



# The Neuropathologist

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## Introduction

The brain is the most complex structure in the known universe, with about 300 billion cells and 100 trillion synapses (the connections between nerve cells). As might be expected for anything so complex, things can go wrong.

The development and maintenance of the brain depends on the genes encoded by the DNA in the nuclei of the cells. Humans have only got about 30,000 genes, a surprisingly small number.

To develop a tumour anywhere in the body, you need one of the billions of cells to lose the regulation of its cell division, down-regulate its apoptotic pathways (the programmed cell death that regulates the number of cells) and encourage in-growth of new blood vessels to feed and oxygenate the tumour by secreting proteins that stimulate vessel growth.

There are a complex web of molecular pathways that control these processes, and the combined effects of mutations of several genes results in brain tumours in approximately 6500 patients each year in England and Wales. 58% of these tumours are malignant.

DNA is constantly being damaged, and the cells are constantly attempting to repair the damage, or to kill off in a controlled way any cells that are beyond salvage. Occasionally a damaged gene will escape detection. A small minority of patients may have an inherited increased risk of brain tumours, and some patients develop tumours years after exposure to radiation.

## What is a neuropathologist

A neuropathologist is a medically qualified doctor who specialises in the diagnosis of disorders of the nervous system and muscle. After medical school we enter a training programme lasting at least five

years. Most of our work involves the diagnosis of brain tumours under the microscope. We also investigate the deaths of patients with complex neurological disorders.

Neuropathologists are core members of the multidisciplinary brain tumour team. We help provide the diagnosis, predict prognosis, and provide information used to guide therapy. Without knowing the type of tumour a patient has, it is impossible to decide what treatment is likely to be most effective.

We have a key role in integrating the morphological, molecular, and clinico-radiological findings. We can also give a provisional impression of the likely diagnosis during the operation in selected cases.

## How do we make a diagnosis

Even during the operation itself, while the patient is still under anaesthetic, we can examine small pieces of tissue under the microscopic. This can help guide the surgeon during the operation but is not as reliable as the final histological result after the tissue has been fixed in formalin to preserve the structure of the cells, embedded in wax, cut into thin sections, and stained.

In addition to the traditional stains that have been used in histology for many years, we can also stain for specific proteins that help classify tumour types, and can use molecular and genetic tests in relevant cases.

One of the great difficulties in brain tumour diagnosis is that it is essentially a subjective process. In rare complex tumours, such as those affecting the brain, the variation in opinions from highly qualified and respected individuals can be substantial. In one study 4 leading American neuropathologists independently classified over 200 gliomas. In only 52% of cases did all 4 agree

on the diagnosis.

With this caveat in mind we can now look at the process of how we diagnose a brain tumour.

First of all we need to exclude any other disease process, including infections, inflammatory disorders, infarcts, haemorrhages, and malformations, any of which can occasionally mimic a tumour clinically, radiologically, or under the microscope.

If we are confident that there is a tumour we then need to consider whether it is a primary intrinsic brain tumour, a tumour arising from cells within the central nervous system, such as a glioma, an extrinsic tumour pressing on the brain, such as meningioma, or a metastatic tumour, a tumour which has spread from a primary tumour elsewhere in the body, for example from a lung carcinoma or a melanoma.

We classify primary brain tumours according to the normal cell type that they resemble. For example the cells in astrocytic tumours are thought to resemble astrocytes, the cells that support the neurons in the normal brain. The cells in oligodendroglial tumours are thought to resemble oligodendrocytes, the cells that provide the insulation around the axons, the processes connecting nerve cells. We use the WHO classification system to classify brain tumours. The grade ranges from I (1, the most benign) to IV (4, the most malignant).

The whole concept of benign and malignant is difficult to apply in the brain. Brain tumours rarely spread to other organs, and the damage they cause is usually due to their effect on vital brain structures and by producing brain swelling. This means that tumours that appear benign under the microscope may have a poor outcome in the brain if they are in a location that makes surgery difficult.

Astrocytic tumours are the most common intrinsic brain tumours. They are divided into two main categories, the circumscribed tumours, such as pilocytic astrocytoma (WHO grade I), which typically affect children and has a relatively good prognosis, and the diffusely infiltrating astrocytic tumours (astrocytoma WHO grade II, anaplastic astrocytoma, WHO grade III, and glioblastoma

WHO grade IV). The circumscribed astrocytic tumours and the diffusely infiltrating astrocytic tumours are completely different types of tumour, with different genetic abnormalities and prognosis.

Unfortunately the most common intrinsic brain tumour is glioblastoma, which is an aggressive tumour. Lower grade diffuse astrocytomas (astrocytoma WHO grade II and anaplastic astrocytoma grade III) have a tendency to accumulate further genetic mutations over time that allow them to develop into glioblastoma.

The features we look for under the microscope to determine the grade of a diffuse astrocytic tumour are mitotic activity (cell division), necrosis, and proliferation of blood vessels.

### **What is the point of an accurate diagnosis?**

Knowing the precise type of a brain tumour is essential in order to predict the prognosis and to select treatments that are most likely to be effective (and to avoid toxic treatments if they are not likely to help). The different types of brain tumour vary enormously in their prognosis and response to different treatments.

### **The future of neuropathology**

Neuropathology will increasingly use molecular and genetic analysis to complement the morphological interpretation of brain tumour samples. We expect to be able to help the selection of treatments based on the biology of the individual patient's tumour.

### **Conclusion**

The subjective impression of the morphology (appearance under the microscope) of a brain tumour is currently the best guide to prognosis, but with increasing understanding of the biology of brain tumours, we expect in the future to be able to integrate the morphology, protein expression patterns and genetic changes to support individualised therapy.