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Review

Applications of positron emission tomography in neuro-oncology: A clinical approach

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ABSTRACT

The field of neuro-oncology is concerned with some of the most challenging and difficult to treat conditions in medicine. Despite modern therapies patients diagnosed with primary brain tumours often have a poor prognosis. Imaging can play an important role in evaluating the disease status of such patients. In addition to the structural information derived from MRI and CT scans, positron emission tomography (PET) provides important quantitative metabolic assessment of brain tumours. This review describes the use of PET with radiolabelled glucose and amino acid analogues to aid in the diagnosis of tumours, differentiate between recurrent tumour and radiation necrosis and guide biopsy or treatment. [^{18}F]Fluorodeoxyglucose (FDG) is the tracer that has been used most widely because it has a 2 h half life and can be transported to imaging centres remote from the cyclotron and radiochemistry facilities which synthesise the tracers. The high uptake of FDG in normal grey matter however limits its use in some low grade tumours which may not be visualised. [^{11}C] methionine (MET) is an amino acid tracer with low accumulation in normal brain which can detect low grade gliomas, but its short 20 min half life has limited its use to imaging sites with their own cyclotron. The emergence of new fluorinated amino acid tracers like [^{18}F]Fluoroethyl-L-tyrosine (FET) will likely increase the availability and utility of PET for patients with primary brain tumours. PET can, further, characterise brain tumours by investigating other metabolic processes such as DNA synthesis or thymidine kinase activity, phospholipid membrane biosynthesis, hypoxia, receptor binding and oxygen metabolism and blood flow, which will be important in the future assessment of targeted therapy.

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Introduction

Primary brain tumours

Primary brain tumours can originate from a wide array of cell types. Most commonly, brain cancers arise from glial cells or the meninges, however other cells can also form tumours including neurons, neuroglial precursor cells, hypophyseal cells, pinealocytes, choroid plexus and lymphocytes (Fig. 1). With an incidence of 6–8 per 100,000 people, gliomas account for approximately 45% of all primary brain tumours. Adults tend to develop high-grade gliomas whereas low-grade tumours are more frequent in children. Gliomas can be categorised into different histological subtypes, from oligodendrogliomas and astrocytomas to ependymal tumours and tumours of the choroid plexus. Severity and aggressiveness of tumours is denoted by their grade. The World Health Organisation (WHO) has established grading criteria, based on cellular alterations related to cancer aggressiveness.[1,2] Fifty per cent of all gliomas are highly malignant glioblastomas (WHO grade IV).[3] Prognosis for patients with glioma is poor, in part due to their location, despite multimodal treatment strategies. The median survival for patients varies according to tumour grade and age at diagnosis.

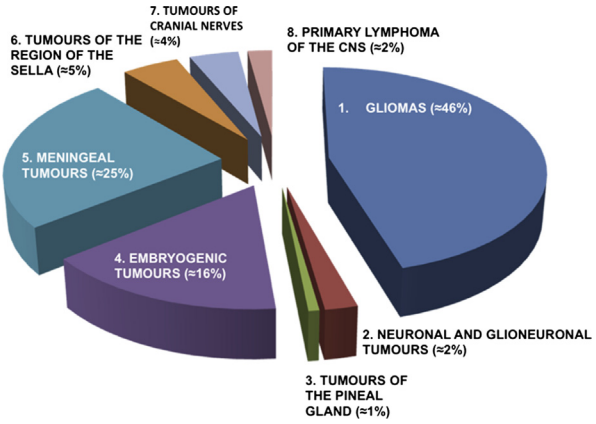

Fig. 1 – Overview of primary brain tumours according to incidence. Each main category of primary brain tumours can be further subdivided into histological subtypes. Gliomas can be pilocytic astrocytomas, astrocytomas, glioblastomas, oligodendrogliomas, oligoastrocytomas, ependymomas, choroid plexus papillomas and gliomatosis cerebri. In the neuronal and glioneuronal category the different types are: dysembryoplastic neuroepithelial tumours, dysplastic gangliocytomas, gangliomas and central neurocytomas. The pineal gland can form pineocytomas, pienoblastomas and germinomas while medulloblastomas and primitive neuroectodermal tumours are of embryogenic origin. Meningeal tumours can be meningiomas and hemangiopericytomas whereas craniopharyingiomas and adenomas of the hypophysis are tumours of the region of the sella. Finally the cranial nerves normally form neurinomas. Percentages included in the figure represent a percentage of total primary brain tumours.[3]

Tumour genetics

In order to tackle the limitations of current therapy, it is essential to comprehend the complex cellular and genetic changes that lead to glial cell tumour formation. As with most tumours, such changes result in deficits in cell cycle regulation, abnormal apoptosis and cellular differentiation. Adaptations occurring in more advanced stages of the disease include formation of new blood vessels, by angiogenesis, migration of tumour cells and invasion to the surrounding brain tissues. Damage to the genetic material of a cell is the known trigger of tumorigenesis. In the particular case of gliomas, genetic alterations concentrate around a specific set of genes including the tumour suppressor gene TP53, genes that participate in the regulation of the cell cycle, such as p16 and p14ARF, and oncogenes such as cdk4, cyclin D1 and D3, EGFR (epidermal growth factor receptor), VEGF (vascular endothelial growth factor) and PDGFR (platelet-derived growth factor receptor).[4] In anaplastic oligodendrogliomas clinically relevant mutations have been discovered, which make these tumours characteristically sensitive to procarbazine, lomustine and vincristine chemotherapy, thus prolonging patient survival.[5–7]

Biological context of PET

Proliferating gliomas are characterised by increased glycolysis, protein and DNA synthesis. The enhanced metabolism of cancer cells compared with healthy cells, is caused by increased activity of membrane transporters acting on nucleosides, glucose or amino acids and increased expression of phosphorylating enzymes e.g. hexokinase and thymidine kinase.[8] Positron emission tomography (PET) imaging can provide important quantitative data regarding the metabolic state of primary brain tumours such as gliomas.[3,9–11] Depending on the radiotracer molecule applied, it allows measurement of a wide range of cellular activities involved in cell proliferation and metabolism. For example, it permits quantification of expression of the enzymes or transporters important for energy production, DNA and protein turnover as well as assessment of membrane biosynthesis or oxygen metabolism (Fig. 2). Information on the quantitative localisation of expression of genes coding for enzymes or receptors obtained from PET relies on the accumulation of radiolabelled enzyme substrates or receptor ligands, respectively.[12,13]

[^{18}F]Fluorodeoxyglucose-PET

[^{18}F]Fluorodeoxyglucose-PET (FDG-PET) images the increase in glucose uptake that occurs in cancer cells. Anaerobic glycolysis has been shown to occur in advanced cancers, even in abundance of oxygen, a process named the Warburg effect.[14] In tumour cells, hypoxia triggers a process called glycolytic switch where the main source of ATP becomes glycolysis.[15]

The greater demand for glycolytic substrates causes increased transport of glucose into cells and, consequently, of the glucose analogue, ^{18}F-FDG.