NCRI Advancing Cancer Research Together

Position Statement on Early Diagnosis of Brain Tumours

Position Statement on Early Diagnosis of Brain Tumours –

Symptom Combinations, Referral Pathways and Protocols

Summary/Abstract

Problems with case recognition and referral pathways for patients with suspected brain tumour may result in late diagnosis. Only 1% of brain tumour patients end up being referred through the NHS Cancer Plan – two-week wait pathway – and most are seen eventually through emergency or urgent neurology with focal deficits, having previously presented to primary care. NICE guidance focuses on progressive focal neurological deficits, which paradoxically feature in those cases that are recognised and referred early, rather than the more difficult-to-identify cases with headache and cognitive or personality change.

Epidemiological studies highlight that delays in diagnosis are most common with headache and cognitive presentations. Symptom combinations (e.g. headache plus cognitive disturbance, personality change or visual symptoms) improve prediction of brain tumours. In addition, poor performance on a simple cognitive test of semantic verbal fluency in cases with suspicious headache is a red flag, even if the patient is not aware of cognitive slowing. NICE guidance emphasises the importance of looking for papilloedema when assessing suspicious headache, without acknowledging the low confidence of frontline clinicians in recognising optic nerve head swelling. Community optometry services are increasingly well equipped to offer an opinion on possible early disc swelling, or field defects, and often have access to specialist advice, through their local eye emergency department, and the mechanism to initiate or facilitate referral of papilloedema urgently, as per College of Optometry referral recommendations.

'Advice and Guidance' from neurology specialists, may help with the decision on whether further investigation should be expedited, but advice will depend on the quality of history and examination findings obtained from the referrer, and it is likely to give precedence to focal and seizure presentations at the expense of headache or cognitive presentations. Direct-access MRI is far from widely available to general practitioners, and scan waiting times and reporting times are increasing, such that it is unlikely to shorten the time to diagnosis appreciably in the next decade, as recommended by NICE NG12 pathways guidance in 2015 (updated 2021). Targeted or expedited use of CT scanning may be a better option to improve time to diagnosis, especially in cases of suspicious headache or semi-acute progressive cognitive or personality change.

An expert working group met to discuss the existing evidence around early diagnosis, referral processes and NICE guidelines, and to consider what future research is required to expedite diagnosis in suspected brain tumour patients.

Background

Primary and secondary intracranial tumours affect more than 20,000 people each year in the UK (Pobereskin 2000), and the incidence is increasing (Philips et al. 2018). The UK has one of the worst survival rates for primary brain tumours compared to other EU nations – ranked 21 out of 27 countries (Allemani et al. 2018). Brain tumours have the worst 'years of life lost' of all cancers, with 20 years lost life on average (Burnet et al. 2005). It has been suggested that the poor survival rates in the UK are likely a reflection of later diagnosis.

The National Cancer Patient Experience Survey 2018 shows that 22% of people diagnosed with a brain tumour visited their GP three times or more prior to being referred; 32% two times. This suggests missed opportunities for earlier diagnosis. Clinical decline while waiting for tests occurred in 33% of brain tumour patients (Lyratzopoulos et al. 2013). Of patients with brain tumours, 20% are unhappy with the care received from their GP (Fraulob and Davies 2019). Patients with brain tumours are the third most likely of all cancer patients to change practice before the diagnosis is made, and the second most likely after the diagnosis has been made, which may be an indication of a lack of satisfaction (Grooss et al. 2016).

The UK has fewer doctors, shorter consultation times (Irving et al. 2017) and fewer imaging resources (Papanicolas et al. 2018) than many European countries. This lack of resources is reflected in long waiting times to be seen in both primary and secondary care for clinical opinion and for brain scanning. In January 2022, 29% of patients were waiting more than six weeks for an MRI scan, and there was a growth of 44% in requests over the preceding year (NHS England and NHS Improvement 2022). Brain tumours are the least likely of 35 primary cancer sites to be fast-tracked for referral (Zhou et al. 2018). In addition, Covid-19 disruption of services has affected urgent cancer diagnostic pathways and prompted a move away from face-to-face consultations to telephone clinics, with all the associated limitations. However, once diagnosed, the treatment options in the UK are the same as in most European healthcare systems.

Symptom Recognition

Different brain tumours will present in different ways depending on site, size and speed of growth, although broadly they will have similar symptom

presentations. There is general agreement that the five most common 'first symptoms' or 'symptoms at hospital presentation for intracerebral brain tumours' are headache, seizures, cognitive deficits, motor deficits and non-specific symptoms, such as dizziness or unsteadiness. (Grant 2004, IJzerman-Korevaar et al. 2018, Rasmussen et al. 2017, Ozawa et al. 2019, Alther et al. 2020). A past history of cancer increases the likelihood of CNS symptoms being related to a brain tumour (metastasis).

a) **Headache**, or pain, will be a feature of intracerebral tumours in less than 50% of cases at hospital presentation (Grant 2004). There are pain endings in the blood vessels, ependyma and meninges, and thus an intracerebral mass can cause 'tumour headache', along with other neurological symptoms. Intracerebral tumours above the tentorium cerebelli that displace the vessels, meninges or ependyma will generally refer pain frontally on the same side or to the vertex, while tumours in the pons, medulla or cerebellum will refer to the occiput or neck.

   Most intracerebral tumours are malignant (e.g. glioblastoma or metastasis) and will grow quickly or block cerebrospinal fluid pathways, resulting in hydrocephalus, which can exhaust the normal compensatory mechanisms that mitigate against raised intracranial pressure (Monro–Kellie hypothesis) and lead to raised intracranial pressure headache that develops over some weeks. Both raised intracranial pressure headaches and tumour headaches are almost always accompanied by impaired concentration and other cognitive symptoms, with or without focal neurological deficits or seizures. It is rare (in just 1%–3% of cases) that an intracerebral tumour will cause headache as a sole symptom (Grant 2004, Rasmussen et al. 2017, Ceronie et al. 2021). Patients with intracerebral tumours may or may not have optic disc swelling (papilloedema). Estimates indicate that between 12% and 15% of intracerebral brain tumours have papilloedema recognised on admission. Low-grade glial tumours generally infiltrate slowly and present with seizures. Headaches are unusual unless they reach a considerable size or block CSF pathways.

   Tumours of the meninges and cranial nerves are generally slow-growing masses, which can be accommodated by compensatory mechanisms with reductions in intracranial CSF or blood volume, and as a result, they do not generally cause raised intracranial pressure headaches, unless the CSF pathways are blocked. Tumours close to cranial nerves or around the pituitary fossa often produce frontal headache or orbital pain. The pain often has neurogenic features (e.g. sharp stabbing, burning and boring) and is generally continuous and sometimes accompanied by cranial nerve deficits or pituitary hormone insufficiency or excess. In tumours involving the posterior fossa meninges, vessels or lower cranial nerves (VII–XII), pain is referred to the mastoid, occiput or neck.

b) **Seizures** may be a presenting feature when tumours involve the cerebral cortex, and they generally reflect excess neuronal activity rather than neuronal destruction. Seizures are therefore more common with lower-grade intracerebral tumours (e.g. low-grade glioma more than glioblastoma) or extrinsic tumours (e.g. meninges or pituitary region) abutting the cortex. As the tumours are slow-growing or infiltrative, seizures often present as the sole symptom, although up to half may have other subtle cognitive changes, visual field defects or other focal neurological symptoms. Although it is more common in lower-grade lesions, any grade of tumour can present with seizures. Low-grade glioma patients often present with seizures only, whereas those associated with more aggressive tumours are more likely to have seizures plus other accompanying neurological deficits (e.g. unilateral weakness, numbness, dysphasia, field defect), cognitive deficits or headache.

c) Focal neurological deficits, such as unilateral weakness, numbness, dysphasia, visual field defects, incoordination/unsteadiness, are rarely first symptoms, but taken together as worrying 'focal' symptoms, they account for 20%–30% of first symptoms and are frequently seen at the time of hospital presentation. The time to GP or hospital presentation is generally short when patients have these red-flag symptoms.

d) **Cognitive problems** are common, especially at the time of hospital presentation, but initially are subtle and vague (e.g. problems with attention, concentration or memory). Cognitive changes may be one of the very first symptoms mentioned in retrospect, when patients are informed of their diagnosis, but are often subtle, not alarming and sometimes unrecognised by the patient (Walter et al. 2019). They are often attributed to non-threatening causes initially, such as poor sleep or anxiety, but later other symptoms accumulate, such as headache, seizure or focal neurological deficits. Brain tumour patients commonly score poorly on simple cognitive screening tests at the time of diagnosis (Kerrigan et al. 2014, Hoffermann et al. 2017).

e) Non-specific neurological symptoms in combinations (e.g. dizziness, unsteadiness and blurring of vision) or "**plus" systemic symptoms of suspicion of cancer** (e.g. cough, breathlessness, fatigue and appetite problems) (NICE NG12) were more common in studies that included secondary brain tumours than in retrospective studies on presenting symptoms in cases of proven primary brain tumour (Ozawa et al. 2019).

Speed of Diagnosis

In a recent study examining time to brain tumour diagnosis, those presenting with 'fits, faints or falls' had a median time to diagnosis of only 10 days, while

those with focal neurological symptoms (unilateral weakness, numbness, dysphasia) had a median time to diagnosis of 21 days (Ozawa et al. 2018). This contrasted with patients presenting with headache or memory problems, who waited a median of two months for diagnosis. GPs felt that there were avoidable delays in one-third of all cases (Ozawa et al. 2018). Avoidable delay was more common where the first symptom was headache, behavioural or cognitive change or non-specific symptoms. Such patients were between six and eight times more likely to visit their GP three or more times before being referred, compared to those presenting with fits, faints or falls. To improve speed of diagnosis, strategies should focus on these difficult-to-diagnose cases that present to general practice multiple times.

Likelihood of Tumour with Different Presentations

a) Headache

Headache is a very common symptom in the general population. Most headaches have no structural or serious underlying cause and are termed 'primary headache'. Headaches that are due to an underlying cause, such as tumour, infection or bleeding, are called 'secondary headache'. Development of a new headache alone in someone without prior headache has a low positive predictive value (PPV) for brain tumour (0.1%), and although certain features in headache history may suggest a secondary headache, they are also common in primary headache and have never been evaluated prospectively. Red flags for secondary headache include the SNOOP4 factors:

- **Systemic** – past medical history (PMH) of cancer/HIV/fever/jaw claudication
- **Neurological** – additional focal or global symptoms
- **Onset** – sudden
- **Onset** – age >65 new headache
- **Progressive**, worse with Valsalva, postural
- **Papilloedema**
- **Pregnancy**
- **Phenotype** of rare headache, induced by exercise, cough, sex-induced.

NICE headache guidelines (CG150) assume that clinicians can easily distinguish migraine from secondary headaches, and advise that patients with migraine should follow a medication protocol and not be referred for brain

scanning. In practice, headaches are rarely a classical symptom, and there is often overlap between features of primary and secondary headaches.

- Headaches that are new and progressive should raise suspicion of an intracranial cause, especially if they are occurring during the night or early morning and are worse on coughing, sneezing or bending over.

- Headache plus papilloedema has a high specificity for an intracranial cause. Papilloedema is optic disc swelling due to high intracranial pressure. Conditions causing papilloedema include intracerebral tumours, cerebral haemorrhage, head trauma, meningitis, hydrocephalus, cerebral venous sinus thrombosis and idiopathic intracranial hypertension. The presence of papilloedema in someone with headache should elicit urgent/emergency referral for scanning. However, GPs and emergency hospital clinicians frequently do not check optic fundi in neurological presentations and are not confident about correctly identifying papilloedema. One study on A&E showed that optic fundi were examined in only 12.6% of patients presenting to A&E with a seizure (Dixon et al. 2015).

- Headache plus additional cognitive or behavioural symptoms, focal neurological deficits or seizures should raise immediate suspicion, as cerebral tumours and other secondary causes usually disturb brain function in addition to causing a mass. Symptom combinations that include headache ('headache plus') should be red flags (e.g. headache plus cognitive symptoms increased PPV to 5.9%) (Ozawa et al. 2019).

b) 'Fits, faints and falls' (seizures)

New onset epileptic seizures in people over the age of 18 are uncommon and alarming, especially tonic-clonic seizures, and lead to urgent hospital presentation. Approximately 10% of patients referred with first seizure after 18 years of age will be found to have a brain tumour. Seizures are the first presenting symptom in about 20%–25% of cases with intracerebral tumour. Other important cerebral causes of seizure are stroke, dementia and infection, and systemic causes include electrolyte disturbance, hypoglycaemia, syncope and drugs or medication. Suspected major epileptic seizure or convulsion is often easily identified; patients are often taken directly to emergency services. Minor epileptic seizures (focal seizures) may be less easily recognised.

A combination of seizures and other neurological symptoms or signs will increase the likelihood of a structural intracranial cause.

c) Focal neurology

Focal symptoms are generally alarming to the patient and also stimulate a directed clinical examination by the clinician to look for neurological signs (e.g. hemiparesis, hemisensory loss, dysphasia, ataxia or visual field defect). Studies

of TIA and stroke services find 3%–5% of cases have intracerebral tumour (Morgenstern and Frankowski 1999). Strategies to expedite potential high-risk cases with seizures or focal symptoms, because they have 'alarm' symptoms, paradoxically may have less impact on overall delayed diagnosis. NICE guidelines (NG12) focus on alarm symptoms or signs that usually lead to earlier presentation anyway (progressive neurological weakness, seizures, headache with papilloedema).

d) Cognitive function

Problems with concentration or cognition have between a 0.2% and 0.7% PPV for tumour, and confusion has a PPV of 1.4%. Like headache, most reasons for problems with concentration are unrelated to a structural brain disorder and are more commonly related to anxiety, low mood and medication.

A symptom combination of cognitive symptoms plus weakness increases the PPV to 9.6%, and cognitive symptoms plus headache increases PPV to 7.2% (Ozawa et al. 2019).

Poor performance of cognitive screening tests increases the likelihood of an underlying cerebral cause. Asking the patients to perform a semantic verbal fluency test (SVFT) – e.g. 'Name as many animals as you can in a minute' – has been used as a quick cognitive screening test in many neurological conditions, including dementia, multiple sclerosis and brain tumour. A recent study requiring an SVFT to be performed by the GP, at the time of referral for outpatient CT scan, for 381 patients with headache suspicious of cancer demonstrated that if the SVFT score was <17, it was associated with tumour in 5.3%, compared with 0.5% of patients with a headache suspicious of cancer but an SVFT score of ≥17 (Grant 2021). A low SVFT score in patients with headache suspicious of cancer may be considered a red flag. Not only did about 5% have a cancer on CT, but a further 15% had other likely cerebral causes for a low SVFT score (e.g. dementia, small vessel disease or previous encephalitis).

e) Non-specific neurological symptoms

Dizziness, unsteadiness, blurring vision and tinnitus are common and, in isolation, are unlikely to raise suspicion of brain cancer, as all individually have a PPV of between 0.1% and 0.3% (Ozawa et al. 2019). However, their presence in combination with other symptoms, such as headache, increases the likelihood of a structural central nervous system cause, especially if the tinnitus is pulse-synchronous tinnitus, or the visual change is obscuration of vision on standing. Both are commonly present with raised intracranial pressure, either with a brain mass or without (e.g. idiopathic intracranial hypertension). Headache plus obscuration of vision or pulse-synchronous tinnitus would mandate a specialist opinion of the optic fundi from optometry or ophthalmology and also brain scanning.

Past medical history of cancer and the presence of unexplained neurological symptoms should lead to consideration of a brain scan for brain metastasis.

Brain Tumour Referral Pathways

a) Emergency pathway (e.g. A&E)

UK cancer registry statistics show that emergency presentations of cancer have poor outcomes and tend to be associated with more extensive disease (National Cancer Intelligence Network 2015). Emergency pathways account for 17.6% of all cancer presentations. By comparison, 50.1% of brain tumour diagnoses are through emergency pathways. Approximately one-third of these cases had already visited their GP at some point before the emergency presentation. Many patients may have self-referred to emergency pathways (e.g. with seizures or stroke-like presentations) or have been referred to emergency departments by GPs or optometry.

b) Urgent GP direct-referral imaging pathway

Only a small proportion of GP practices have direct access to MRI. In areas where secondary care services can offer GPs brain imaging within two weeks via this urgent suspected cancer pathway, only 3.3% of brain tumours are detected by this referral route. Of those patients not subsequently found to have brain tumours who are referred to hospital for a specialist appointment, 24% are referred to neurology; 22% to general medicine or care of the elderly; about 8% each to A&E, ophthalmology and neurosurgery; and about 4% each to stroke services and paediatrics, with the rest being miscellaneous or unknown (Ozawa et al. 2018). Median pathway interval from first symptom to neurology/neurosurgery consultation was 43.5 days (interquartile range: 10–83 days).

c) Urgent suspected cancer pathway

NICE guideline NG99 recommends MRI referral or secondary care referral within two weeks for patients with progressive subacute neurological deficit. However, only 0.9% of all brain tumours come through the urgent suspected cancer pathway, compared with 6.6% of all cancers.

Only a small proportion of GP practices have direct access to MRI. In areas where secondary care services can offer GPs brain imaging within two weeks via this urgent suspected cancer pathway, only 3.3% of brain tumours are detected by this referral route. This compares with a detection rate via this pathway for all cancers of 53.5%.

Where GPs could not directly access MRI, a referral to specialties for assessment within two weeks is recommended. Local referral pathways differ (e.g. neurology, neurosurgery or oncology). However, audits of neurosurgical centres accepting urgent suspected cancer referrals directly conclude that they are not the most appropriate specialists, due to the high rate of normal scans or other diseases found where neurology would be more appropriate (Hamdan and Mitchell 2013). Referral through oncology may be appropriate for those with a past history of cancer, but where there is no past history of cancer, the positivity rate of scans is low.

d) Urgent neurology pathway

There are no good data on the value of urgent neurology pathways outside the two-week-wait referral. Telephone or secure email Advice and Guidance services are becoming more widespread, and e-referrals are usually vetted and triaged by consultant-led teams. These services may triage specific neurological symptoms (e.g. first seizure or suspected TIA/stroke) to appropriate clinics, or they may organise scans while awaiting a neurological appointment. When scans show a suspected tumour, they are subsequently referred for discussion at neuro-oncology multidisciplinary meetings.

Brain tumour patients presenting with focal symptoms or epilepsy are diagnosed quickly, outside the two-week cancer referral pathway.

Patients with new onset of neurological symptoms and neurological signs are usually seen within a few weeks. However, in the absence of neurological signs, patients are often given routine appointments.

In general, patients with headache are only triaged to urgent appointment or scan if the headache is a suspected subarachnoid haemorrhage, infection or giant cell arteritis, or if there is accompanying papilloedema.

e) Urgent optometry/ophthalmology pathway

Approximately 20%–33% of brain tumour patients have ophthalmic symptoms or signs prior to diagnosis. Patients may attribute new headaches to uncorrected refractive error (i.e. needing new glasses), and some brain tumours produce ocular symptoms that often prompt them to visit their optometrist prior to visiting their GP. Optometrists and ophthalmologists diagnose at least 5%–10% of brain tumour patients before or shortly after GP presentation. If the optometrist considers there is papilloedema or other concerning findings, they have a referral path to ophthalmology or may advise the patient to attend an emergency department.

Position Paper on Earlier Diagnosis of Brain Tumour Patients

Aim

A multidisciplinary specialty early-diagnosis group coordinated through the NCRI Brain Group was convened to focus on what system changes and research is required to improve identification of brain tumour patients and better expedite their diagnosis through scanning. The group comprised clinical leads from primary care cancer, leads from NHS England's neurology and neuro-ophthalmology departments, Getting It Right First Time (GIRFT) and national optometry leads, primary researchers active in the field of early diagnosis of brain tumour in the UK, and representatives of the patient community.

a) Clinical research to improve evidence base

There are no controlled intervention studies or high-quality before-and-after studies in early diagnosis of brain tumours on which to base guidelines (Grant et al. 2020).

Position

- Quality of research in early diagnosis needs to improve.
- Studies may be prospective, or before-and-after studies, assessing the value of symptom combinations, additional tests, protocols for scanning and protocols for expediting scanning.
- Consideration should be given to assessing the value of symptoms that occur in serious intracranial disease, which may include brain tumour but may also include other conditions, such as intracranial infection, vascular disease or inflammation, where early treatment may also improve not only diagnosis but also outcome or survival.
- Interventions aimed at increasing the predictive value, minimising needless scans and optimising strategies to expedite scanning (CT or MRI) in higher-risk patients should be considered.

b) Patient symptom recognition and primary care waiting times

Educating the population through national campaigns on when to present promptly to primary care is difficult, and benefits are usually temporary. Some attempts have been made in children (Liu et al. 2012) but not in adults.

Certain patient groups are at particularly high risk of having brain cancer (e.g. patients with certain systemic cancers or hereditary neurocutaneous syndromes).

Fully trained GP numbers in the UK are down on previous years for a variety of reasons (The British Medical Association 2023). Face-to-face appointments with GPs are less common; telephone appointments and advice are more common. Previous tasks performed by GPs are being delegated to advanced nurse practitioners, advanced paramedic practitioners, practice pharmacists, social prescribers, optometrists, etc. so that GPs can prioritise more urgent cases.

Position

- An awareness campaign for adult presentations of brain tumour may be feasible with charity support, highlighting the range of common presentations and routes to diagnosis.
- An awareness campaign is recommended for clinicians managing patients with systemic cancer or hereditary neurocutaneous syndromes (e.g. neurofibromatosis) to highlight symptom combinations, cognition screening and value of optometry and advising patients to present for urgent evaluation to their secondary or primary care teams should symptom combinations occur.
- Awareness campaigns for the red flags are recommended, aimed at nurse practitioners, advanced paramedics and optometrists, who may be the first to see and assess patients.
- Strategies to reduce GP waiting times (e.g. recruitment and retention of GPs and associated practitioners) may influence general primary care waiting lists.
- Safety-netting is recommended for patients with progressive symptoms to ensure a face-to-face appointment for clinical exam and fundoscopy.

c) Primary care and allied healthcare education

Primary care practitioners, medical students, paramedics and emergency department staff are taught about the ‘classical’ presentations of brain cancer at university and through postgraduate education opportunities. What is less well known is the importance of symptom combinations and clusters of symptoms. Primary care clinicians cannot be expected to be expert in identifying subtle neurological or ophthalmological signs (e.g. early papilloedema).

Cancer decision support tools (CDSTs) are available for many cancer symptoms, (e.g. Cancer Maps, which has been endorsed by NICE and the Royal College of General Practitioners).

Position

- Education of the importance of symptom combinations and clustering and their importance in expediting investigations is recommended.
- The value of simple cognitive testing in suspicious headache should be recognised.
- Education on identification of the importance of identifying papilloedema is recommended.
- Education on appropriate referral of uncertain disc swelling or suspicious visual field defects in optometry is recommended.
- Cancer Maps could be expanded to include CNS symptom clusters, optometry referral and cognitive tests.

d) Primary care symptom recognition

i) Headache

Headache as a sole symptom of a brain tumour is a rare finding. Headache plus cognitive symptoms or poor results on cognitive screening increases the likelihood of a secondary cause. A low semantic verbal fluency test score increases the likelihood of a secondary cause. Confidence in identification of visual signs (papilloedema, visual field loss) is important for diagnosis of brain tumour. Optometry is increasingly becoming involved in diagnosis and management of a wide range of eye conditions in the community, taking pressures off ophthalmology (MacEwen, Davis and Chang 2019). A report on 'Improving patient safety and experience when referring to hospital in England' (The Royal College of Ophthalmologists and College of of Optometrists 2020) emphasises the values of education and good referral practice and feedback to enhance collaboration. Community optometrists have the experience and often specialist equipment, such as optical coherence tomography (OCT) scanners, which assists in the interpretation of disc swelling. The 'Scottish Referral Guidelines for Suspected Cancer' already recommends referral to dedicated optometry pathways where there is uncertainty over optic disc appearance or visual field loss, along with referral to secondary care.

Position

- Headache management pathways can be followed without recourse to referral for scanning for those with episodic headache alone and where a diagnosis of primary headache is not in doubt.
- In cases where there is uncertainty about a primary headache diagnosis, clinicians should enquire about headache plus neurological symptoms (cognitive or personality symptoms, obscuration of vision, visual field loss), past medical history of cancer, neurological combinations (pulse-synchronous tinnitus, unsteadiness) and systemic combinations (e.g. cough, shortness of breath, fatigue, weight loss).
- Where secondary headache is considered possible, an SVFT should be performed, and a result of <17 should be considered a red flag.
- Consideration should be given to direct-access CT brain scan referral of suspicious headache plus cognitive or SVFT <17, as direct-access brain MRI availability is currently patchy and waiting times longer and likely to remain so for many years.
- GP referral for community optometry for urgent fundoscopy or field assessment should be made more widely available for cases with suspicious headache or possible papilloedema or field defect.
- Optometry ability to directly refer to secondary care should be considered where papilloedema or concerning field defect is found.

ii) Seizure

A recent case-control study using Clinical Practice Research Datalink (CPRD) data comparing individual first symptoms from 8,184 patients with tumours and 28,110 controls showed that the largest positive predictive value (PPV) for single symptoms was for seizure. This had a PPV of 1.6% for a single symptom, but the odds of having a tumour were higher in cases with seizure plus a second neurological symptom (e.g. headache) (Ozawa et al. 2019).

Position

- Patients with first suspected late-onset seizure should be discussed with neurology Advice and Guidance services or referred to a first seizure clinic.
- Patients with suspected seizure plus should be discussed with the intention of rapid-access scanning.

iii) Focal neurology

Patients who present with focal neurological symptoms generally also have neurological signs (Grant 2004). Patients generally present to GP services and are seen quickly and referred to secondary care without undue delay (Ozawa et al. 2018).

NICE cancer referral guidance (NG12) adequately reflects the urgency of referral and suggests MRI. This is not yet widely available to GPs across the UK. The presence of imaging diagnostic hubs is still in its infancy. Patients with focal neurology are largely seen in secondary care quickly, either in neurology, care of the elderly, TIA/stroke or emergency departments (A&E). They may have a variety of serious conditions, including tumour, stroke, demyelination or infection. Some patients with progressive neurological deficits are seen via the 'urgent suspected cancer' two-week wait. In view of the low number of cases that subsequently have a tumour diagnosis, compared with other conditions (stroke, multiple sclerosis, functional neurological disorders, etc.), neurology is the most logical route. For patients with known cancer and focal neurological symptoms or signs, an oncology referral is logical, especially if they are under oncological review.

Position

- Patients with acute focal neurological symptoms and signs should be discussed with neurology or stroke services.
- Patients with progressive focal neurological symptoms and signs should be discussed with neurology Advice and Guidance services.
- Patients with systemic cancer who are under oncological services and who develop focal neurological signs should be discussed with their consultant.
- Direct referral from GP for cerebral imaging would not be the most appropriate route, especially for more acute cases or those with neurological signs (hemiparesis, dysphasia, visual field loss).

iv) Cognitive or personality changes

Cognitive or personality changes may have several causes, including degenerative, vascular, neoplastic, deficiency, autoimmune, endocrine, toxic, drug-related and psychological. In cases of possible dementia, a GP will assess for other possible treatable causes of cognitive difficulties, such as anxiety, depression, delirium, underactive thyroid and side effects of medication. Investigations will include blood tests and performing a simple cognitive screening test before considering referral to psychiatry, care of the elderly or a neurologist. The speed of development of the changes, severity and associated history is usually helpful when considering differential diagnosis. Subacute progressive changes and combinations of cognitive symptom plus headache,

seizures or focal neurological symptoms would increase the likelihood of a cerebral structural cause. A Clinical Practice Research Datalink study (Ozawa et al. 2019) noted that cognitive symptoms plus headache increased PPV for tumour from 0.7% to 7.2% and cognitive plus weakness increased PPV from 0.7% to 9.6%. This highlights the importance of symptom combinations and the need to expedite imaging for these cases.

Position

- Patients with subacute cognitive decline or symptom combinations require urgent discussion and investigation. Neurology Advice and Guidance services or care for the elderly would be appropriate routes.
- Patients with slow progressive cognitive or personality change signs should be discussed with the neurology Advice and Guidance services or care for the elderly.
- Direct referral for CT or MRI brain scan may be appropriate, prior to referral if this is quickly available to the GP.

e) Imaging of choice, brain imaging resources in the UK and research

The demand on MR imaging in the UK is continuously increasing and outstripping ability to adequately report the scans. There has been a 4.6% annual increase in brain MRI scans since 2012, and in the six-year period of 2013 to 2019, only 1% of NHS trusts met their imaging reporting requirements (Dixon 2018, The Royal College of Radiologists 2020).

As MRI scanning becomes more available, so do competing demands for new and complex imaging for monitoring disease, as well as new indications for expedited diagnosis, such as MRI within two weeks for cases of suspected brain cancer.

In November 2022, NHS England released the news that 'every GP team will start to be able to directly order CT scans, ultrasounds or brain MRIs for patients with concerning symptoms, but who fall outside the NICE guideline threshold for an urgent suspected cancer referral'. NHS England hopes that 'under the ambitious Direct Access scheme, around 67,000 people who are usually diagnosed with cancer through non-urgent testing will now be eligible for fast-tracking – and can have a better chance of having their disease picked up at an earlier stage, when survival chances are higher'. The aspiration is 'to open up to 160 [Community Diagnostic Centres] in total over the next two years, with around nine million annual checks delivered by the end of 2025'. However, currently, hospital radiology services are under severe pressure, and these additional centres will require additional staff at all levels. It is not

immediately clear where the trained staff will come from to perform and promptly report these additional scans.

Currently, many GPs do not have direct access to brain CT, and those few that have access to MRI brain scans may have prolonged waits of several weeks or months for scans to be performed and reported, making it unlikely they will precipitate early diagnosis unless protocols are available to select priority cases to receive expedited scans.

It remains to be seen whether Community Diagnostic Centres will speed up brain cancer diagnosis over the next decade. Radiologists have developed the iRefer clinical decision support tool to enable GPs to 'book the right scan first time' and limit what are considered unnecessary scans. These clinical decisions need to take note of recent research on brain tumour presentation, including symptom combinations and the value of additional helpful screening tests. The 'right' scan to enable earlier diagnosis has to be the fastest scan that can be performed, reported and actioned and that will lead to earlier surgery. Although MRI scanning is more sensitive and frequently identifies incidental tumours (Morris et al. 2009), CT scanning for headache suspicious of cancer and subacute cognitive presentations will be the fastest route for those with the slowest pathway to diagnosis for the foreseeable future. CT brain scans are more widely available, cheaper and have shorter waiting times. Importantly, an analysis of the direct-access CT referral pathway had no false-negative scans for brain tumour (Zienius et al. 2019). New-generation CT brain scans give high-quality images and will identify tumours with mass effect, hydrocephalus and haemorrhage and most infiltrative brain tumours. GP access to CT scans may reduce diagnostic costs, but further controlled studies are required (Keeney et al. 2021). While in its infancy, developments in AI may allow faster scan triaging, which, alongside clinical decision support, has the potential to improve time to diagnosis (Wood et al. 2022).

Position

- MRI is the investigation of choice for seizure presentations and subacute focal neurology with neurological signs.
- Pragmatic use of CT scans for brain imaging in headache and cognitive diagnoses is justified, as symptomatic intracerebral tumours would be large or associated with hydrocephalus. When MRI scanning becomes more widely available to primary care, fast to obtain and quickly reported, it would be the imaging of choice.
- More resources to allow more equitable direct-access cerebral imaging for primary care and expeditious reporting are required.

- To have the greatest impact on time to diagnosis, iRefer guidance for suspected brain tumour needs to target the fastest route to positive brain scan in those cases with the slowest presentations.

Research

- The effect of wider primary care access on clinical pathways and time to brain tumour diagnosis needs further research.
- The impact of Community Diagnostic Centres on earlier diagnosis of symptomatic brain tumour should be audited.
- Prospective research on the pros and cons of CT versus MRI scanning for headache suspicious of cancer and cognitive conditions should be encouraged.
- The impact of the iRefer clinical decision support tool for suspected brain cancer should be audited.
- The impact of AI in shortening the time to reporting of suspected brain cancer requires more research.

f) GP protocol-based headache referrals for scanning

One in 1,000 people presenting to a GP with new headache will have a brain tumour (Hamilton and Kernick 2007). Fourteen in 1,000 people with headache or cognitive symptoms referred for direct-access brain scanning will have symptomatic brain tumours (Zienius 2019). GP streaming of cases into fast stream 'expedited' and slow stream 'low risk' based on clinical judgement and 'headache plus' showed some difference between streams in the likelihood of identifying a tumour. Electronic protocol-based GP referral for expedited CT scans shows the likelihood of having a tumour to be 2.2% with headache suggestive of tumour plus cognitive or behavioural symptoms. Prospective studies of suspicious headache cases that have an SVFT score of <17 increase the percentage of cases with tumour to more than 5%.

Position

- Protocol-based referral may be helpful to prioritise urgency of scans.

g) Neurology resources in the UK

Neurology active referral management (Advice and Guidance)

Changes in working practice during the pandemic have reinforced the need for a robust, responsive referral management process. The Association of

British Neurologists' Services Committee established a working group that reviewed the available evidence on referral management processes. From the limited available evidence, offering Advice and Guidance based on referral information is considered safe. Headache was the most common symptom dealt with via triage rather than face-to-face consultation (Anderson et al. 2022). The GIRFT report recommends that all neurology units implement Advice and Guidance and a triaging system of outpatient referrals.

Position

- It needs to be established whether the development of neurology advice and a triage system is a faster and more effective use of resources and whether it shortens the time to diagnosis of cases with suspected brain tumour.

h) Optometry resources in the UK

Patients may present to optometry with ocular symptoms or headaches prior to seeing their GP and have the investigations to diagnose papilloedema or visual field defects. The 'Scottish Referral Guidelines for Suspected Cancer' recognises the important role that optometry can play in diagnosing brain tumours.

Position

- Locally commissioned community optometry services should offer an important step in the assessment pathway in uncertain cases.
- Further research is required to evaluate the implementation of such a service. The objective of such research should be to establish whether changes to pathways and practice (e.g. refined use of OCT scans in primary care optometry, and closer cooperation between GPs and optometrists) result in improvement in time to diagnosis or health economic gains, such as reduced numbers of scans or faster time to formal diagnosis and resolution of symptoms with advice.

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Involved:

NCRI

Dr Robin Grant – NCRI Brain Group, Supportive and &Palliative Care Lead; Consultant, Neurology, Edinburgh

Prof. Michael Jenkinson – NCRI Brain Group, Lead; Neurosurgery, Liverpool

Dr Paul Brennan – NCRI Brain Group, Reader; Neurosurgery, Edinburgh

Dr Helen Bulbeck – NCRI Brain Group, Supportive and & Palliative Care; *brainstrust-the brain cancer people*, Cowes

Primary Care

Dr Ben Noble – Cancer Lead, East Midlands Cancer Alliance; Cancer Research UK; Cancer Maps

Prof. Willie Hamilton – Primary Care Diagnostics, Exeter; NICE Guideline NG12 (2015)

Dr Richard Roope – Sessional GP; Cancer Research UK Primary Care Adviser; Wessex Cancer Alliance GP Adviser

Dr Stephanie Edgar – Cancer Research UK; Strategic GP for South Yorkshire and Bassetlaw

Neurology

Prof. Phil Smith – Professor of Neurology, Cardiff; Epilepsy; Association of British Neurologists; NICE

Prof. Geraint Fuller – Association of British Neurologists; GIRFT Clinical Lead for Neurology

Optometry and Ophthalmology

Dr Paramdeep Bilkhu – Clinical Adviser, College of Optometrists

Dr Susan Mollan – Consultant, Neuro-Ophthalmology, Birmingham; Consultant, Ophthalmology

Neuroradiology

Dr Jagrit Shah – Clinical Lead for MRI, Nottingham University Hospitals

Dr Thomas Booth – NCRI Brain Group; Consultant, Neuroradiology, King's College Hospital

Patient Representative

Dr Jenny Schaefer

Advancing Cancer Research Together

National Cancer Research Institute
2 Redman Place,
London, E20 1JQ

T: +44 (0)20 3469 8798
F: +44 (0)20 3014 7658

info@ncri.org.uk
www.ncri.org.uk