade 2 gliomas, WHO grade 3 gliomas, and WHO grade 4 astrocytomas/glioblastoma.

radiotherapy that covers the affected radial units, and systemic therapy adapted to the histological and molecular tumour profile.[14]

Post-surgical management of patients with neuroepithelial tumours is determined by tumour histopathology and molecular profile, presence of residual tumour and the clinical condition of the patients.[14,148-150] The initial anatomical tumour stage, the extent of resection relative to the hosting radial unit as well as the spatio-temporal behaviour during follow-up could gain additional significance for specific neuroepithelial tumour types and subtypes.

Adult-type diffuse gliomas

The anatomical stage of an adult-type diffuse glioma at diagnosis harbours a prognostic significance that is independent of tumour histology and molecular profile, tumour volume, patient age and Karnofsky Performance Status or choice of postoperative therapy.[26,27] Therefore, an advanced anatomical stage, e.g. higher order radial confinement or evidence of subventricular spread, in a WHO grade 2 astrocytoma or oligodendroglioma could argue for initial postoperative therapy and against watchful waiting, despite favourable conventional prognostic factors (i.e. age <40 years, no neurological deficits and no or little residual tumour).[14] In contrast, a far-advanced anatomical stage (AS3) could justify systemic therapy alone and limits the likelihood of benefit from local therapies.[14] Since neoplastic cells extend beyond imaging abnormalities in diffuse gliomas, the extent of resection compared to the preoperative image-based tumour mass is arguably an insufficient prognostic parameter.[161] A more significant prognostic factor could be whether the ontogenetic unit hosting the tumour was removed in its entirety through microsurgery (Supplementary Fig. 3).[25-27] Recurrence patterns in tumours with sub-segmental resection indicate an origin from non-resected parts of the respective ontogenetic units (Supplementary Fig. 3).[26] Currently, the recommended clinical target volume for radiotherapy of higher grade adult-type diffuse gliomas is composed of the surgical bed, residual tumour identified on MRI and a margin of 1–2 cm to account for microscopic tumour invasion.[14,162] *In situ* and radially confined adult-type diffuse gliomas (AS1) may benefit from having the entire affected ontogenetic unit covered by the clinical target volume of radiotherapy. In support of this, increased irradiation of the ipsilateral periventricular area with a mean radiation dose of 40 Gy or greater has been shown to be associated with longer progression-free and overall survival in glioblastoma patients after gross total resection.[163] In the case of subventricular tumour spread (AS2), the associated subventricular and parenchymal segments may be integrated into the planning whenever possible. In cases of CSF spread (AS3), craniospinal radiotherapy may be warranted. Currently radiological surveillance is oriented along the Response Assessment in Neuro-Oncology (RANO) criteria.[164,165] Tumour progression is defined as an increase in the size of contrast-enhancing lesions of at least 25% based on bidirectional length measurements, a significant increase in non-enhancing FLAIR/T_2 lesions, or the appearance of new lesions.[164,165] Regular anatomical restaging might facilitate the recognition of recurrence in the residual hosting radial unit or of an anatomical phenotype switch. The stochastic pathophysiology of progressive tumour de-differentiation may be better served by the identification of anatomical phenotype switches than by mere size monitoring, e.g. a new extension into a higher order radial unit, a new subventricular spread or the emergence of mesenchymal anatomical patterns.

Ependymal tumours and circumscribed astrocytic, glioneuronal and neuronal tumours

These tumours adhere to comparable cerebral and cerebellar anatomical phenotypes and appear to follow similar anatomical progression sequences as adult-type diffuse gliomas.[26,27] Microsurgical resection is the cornerstone of therapy and the extent of surgical resection is

the most important prognostic factor in all those tumours.[148,149,166,167] Both surgery and radiotherapy may benefit from stage-adaptation and anatomical tailoring. In contrast to the invariable progressive nature of diffuse gliomas, the majority of circumscribed astrocytic, glioneuronal, and neuronal tumours have an indolent course.[148] Some tumours, however, exhibit aggressive behaviour, for which WHO grading is an insufficient indicator.[148] Anatomical phenotyping at diagnosis and restaging during follow-up could aid in identifying aggressive tumours with unfavourable prognosis, adjust their therapy, and guide imaging surveillance.[148,149,166,167]

Medulloblastoma

In 1969, Chang *et al.*[144] proposed a surgical staging system for medulloblastomas based on the local extent of the tumour (T_1: <3 cm in diameter; T_2: >3 cm in diameter; T_3: invasion of the fourth ventricle; T_4: invasion of midbrain, third ventricle or upper cervical cord) and metastatic state (M_0: no evidence for metastases; M_1: microscopic tumour cells in the CSF; M_2: gross nodular seeding in the cerebral CSF space; M_3: gross nodular seeding in the spinal CSF space; M_4: extra-CNS metastases). Enhanced understanding of the spatiotemporal behaviour of medulloblastomas and cerebellar development might allow for an anatomical staging of medulloblastomas, anatomically tailored supratotal resection and individualization of radiotherapy through stage-specific dose and irradiation field adjustment.[26,27] How these concepts would differ from that for adult-type diffuse gliomas, given their differences in tumorigenesis, requires further research.

Conclusions

Analogous to numerous other neurological diseases, neuroepithelial tumours conceal specific anatomical patterns. The anatomical phenotypes and sequences seen in neuroepithelial tumours share remarkable similarities with the ontogenetic architecture and developmental program of the human brain. This macroscopic coherence is reinforced by cellular and molecular observations that the initiation of various neuroepithelial tumours, their intratumoural hierarchy and tumour progression are associated with the aberrant reactivation of surprisingly normal ontogenetic programs. Further research is needed to identify the precise mechanisms that dictate the anatomical behaviour of neuroepithelial tumours.

Generalizable topological phenotypes may allow to enhance the current classification of neuroepithelial tumours by a more in-depth anatomical dimension. In addition, an anatomical staging system has been proposed, based on the prognostically critical steps along the anatomical sequence of tumour progression. More data on specific neuroepithelial tumour types and subtypes is needed to increase the anatomical granularity in the anatomical classification and to determine the clinical impact of stage-adapted and anatomically tailored therapy and surveillance.

Supplementary material

Supplementary material is available at *Brain* online.

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