24.10.4 Intracranial tumours 6048 Jeremy Rees

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section 24 Neurological disorders 6048 24.10.4 Intracranial tumours Jeremy Rees ESSENTIALS Intracranial tumours represent about 2% of all cancers. There are no known risk factors apart from prior irradiation to the skull and brain and a few rare neurogenetic syndromes (e.g. neurofibromatosis, von Hippel–Lindau syndrome, Li–Fraumeni syndrome). They may be intrinsic or extrinsic, which determines potential resectability. Neuroepithelial tumours (predominantly gliomas) account for
50–60% of all primary tumours. Molecular analysis has now been added to the histological grade and subtype to provide an integrated diagnosis which provides more accurate information for treatment and prognosis. As systemic anti-cancer treatments evolve and pro- duce long-term control of visceral and bone disease, brain metas- tases are becoming increasingly common and are best treated with either stereotactic radiosurgery or neurosurgery to avoid the cogni- tive decline associated with whole brain radiotherapy. Clinical features Early neurological symptoms of intracranial tumours are nonspecific. Typical manifestations include (1) progressive focal neurological deficit—typically subacute; present in over 50% of patients at time of diagnosis; (2) seizures—may be focal or secondarily generalized; the presenting symptom in 25–30% of patients and particularly frequent in patients with low-grade gliomas; (3) raised intracranial pressure— the classic picture of headache, vomiting, visual obscurations, and papilloedema is easily recognized, but most patients present before this develops; and (4) altered mental state—cognitive and personality changes. More incidental tumours are now being discovered as a re- sult of the increased availability of cranial imaging. Diagnosis, treatment, and prognosis Diagnosis—this is made by a combination of CT/MRI scanning and pathological examination of either a biopsy or resection specimen. Genetic information relating to 1p19q, IDH, and MGMT methylation status is becoming increasingly important for guiding treatment and prognosis. Treatment—the conventional methods are (1) surgery—may be curative for extrinsic tumours, but rarely so for intrinsic tumours; (2) radiotherapy—as primary or adjuvant treatment; (3) chemo- therapy—concomitant treatment with temozolomide and radical radiotherapy followed by adjuvant temozolomide has improved survival in glioblastoma; certain tumours may respond particularly well to the combination of radiotherapy and chemotherapy, for ex- ample, oligodendrogliomas with

chromosome 1p/19q deletion. (4) biological agents—antiangiogenic agents are being used in re- lapsed malignant glioma but they do not improve overall survival. There is increasing interest in immunotherapy either as a tumour vaccine or as immune checkpoint inhibitors but, to date, the evi- dence for a clear survival benefit is not available. Prognosis—this is determined by age at presentation (young > old), performance status (high > low), histological grade (low > high), and genetic mutations (1p19q, IDH mutation). As a general rule, survival with glioblastoma is 1–2 years, anaplastic astrocytomas 2–5 years, anaplastic oligodendrogliomas and low-grade gliomas 5–15 years. Benign tumours, such as meningiomas and pituitary adenomas, have over 90% 10-year survival if diagnosed before irreversible neuro- logical damage has occurred. Introduction Intracranial tumours comprise primary tumours that originate from the brain, cranial nerves, pituitary gland, or meninges, and secondary tumours (metastases) that arise from organs outside the nervous system. These tumours present to many different specialists and their management is difficult because of their anatomical loca- tion, variable clinical manifestations, and innate resistance to con- ventional cytotoxic treatments. Aetiology There are no known risk factors apart from prior irradiation to the skull and brain and a few rare neurogenetic syndromes, such as neurofibromatosis (optic nerve glioma, meningioma, vestibular schwannoma) (Fig. 24.10.4.1), von Hippel–Lindau syndrome (haemangioblastoma), and Li–Fraumeni syndrome (glioma). The role of mobile (cellular) phones has not been proven. Epidemiology Intracranial tumours represent the eighth most common neoplasm in adults (c.2% of all cancers) and the second most common neoplasm in children. After stroke, intracranial tumours are the leading cause of death from neurological disease in the United Kingdom and are responsible for 7% of years of life lost from cancer before the age of 70. The crude annual incidence for primary intracranial tumours is 7.4 per 100 000 (males 9.1/100 000, females 6.1/100 000) and for secondary tumours 14.3 per 100 000 population. Just under 10 000 new cases of brain cancer present every year in the United Kingdom. The incidence has increased by approximately 25% over the last 40 years, particularly in older patients. Different tumour types present at different ages. Supratentorial gliomas, the most frequent primary brain tumour, are rare under the age of 30 years, but become increasingly prevalent thereafter. The most frequent tu- mours of middle life (third and fourth decades) are astrocytomas, meningiomas, pituitary adenomas, and vestibular schwannomas, whereas glioblastoma and metastases are more frequent in the fifth and six decades of life. In contrast, children tend to have infratentorial tumours: 70% of childhood primary intracranial tu- mours originate in the posterior fossa, whereas in adults the figure is only 25%. There is a strong female preponderance of meningiomas and schwannomas, whereas gliomas are more common in men. Pathogenesis Gliomas are thought to arise from neoplastic transformation of glial cells. Recently, there has been increasing incidence in the role of stem cells in the origins of brain tumours—stem cells are defined as having the ability to renew themselves in perpetuity and to differentiate into

 mature cells. The existence of a cancer stem cell has now been proven for glioblastoma and medulloblastoma, and may explain why these tumours recur after treatment. Certain genetic lesions are associated with brain tumours. Chromosomal deletions—particularly chromo- some 10, which contains multiple tumour-suppressor genes—are found in astrocytic tumours, occurring in up to 70% of glioblast- omas. Mutations of a tumour-suppressor gene, TP53, located on chromosome 17p, have also been reported in approximately 40% of astrocytic tumours. A novel mutation of isocitrate dehydrogenase- 1 (IDH1) has been found in a large percentage of gliomas of many different grades and histologies. This is a favourable prognostic marker in low-grade and high-grade gliomas and is being used to help with diagnosis of

various histologically ambiguous tumours. As a metabolic enzyme in the Krebs cycle, it presents a unique in- sight into the understanding of gliomas and raises the potential for new mechanisms of treatment. In general, the accumulation of pre- dictable genetic alterations is associated with increasing malignant progression. Primary glioblastomas arise in older patients and are associated with wild-type IDH, amplification and overexpression of the epidermal growth factor receptor (EGFR) gene, whereas sec- ondary glioblastomas occur in younger people and are associated with IDH mutations and early loss of TP53. Recent data have shown that IDH wild-type astrocytomas (irrespective of grade) are molecu- larly similar to glioblastoma, with implications for management. Clinical features With increasing sophistication of neuroimaging, tumours are being detected at an earlier stage than before. Patients typically present with one or more of four clinical syndromes: • progressive neurological deficit • seizures (e) (b) (a) (c) (d) Fig. 24.10.4.1 Contrast-enhanced CT and MR scans of a patient with neurofibromatosis type 2 and multiple intracranial tumours. (a) CT of the brain with contrast enhancement showing a large right parietal convexity meningioma surrounded by vasogenic oedema exerting considerable mass effect. There is also a smaller falx meningioma in the right occipital region. (b) Coronal T1-weighted MRI of the brain with gadolinium enhancement showing multiple meningiomas in the right temporoparietal region, right parafalcine region, and both cavernous sinuses. (c) Contrast-enhanced CT scan of the orbits showing bilateral optic nerve sheath meningiomas with intracranial extension into the right cavernous sinus, causing partial right nerve III and nerve VI palsies. (d) Axial T1-weighted MRI of the brain with gadolinium enhancement, showing bilateral vestibular nerve schwannomas and a large cisterna magna tumour. (e) Sagittal T1-weighted MRI of the spinal cord with gadolinium enhancement showing three discrete meningiomas encroaching on the spinal column at midcervical, midthoracic, and upper lumbar levels.

section 24 Neurological disorders 6050 • raised intracranial pressure • altered mental states The particular combination of clinical features varies depending on the location, histology, and rate of growth of the tumour, for example, patients with low-grade gliomas present typically with a seizure disorder that may remain static for many years, whereas pa- tients with malignant gliomas typically develop a rapidly progressive neurological deficit and raised intracranial pressure. More patients are being diagnosed with incidental tumours as a result of the in- creased availability of CT and MRI scans. Progressive neurological deficit Focal neurological symptoms due to brain tumour are typically sub- acute and progressive, with over 50% of patients having focal signs by the time of diagnosis. However, they may also present as a ‘stroke’ mimic and even as a transient ischaemic attack. Cortical tumours produce contralateral weakness, sensory loss, dysphasia, dyspraxia, and visual field loss depending on their location. Bilateral tumours (e.g. butterfly gliomas), may present with confusion, unsteadiness, and urinary incontinence. Posterior fossa tumours cause ataxia and cranial nerve palsies. Vestibular schwannomas cause progressive unilateral deafness fol- lowed by ipsilateral facial sensory loss and ataxia due to brainstem compression. Pituitary tumours may cause a bitemporal hemianopia if there is chiasmal compression or endocrine disturbances due to ei- ther hypopituitarism or hypersecretion of specific hormones. Seizure disorder Brain tumours account for about 5% of epilepsy cases although they are overrepresented in cases of intractable epilepsy. Seizures are the presenting symptom in 25–30% of patients with brain tu- mours and are present at some stage of the illness in 40–60% overall. Approximately one-half of the patients have focal seizures (usually frontal or temporal lobe) and the other half have secondarily gen- eralized seizures. Low-grade gliomas are associated with seizures in over 90% of cases and these frequently remain the only complaint for many years.

About 50% of low-grade glioma patients have intract- able seizures. Conversely, patients with malignant gliomas have a lower frequency of seizures, presumably because of their more rapid growth and destructive characteristics. In these patients, seizures are associated with a better prognosis. Seizures are also common initial manifestations of meningiomas (40–60%) and metastases (15–20%). Supratentorial tumours and those located in the cortex are particu- larly likely to cause seizures, particularly in the frontal and temporal lobes. Todd's paresis, which may persist, is an uncommon but charac- teristic feature of tumour-associated epilepsy. About 10% of patients presenting anew in status epilepticus have an underlying tumour. Raised intracranial pressure Intracranial tumours increase intracranial pressure by a direct mass effect, provoking cerebral oedema, or producing obstructive hydro- cephalus. The most common symptom of raised intracranial pressure is headache, which is the initial presenting symptom in 25% of pa- tients and in 50% of patients at hospital presentation; papilloedema is found in up to 50% of patients with headache due to tumours. The classic picture of headache, vomiting, and visual obscurations (tran- sient fogging of vision usually on rapid changes in posture) due to raised intracranial pressure is well known and easily recognized, but most patients present before this develops. Less than 0.1% of patients presenting with isolated headache have a brain tumour. Most brain tumour headaches are intermittent and nonspecific and may be indistinguishable from tension headaches. Supratentorial tumours typically produce frontal headaches, whereas posterior fossa tumours usually result in occipital headache or neck pain. Certain features of a headache are suggestive but not pathogno- monic of raised intracranial pressure. These include headaches that wake the patient at night or are worse on waking and improve over the course of the day. Patients with rapidly expanding tumours or who have cystic com- ponents or intratumoral haemorrhage may present with increasing drowsiness, vomiting, pupillary dilatation, and visual loss due to downward uncal and transtentorial herniation. Mental state changes These are an uncommon presentation of brain tumours, usually found in slow growing orbitofrontal tumours (e.g. meningiomas). Personality changes may initially be quite subtle and may show themselves as an inability to cope at work, apathy, and loss of social inhibition. In these cases, it is essential to obtain a collateral history from relatives or colleagues at work. Later, as the tumours progress, personality change is quite common and may lead to breakdown of family relationships. Pathology Neuroepithelial tumours (predominantly gliomas) account for approximately 50 to 60% of all primary brain tumours. The other common types are meningiomas (20%), pituitary adenomas (15%), vestibular schwannomas (5%), and primary central nervous system (CNS) lymphomas (5%) (Fig. 24.10.4.2). Brain metastases are much Fig. 24.10.4.2 Axial T1-weighted MRI with gadolinium enhancement showing a homogeneously enhancing left anterior temporal lesion which was biopsied and shown to be a primary CNS lymphoma.

 more common than primary brain tumours and are increasing in frequency due to improvements in systemic anti-cancer treat- ments. The most common sites of origin of brain and meningeal metastases are lung (50%), breast (15%), melanoma (10%), and unknown (15%). The classification systems that have been traditionally used to describe degrees of anaplastic change are the basis of histo- logical diagnosis and grading correlate with prognosis. The most widely accepted classifications of gliomas is the World Health Organization (WHO) system (Table 24.10.4.1). These systems have been retrospectively applied to large series of patients and have been shown to provide reproducible and prognostically useful information. They have recently been updated to include some new diagnostic entities. The gliomas are a family of neoplasms that are thought to arise from astrocytes, oligodendrocytes, and ependymal cells. Astrocytomas are the

most common type of glioma and are infiltrating neoplasms composed of fibrillary astrocytes. WHO grade II gliomas have the propensity to undergo anaplastic change to a more malignant le- sion. Thus, a fibrillary astrocytoma (Fig. 24.10.4.3) progresses to an anaplastic astrocytoma (Fig. 24.10.4.4) and then to the most malig- nant form, glioblastoma (Fig. 24.10.4.5). The oligodendroglioma is WHO grades of select CNS tumours Diffuse astrocytic and oligodendroglial tumours Diffuse astrocytoma, IDH-mutant Anaplastic astrocytoma, IDH-mutant Glioblastoma, IDH-wildtype Glioblastoma, IDH-mutant Diffuse midline glioma, H3K27M-mutant Oligodendroglioma, IDH-mutant and 1p/19q-codeleted Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted II III IV IV IV II III Other astrocytic tumours Pilocytic astrocytoma Subependymal giant cell astrocytoma Pleomorphic xanthoastrocytoma Anaplastic pleomorphic xanthoastrocytoma I I II III Ependymal tumours Subependymoma Myxopapillary ependymoma Ependymoma Ependymoma, RELA fusion–positive Anaplastic ependymoma I I II II or III III Other gliomas Angiocentric glioma Chordoid glioma of third ventricle I II Choroid plexus tumours Choroid plexus papilloma Atypical choroid plexus papilloma Choroid plexus carcinoma I II III Neuronal and mixed neuronal-glial tumours Dysembryoplastic neuroepithelial tumour Gangliocytoma Ganglioglioma Anaplastic ganglioglioma Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) I I I III I Desmoplastic infantile astrocytoma and ganglioglioma Papillary glioneuronal tumour Rosette-forming glioneuronal tumour Central neurocytoma Extraventricular neurocytoma Cerebellar liponeurocytoma I I I II II II Tumours of the pineal region Pineocytoma Pineal parenchymal tumour of intermediate differentiation Pineoblastoma Papillary tumour of the pineal region I II or III IV II or III Embryonal tumours Medulloblastoma (all subtypes) Embryonal tumour with multilayered rosettes, C19MC-altered Medulloepithelioma CNS embryonal tumour, NOS Atypical teratoid/rhabdoid tumour CNS embryonal tumour with rhabdoid features IV IV IV IV IV IV Tumours of the cranial and paraspinal nerves Schwannoma Neurofibroma Perineurioma Malignant peripheral nerve sheath tumour (MPNST) I I I II, III or IV Meningiomas Meningioma Atypical meningioma Anaplastic (malignant) meningioma I II III Mesenchymal, nonmeningothelial tumours Solitary fibrous tumour / haemangiopericytoma Haemangioblastoma I, II or III I Tumours of the sellar region Craniopharyngioma Granular cell tumour Pituicytoma Spindle cell oncocytoma I I I I Fig. 24.10.4.3 Low-grade glioma. Coronal and axial T2-weighted MRI of the brain showing a diffuse lesion in the right frontal lobe, which returns high signal. It is seen extending from the cortex into the deep white matter and infiltrating across the corpus callosum. There is mass effect causing compression of the frontal horn of the lateral ventricle. The tumour does not enhance with gadolinium. This patient presented with generalized seizures and has remained well after 8 years of follow-up. Biopsy revealed a fibrillary astrocytoma (WHO grade II). Table 24.10.4.1 Pathological classification of astrocytomas

 characterized by the presence of uniform round nuclei with small nu- cleoli. This also has the propensity to undergo anaplastic change but, unlike anaplastic astrocytomas, oligodendrogliomas are frequently chemosensitive (see next) and patients may live for many years. Diagnosis The diagnosis of a brain tumour is made by a combination of CT/MR scanning and pathological examination of either a biopsy or a resection specimen. Advanced MRI techniques include MR spectroscopy, perfusion and permeability sequences, and meta- bolic imaging (positron emission tomography (PET)). These may permit a noninvasive method of differentiating between low-grade and high-grade gliomas and between tumour recurrence and ra- diation necrosis. However, histology is still the gold standard, now complemented with molecular information, for example, IDH mu- tation, chromosomal deletions of 1p19q (found in

oligodendroglial tumours and associated with a better prognosis), and methyl guanyl methyl transferase (MGMT) promoter methylation (which predicts response to temozolomide chemotherapy in glioblastoma). Treatment The three conventional methods of treatment for brain tumours are surgery, radiotherapy, and chemotherapy. Targeted biological agents, gene therapy and immunotherapy have still not been widely taken up because of the lack of proven benefit over and above standard therapies. In line with other areas of oncology, there is increasing use of combination therapies, particularly concomitant chemoradiation to improve survival. Surgery Advances in tumour neurosurgery include the use of computerized frameless neuronavigation techniques, intraoperative imaging with ultrasound and MRI and intraoperative cortical mapping during awake craniotomy. Preoperatively, important anatomicofunc tional information can be derived from functional MRI (fMRI) which allows localization of eloquent motor, speech, and memory cortex as well as diffusion tractography, which can delineate the anatomical relationship between tumour and important white matter tracts. Fluorescence guided resection using the porphyrin 5-aminolaevulinic acid (5-ALA) has been shown to increase com- plete resection of glioblastoma, resulting in a prolonged period free of progression (but not overall survival) and delayed neurological deterioration. Fig. 24.10.4.5 Glioblastoma. Axial T2-weighted (a) and coronal T1-weighted with gadolinium enhancement (b) MRI showing large vascular (dark serpiginous structures) and heterogeneous intrinsic architecture with extensive peritumoral vasogenic oedema (shown as white matter ‘fingers’ on (a)) and the irregular rim enhancement and central necrosis (on b). Fig. 24.10.4.4 Anaplastic astrocytoma. Coronal T1-weighted MRI of the brain with gadolinium enhancement showing a large heterogeneous enhancing tumour arising from the right frontal lobe exerting considerable mass effect in a patient presenting with a 2-month history of complex partial seizures, headaches, and papilloedema.

24.10.4 Intracranial tumours 6053 Surgery is indicated as a first-line treatment for gliomas, meningiomas, and nonsecreting pituitary adenomas. As a gen- eral rule, extra-axial tumours (e.g. meningiomas), may be cured by surgery alone as well as a small proportion of low-grade gliomas (e.g. pilocytic astrocytomas). For most types of glioma, however, surgical removal is not curative. Although surgery is of undoubted benefit in relieving the symptoms and signs of raised intracranial pressure or an evolving focal deficit, there are no prospective randomized data to support its use for prognostic purposes alone, particularly in pa- tients with malignant gliomas. However, the conventional surgical wisdom is that maximal safe resection (cytoreduction) improves pro- gression-free survival in patients with high-grade gliomas and that complete macroscopic or subtotal resections (leaving a residual tu- mour volume of <10 ml) improves overall survival in patients with low-grade gliomas when compared with tumours that are biopsied and treated with radiotherapy alone. Overall, about 50% of patients with medically refractory seizures derive considerable seizure reduc- tion from surgery. Complete resection of solitary or oligo (2–3) brain metastases is becoming increasing accepted as the gold standard of treatment for patients with good performance status and controlled systemic dis- ease. In contrast, the only role of surgery in primary CNS lymphoma (PCNSL) is for tissue diagnosis—therefore, any patient with a sus- pected PCNSL (on radiological grounds) should have a biopsy only, ideally without previous treatment with corticosteroids. Radiotherapy Radiotherapy is the only treatment that has been proved to extend survival in patients with primary malignant brain tumours and may be given with radical or palliative intent. Patients with malignant gliomas are treated with radical radiotherapy to a dose of 60Gy in 30 fractions over 6 weeks. Temozolomide, an oral alkylating agent, has been shown to improve survival in patients with newly diag- nosed glioblastoma when given together with radiotherapy (con- comitantly) and then for six monthly cycles after chemoradiation (adjuvantly).

This is known as the Stupp protocol and was the first significant advance in the treatment of glioblastoma for over 30 years. Although the improvement in median survival compared with radiotherapy alone is modest (12.1 vs. 14.6 months), the pro- portion of patients alive at 2 years increased from 10% to 26%, and at 5 years from 2% to 10%. These data were published in 2005 and rekindled enthusiasm for chemotherapy trials in tumours previ- ously regarded as chemoresistant. Whether this treatment can im- prove the survival of patients with anaplastic astrocytomas is being tested in clinical trials. The elderly patient with glioblastoma poses particular challenges, as they have poorer cerebral reserve, less tol- erance of brain radiotherapy and more comorbidities—as a result, they are usually excluded from clinical trials and so the best treat- ment has not been determined. Early radiotherapy for adult low-grade gliomas prolongs progression-free survival by about 2 years but has no effect on overall survival, compared with radiotherapy given at the time of tumour pro- gression. Radiotherapy is effective in controlling seizures in patients with refractory brain tumour-associated epilepsy. Meningiomas are also partially radioresponsive and should be treated with radio- therapy where there is atypical or malignant histology or where there is recurrent tumour that is not surgically accessible. Long-term (>10 years) control rates for meningiomas are around 90%. Advances in technology have allowed greater accuracy of radio- therapy delivery and, in particular, the use of stereotactic frames that permit the focusing of radiation to a small tumour with minimal dosage to the surrounding normal tissue. This can be done either in a single high dose (stereotactic radiosurgery or γ knife) or in smaller fractions (stereotactic radiotherapy) and is predominantly indicated for lesions less than 3 cm in diameter which are well circumscribed, extra-axial, and more than 5 mm away from organs at risk e.g. optic chiasm, or for brain metastases. Intensity-modulated radiotherapy (IMRT) allows more precise ‘dose painting’ whereby different re- gions of the tumour are treated with varying doses of radiotherapy, and minimises the amount of normal brain tissue that is irradiated. ‘Cyberknife’ radiotherapy has incorporated a robotic mounting device with real-time image guidance to improve accuracy of de- livery and to ‘target’ the tumour during normal respiration. None of these advanced techniques have been compared against each other, and nor have they have been shown to be superior to stereotactic fractionated radiotherapy. Recently, two large randomized studies have shown similar survival benefits and functional independence between patients with 1 to 3 brain metastases treated with stereo- tactic radiosurgery (SRS) versus SRS plus whole-brain radiotherapy (WBRT). As a result, WBRT is no longer used routinely in patients with solitary or oligometastases with good performance status. Chemotherapy There has been increased awareness of the chemosensitivity of certain tumours, particularly anaplastic oligodendrogliomas and primary CNS lymphomas in adults, and diencephalic gliomas in children. Approximately two-thirds of anaplastic oligodendrogliomas re- spond dramatically to a combination of treatment with procarbazine, lomustine, and vincristine; updated (12-year follow-up) data from a phase III trial have demonstrated a clear survival benefit for adjuvant vincristine over and above radiotherapy in patients with anaplastic oligodendrogliomas, but only those with the presence of combined deletions of chromosomes 1p and 19q. Similarly, a recently pub- lished phase III randomized trial has demonstrated a 5.5-year im- provement in survival with the addition of procarbazine, lomustine, and vincristine chemotherapy in patients with ‘high-risk’ low-grade glioma over radiotherapy alone. However, the trial was completed over 10 years ago and, in that time novel molecular markers (see next) and newer drugs (e.g. temozolomide) have been developed, so it is difficult to know how to best incorporate these results into clinical practice. Adjuvant nitrosurea chemotherapy is used in patients with malig- nant gliomas although it offers only a marginal survival advantage. Carmustine wafers allow local delivery of carmustine (a nitrosourea) into the resection cavity of a malignant glioma, hence avoiding the systemic toxicity of these compounds,

but are associated with in- creased risk of infection, oedema and wound breakdown so are used in highly selected cases only. The role of temozolomide chemo- therapy in patients with low-grade gliomas over radiotherapy alone is currently being evaluated in a clinical trial and interim data do not suggest any survival advantage. There is no chemotherapy that is effective for the treatment of meningiomas.

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