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Review

Next generation neuro-oncology

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Abstract Neuro-oncology has evolved as a growing, but still small, highly specialised and multidisciplinary field at the interface of several diagnostic and therapeutic disciplines. The major challenge in the field of primary tumours is to translate the almost unique progress in deciphering the highly complex molecular genetic nature of many primary brain tumours, notably glioblastoma, into advances that allow for clinical benefit for affected patients. Furthermore, metastases to the central nervous system are an increasingly prevalent complication in many systemic cancers. Their diagnosis and management require major expertise, notably with consideration of several new systemic therapy options, such as targeted therapy and immuno-oncology approaches. These new treatments contribute to challenges within the third major domain of neuro-oncology, the diagnosis, treatment and prevention of nervous system toxicity of old and new anti-cancer treatments. All these considerations strongly argue for the development of specialised centres of excellence to improve care for patients with brain tumour across Europe.

1. Introduction

Neuro-oncology today is a relatively small but expanding and increasingly complex area of oncology involving several diagnostic specialities, e.g. neuropathology, neuroradiology and nuclear medicine, as well as therapeutic disciplines, including neurosurgery, neurology, radiation oncology, general oncology and paediatric neuro-oncology. The updated World Health Organisation (WHO) classification defines an extensive spectrum of different primary brain tumours with age-specific incidences, highly variable outcomes and very different best practice strategies of management [1]. With approximately 20 new cases of primary brain tumours per 100,000 each year [2], all primary brain tumours are essentially rare

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diseases. Specifically, brain tumours are the leading cause of death from cancer in children, but progress is being made, and many childhood brain tumours will be cured, albeit often at the price of long-term sequelae which represent yet another challenge for the future. Still, neuro-oncology faces more challenges than the differential diagnosis and optimised care of patients with primary brain tumours. Metastatic brain tumours affecting the central nervous system are probably much more common than primary brain tumours, and their incidence, and certainly their impact on quality of life of surviving patients with cancer, is increasing, potentially also because the brain may be a sanctuary for tumour cell dormancy and late recurrence in certain disease constellations, e.g. breast cancer or renal cell cancer where metachronous metastasis in the brain is not uncommon. Conversely, in lung cancer, there is such a high risk of brain metastasis early on in the course of disease, even at diagnosis, that the central nervous system compartment needs to be considered for a comprehensive diagnosis and treatment strategy. Finally, not only classical cancer treatments such as radiotherapy or old pharmacological treatments such as platinum drugs or vinca alkaloids may have dose-limiting toxicity in the nervous system but e.g. immuno-oncology is also associated with rare but potentially severe neurotoxicity. As more and more cancers are transformed into chronic diseases in the future, understanding, treating and preventing neurotoxicity will assume a major role in cancer care. The present perspective on how to best address these challenges is necessarily and by intention a European view that may or may not be applicable in its entirety to other parts of the world.

2. Diagnosis

Primary brain tumours are diagnosed mainly by histology, but the updated WHO classification of 2016 has integrated some molecular markers into the diagnostic algorithm, e.g. isocitrate dehydrogenase 1 and 2 mutations and deletion of chromosomal arms 1p and 19q for diffuse gliomas of adulthood, the histone H3 K27M mutation to define the new entity of diffuse midline glioma or the RELA fusion to define a subtype of ependymoma [1]. Meanwhile, specialised neuro-oncology centres increasingly make use of more extensive molecular testing, using e.g. their own gene panels for next generation sequencing or commercial platforms. In contrast to gene panel sequencing, transcriptomic or proteomic analyses have not assumed clinical relevance to date. Potentially, the most important new approach involves the assessment of methylation profiling which has been used, e.g. for the study of gliomas [3], ependymomas [4] and meningiomas [5], and has been developed into a self-learning algorithm that may in the future offer high-level, but still remote, molecular differential diagnosis [6]. Whether such high-throughput diagnostic tools will remain a complementary strategy to aid where histomorphology reaches its limits or take over the diagnostic process altogether remains to be seen. Importantly, at present, the debate of molecular genetics versus histomorphology should not be equalled to a machine-versus-man competition because histomorphological data can be subjected to new texture analysis approaches too and even methylation profiles will still need to be interpreted in the context of clinical parameters and histomorphology. In the area of metastatic brain tumours, progress in diagnosis is largely being made within the respective subspecialities of oncology.

Beyond molecular neuropathology, neuroimaging, mostly magnetic resonance imaging (MRI), remains the gold standard for diagnosis and monitoring during treatment and follow-up. The specific challenges associated with central nervous system imaging have been recognised and led to the formation of the Response Assessment in Neuro-Oncology initiative [7] which continues to provide guidance for standardisation of MRI techniques, for image interpretation and for the introduction of novel techniques such as positron emission tomography in various fields of neuro-oncology [8,9]. It has now become a common practice to include detailed guidance on how to perform and interpret neuroimaging data within clinical trials, and the criteria to define response or progression are continuously reevaluated within the cooperative clinical trial groups.

3. Therapy

A major proportion of intracranial tumours can be cured by surgery alone. For intrinsic brain parenchymal tumours, the clinical benefit of obtaining a gross total resection has to be weighed against the risk of permanent neurological deficits for each tumour and each patient. Radiotherapy can be used uniformly to improve local control and to delay progression, but is rarely curative, with notable exceptions such as germinoma. With improved survival for many brain tumour entities, timing and dosing of radiotherapy have become an area of debate, given that more and more patients are at risk of experiencing long-term sequelae from radiotherapy. Alkylating agent chemotherapy still plays an important role in the treatment of the common diffuse gliomas of adulthood, notably tumours with O^6-methylguanine DNA methyltransferase promoter methylation, but more targeted therapies are being introduced into the standard treatment of some primary brain tumours, e.g. BRAF inhibitors for BRAF-mutant gliomas, mammalian target of rapamycin (mTOR) inhibitors for subependymal giant cell astrocytomas associated with tuberous sclerosis and sonic hedgehog pathway inhibitors in medulloblastoma. Current treatment of central nervous system metastases is less well standardised, and clinical practice varies widely across centres. Controversial issues concern the role of surgical