THE FARAH SAEED ACADEMIC JOURNAL ON CANCER FOR EARLY CANCER RESEARCHERS

Volume 1
1st June 2025

FOREWORD

The Farah Saeed Academic Journal On Cancer For Early Cancer Researchers (FSAJ-ECR) is a new initiative under the Farah Saeed Project umbrella whose aim is to share their research projects biannually within the field of cancer that will help harness even a small difference towards the cancer world in memory of Dr Farah Saeed who passed away in September 2014 from gastric metastatic cancer.

The FSAJ-ECR is a freely-accessed research journal whose target audience are students and early career researchers in the cancer discipline. Our biannual research journal aims to focus on quality over quantity where one research paper is focused and is driven by passion and interest in the field. Our images are pencil-drawn to emphasis the ongoing journey of learning,

Cancer requires a multidisciplinary effort, and the scope of FSAJ-ECR is to contribute to the universal commitment to better understanding cancer from a diagnostic and therapeutic perspective for a brighter future.

In a world where research and support involve competition, bidding, and networks based on who you know and are connected with, we aim to fill the gap to exist independently through passion, building self-confidence, learning and development one step at a time. We are always looking for new collaborations with the same vision and mission.

Subject Editors

Dr Hafsa Waseela Abbas (Head of Health and Founder of Farah Saeed Project)

Contributors and Acknowledgements

Family and The FST team for their positive moral support to complete this research project.

The NDRS team for being both helpful and modest during initial discussion on the GDO data.

Mr Adnan Khalid (Freelancer/Contributor/Statistician who quality assured the results and peer reviewed FSAJ-ECR Volume I only)

Get Data Out (GDO) programme dataset freely available for public use by the National Health Service.

Submissions: This is a new project and we are currently not accepting any submissions for the initial volumes.

Conflict of interest: The authors claim that the research project was done without any commercial or financial elements that could cause a potential conflict of interest.

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Dr. Hafsa Abbas is strongly interested in cancer research, particularly neurological tumours. She has humble experience in patient care and has participated in various cancer research qualitative and quantitative projects. She learnt different techniques and research methods in her academic journey. She dedicates her time voluntarily to the field through lecturing and research for the diverse community. She enjoys collaborating with fellows who believe in improving cancer care. Through FSAJ-ECR, she hopes to achieve her mission in publishing research about different cancers to benefit the research community.

Farah Saeed Academic Journal-Early Career Researchers
Building abilities, confidence and self-esteem through research and development
FSAJ-ECR
Volume 1
1st May 2025

Original Research Review Article

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Seven year trends in the socio-demographic factors that influences brain cancer incidence among adults across England in the UK, 2013-2020

Hafsa Abbas[1]

ABSTRACT

Background

Neurological cancer is the ninth most common cancer in the UK. It is a global burden particularly gliomas that have poor prognosis.

Aims

To assess the trends in brain cancer incidence in England and explore the underlying sociodemographic factors that influence its prevalence between 2013 and 2020.

Methods

Retrospective secondary data analysis of brain cancer incidence and routes to diagnosis were retrieved from the NHS's Get Data Out programme using Minitab Version 22.1.

Results

The incidence rate (IR) decreased from 18.53 in 2013 to 16.35 in 2020. It varies per tumour type, malignant tumours (IR, 8.12), and less frequent non-benign (IR, 0.28). Patients aged 70 years and above are at the most risk of malignant (IR, 22.81-26.08) and non-malignant tumours (IR, 19.92-23.797). London has the lowest cases for combined sexes. There was no significant difference between male and female patients aged 50-69 in 2013. Midlands and East of England had the highest incidence, whereas, the South of England had the lowest. However, patients aged 70 and above had the highest IR in the South of England but the lowest in the Midlands and East of England. In 2020, the South of England was the dominant region except females aged 70 plus.

Conclusion

This study presents the importance of psycho-oncological care. Cancer incidence increases with age. Geographical variability suggests health inequalities exist and reflects the deprivation scores and marginalized populations in England. The NHS aims to avert high mortality rates through research, training, and artificial intelligence to improve differential diagnosis.

Key Words Oncology, sociology, medicine, culture, religion, age, region, patient care, wellbeing, psych-oncology, communication

1. INTRODUCTION

1.1 What is cancer incidence?

The assessment of incidence is a primitive tool in the research agenda of cancer as it provides a numerical value on how many people are diagnosed with a particular type of cancer within a specific period which helps to identify disease clusters (Cancer Research UK, 2023a). In addition, the routine use of computed tomography (CT) scans for diagnosis and up-to-date accurate incidence rates that are published annually by the National Health Service on the Get Data Out (GDO) database is essential to monitor variations over the time factor per age group, gender, and socioeconomic status (Sehmer *et al.*, 2014; Vernon, 2023).

Recent annual estimates by Cancer Research UK (n.d.) stated there are *ca.* 12,746 people diagnosed with brain, another central nervous system (CNS), and intracranial tumours in the United Kingdom and the incidence is increasing. Neurological tumours are the ninth most common cancer in the United Kingdom (UK) and account for 3% of all cancers where 375,400 people have been diagnosed with cancer annually on average between the years 2017-2019 (Cancer Research UK, 2023b; 2024). There has been a drastic shift in the five-year survival where trends are reflective of treatment regimens, stages, and socio-demographic factors namely age, gender, and deprivation (Cancer Research UK, n.d.).

Initially, almost one in ten (7.2%) survived beyond five years (Cancer Research UK, n.d.). However, this percentage increased by 2.57-fold in 2010 to one in five (18.5%) and today *ca.* one in ten (11.2%) have managed to survive ten years or more (Cancer Research UK, n.d.).

The increase in brain cancer incidence has been profound in England where in recent decades the multi-diverse cultural milieu caused a steady rise in malignant primary brain tumours (Office of National Statistics, 2021; Wanis *et al.* 2021). In 2021, 90.3% of the population (53.8 million) was identified at least with one UK national identity and this is a 1.7% percentage increase from 2011 (Office of National Statistics, 2021).

However, the percentage difference was more apparent in the number of UK residents with one non-UK and one UK from 0.9% (492,000) in 2011 to 2% in 2021 (1.2 million) (Office of National Statistics, 2019). There was a further increase for individuals with non-UK from 8.0% (4.5 million) in 2011 to 9.7% (5.8 million) in 2021 (Office of National Statistics, 2021). A potential region with a rise in glioma cases except for metastases has been notified by neurosurgeons to be in Lancashire and South Cumbria situated in North Western England (Sehmer *et al.* 2014; Ostrom *et al.,* 2018). Glioma patients present similar demographic characteristics as observed in other populations but male patients are affected and predominantly found in the frontal and parietal lobe (Sehmer *et al.*, 2014; Wen and Kesari, 2008).

The rarity of the incidence of primary brain cancer and other tumours of the CNS could explain why neurological research is overlooked, diagnosis in rare cancers (RC) is often delayed, and the risen complexity of their clinical management (Botta *et al*. 2020).

In contrast, the poor prognosis and disproportionate numbers of people with the onset of working age (> 65 years) being diagnosed predominantly with glioblastomas otherwise known as glioblastoma multiforme, a malignant primary brain tumour that accounts for more than one in five diagnoses of the brain have identified the essential need to improve the diagnosis, prognosis, and treatment of neurological cancers (Sehmer *et al.* 2014; Brain Research UK, n.d.).

Neurological tumours have one of the worst survival rates compared to other European nations and reflect a delayed diagnosis and emergency presentation (National Cancer Research Institute, 2023; Sheridan *et al*., 2019). The level of diagnostic accuracy increases when relatively expensive imaging tools are accessible. However, Ilic and Ilic (2023) discovered that this is principally found in primary and secondary care in countries with a higher High Development Index (HDI) compared to less developed countries with poor economies.

The Surveillance of Rare Cancers in Europe (RARECARE) reported the entities for the incidence and survival of brain cancers and found the two indicators to be highly significantly different in the United States of America (USA) than in Europe (Botta *et al*. 2020). Data was mainly focused on neuroendocrine tumours and glial tumours. The incidence data in the USA was extracted from the Surveillance, Epidemiology, and End Results (SEER) database. The cellular origin of neuroendocrine neoplasms (NEN) is the diffuse neuroendocrine cell system and its neuronal phenotype has been disentangled by different disease sites (Sundin *et al.* 2017; Pavel *et al*. 2020). Striking differences in Age-adjusted incidence rates (ASR) were shown in well-differentiated not functioning endocrine carcinoma of gastroenteropancreatic (GEP) 2.62 $\pm$ 0.02 and 0.86 $\pm$ 0.007 for USA and Europe respectively which correspond to the 5-year net survival advantage of 13% whereas the incidence difference was 1.76 (Botta *et al*. 2020).

Other neuroendocrine tumours have minimal to no difference in survival rates. For example, patients with neuroendocrine carcinoma of the skin had an ASR of 0.55 $\pm$0.01 in the USA but the reported rate in Europe was 0.16 $\pm$ 0.003 (Botta *et al.* 2020). There is an incidence difference of 0.388 and a -1% difference in survival rates. However, neuroendocrine carcinoma of other sites had an incidence difference of 0.427 where the ASR for USA and UK was 1.17 $\pm$ 0.014 and 0.75 $\pm$ 0.006 respectively had a 0.427 difference in incidence and the net survival was 1%. The highest annual incidence rates of astrocytic tumours were in the USA where the incidence rate was 4.75% while the lowest reported rate was in Europe (Botta *et al.* 2020). The incidence rate

was 0.444 and the net survival was 3%. This suggests the variability in the incidence rates per type of tumour in the two respective countries.

Possible explanations are the distribution of risk factors, classification, and coding system used to diagnose between the two populations (Botta *et al*. 2020). There is further evidence that tobacco and alcohol increase the potential risk of well-differentiated not functional neuroendocrine carcinoma of the pancreas and digestive tract in Europe. Nonetheless, classification and overdiagnosis have been identified to increase the risk of USA incidence. Diagnostic testing and pathological second opinion are less available in Eastern Europe, a more rigid tumour classification system and new entity registry codes in the ICD-0-3 coding procedures are applicable in the USA (Botta *et al*. 2020).

CT is commonly used as a standardized method for diagnosis because of its wide availability and reproducibility (Sundin *et al.* 2017). It was first introduced in 1971 by engineer Sir Godfrey Hounsfield, before later versions were developed in the 21st century, focusing on improving speed, resolution, and imaging quality for accurate diagnosis. Please see Supplementary Material 3.

Magnetic resonance imaging (MRI) is another sensitive tool essential for the staging and preoperative imaging of neuroendocrine tumours to examine the liver and pancreas. This breakthrough was also developed in 1971 by the physician Raymond Damadian. A few years later, *in vivo* studies on murine models took place by Paul Lauterbur. In 1977, Peter Mansfield used MRI on humans as a diagnostic method (see Supplementary Material 3). This demonstrates the phases in cutting-edge developments on medical devices undergo.

MRI is more sensitive than CT to detect bone and brain (Putzer *et al.* 2009; Sundin *et al*. 2017). Alternative imaging methods that facilitated histopathological diagnosis include Endoscopic ultrasound, intraoperative ultrasound, and fine needle aspiration biopsy for cytology.

However, upon comparative analysis per European region, brain cancer is heterogeneous and retrospective. The UK and Ireland have the lowest incidence rate of 0.55 ±0.01 for neuroendocrine tumours of the skin. The astrocytic tumours of CNS had the highest reported incidence rate with 4.75 ± 0.03 and; this was subsequently followed by a neuroendocrine carcinoma of other sites with 1.17 ± 0.01 (Botta *et al.* 2020).

On a global scale, cancer is responsible for one in six deaths (16.8%) (Bray *et al.* 2024). The Global Cancer Observatory (GLOBOCAN) has announced that tumours associated with the CNS play a considerable part in the global burden of disease where it is positioned 19th for frequent malignancies (1.9% of all cancers) and ranked 12th for cancer mortality (2.5% of all cancers) annually. Such ranking positions emphasize the negative effect neuro-oncological tumours have economically, quality

of life (QOL), and low survivorship (Sung *et al*., 2021; Siegel *et al*. 2022).

In the Middle East, countries such as Iraq were ranked fourth in position in causing deaths independent of age and sex (Howlader *et al.,* 2021; Ferlay, Colombet, and Bray, 2018). Global Burden of Disease Cancer Collaboration (2019) has positioned the brain and CNS as the eight leading causes of absolute Years of Life Lost (YLLs).

Such geographical differences in cancer incidence and mortality are predominantly explained by lifestyle factors mainly behavioural and dietary changes, distribution of cancer types, accessibility to effective prevention, early diagnosis, and curative treatment (Bray *et al.,* 2024; Randazzo and Peters, 2016; Carlson *et al*., 2004). Amongst the newest identifiable factors for paediatric tumours was a combination of environmental and genetic basis (Ostrom, Francis, and Barnholtz-Sloan, 2021).

Ionizing radiation is amongst the environmental risk factors whereas most of the risk factors have a biological origin (Ostrom *et al*., 2019). A UK retrospective cohort study discovered that there was positive correlation between radiation from CT scan and risk of brain tumours in patients aged less than 22 (Pearce *et al*., 2012). Furthermore, there is discrepancy in the research findings on whether exposure to radiofrequency fields from mobile phones where it initially developed in 1980s was a risk factor of brain cancer (Villeneuve *et al.,* 2021). Amongst the reasonings for the variability of the data results are due to study designs and form of measurement rather than sex differences.

Other contributable risk factors are higher birth weight (>4000g), congenital defects with a non-chromosomal origin (e.g. spina bifida and hydrocephaly), hormonal contraception, allergy, and pathological microbes (e.g. Epstein-Barr virus, cytomegalovirus, and Toxoplasma gonii) could elevate brain cancer incidence (Ostrom, Francis and Barnholtz-Sloan, 2021; Hargreave *et al*., 2022). Gatto *et al.* (2021) revealed that exposure to pesticides especially under working conditions can also increase the incidence of brain cancer.

Similar socio-demographic statuses in regions could be explained by genetic susceptibility amongst different populations where female sex have a better survival rate (Kinnersley *et al.,* 2015; Achey *et al.,* 2019 and Schiffgen *et al.,* 2016). Pavel *et al*. (2020) reported there are hereditary causes of neuro-oncological tumours where the onset of multifocal NETs is at an early stage at the time of diagnosis and *ca.* one to two decades before sporadic tumours where there are germline mutations such as DNA repair. This may explain why genetic tests are performed in patients with multiple endocrine neoplasia to determine whether there is a familial history, especially in young patients (Pavel *et al.,* 2020).

Such incidence patterns that vary globally and nationally depict how brain cancer is a threat to the embodied existence that influences the facets of moral, social, and economic burdens in the 21st century (Bray *et al.* 2024). Careful

considerations of the increasing trends in brain cancer incidence should be focused on raising public awareness, improving the efficiency in identification of brain tumour patients where diagnosis is better expedited through scanning. This will facilitate the efficacy of treatment regimens, and minimizing the psychological stress of patients especially glioma are the ongoing essential goals for surveillance and treatment (Broom and Kenny, 2020; Kvale *et al*, 2009; Smittenaar *et al.*, 2016).

The World Health Organisation (WHO) aims to reduce a third of premature mortality by 2030 as one of its Sustainable Development Goals (Bray *et al.* 2024). However, the number of cases is predicted to increase to *ca*. 85.000 and deaths to 70,000 in Europe. It is estimated that 40% increase in new cases will arise in high-income countries but this percentage is superseded in low-income countries by more than 80% (Grassi, 2020). Hypothetically, this is partially may be related to the coronavirus (COVID-19) pandemic where the quality of care, the degree of vulnerability, delay of diagnosis, and lack of access to treatment can explain the increased number of cases (UN General Assembly, 2015 Riera *et al.,* 2021; Graetz *et al.,* 2021; Carai A., Locatelli F., Mastronuzzi 2020; Khazaei *et al*., 2020).

Overall, despite the challenging status and variability in the incidence of brain tumours on a national and global level. The historical development in the diagnostic methods for brain tumours and surgery has grown exponentially since the Pre-Modern era and cannot be unheeded. Please see Supplementary Materials 1 to 3. The initial understanding of the brain and tumours was considerably sacrosanct and depended on trepanation. However, time, technological advancements such as the discovery of X-rays, globalization, research networks, and training have significantly progressed our understanding of the interplay between neuroanatomy and physiology with mechanisms underpinned in pathophysiological conditions such as tumours (Shreykumar *et al*., 2021).

1.2 Types of tumours

The classification of cancer as a disease of civilization has been subjected to extensive multidisciplinary research efforts since the development of radiotherapy in the 1920s and chemotherapy post-Second World War (Szot *et al.,* 2021). Collaborative initiatives by WHO and world-renowned researchers aimed to establish a uniformed histological criterion and the nomenclature for the diagnosis of human neoplasms. It involves a morphological coding and grading system per tumour entity. This facilitates population-based epidemiological studies on brain cancer incidence and mortality on causative factors and therapeutic decisions. It is particularly notable whether adjuvant radiotherapy and chemotherapy improve clinical outcomes and validate novel cancer therapies via clinical trials (Kleihue, Rushing, and Ohgaki, 2017). The latest WHO classification includes molecular markers that appear in glioma cases. This helps in the

prognosis and decision-making of the best suitable treatment for the patient. However, there is still yet to know how to treat the diverse spectrum of brain cancer that is defined as either benign or malignant.

In medical terms, primary brain tumour refers to the pathological heterogenous neoformation of cancer cells that originate in the intracranial tissues and the meninges of the brain (Caponnetto *et al*., 2024; Shreykumar *et al*., 2011). It can also affect the spinal cord.

Brain cancer is subdivided into high-grade glioma, low-grade glioma, and benign brain tumours. A malignant transformation of cancer can spread to other disease sites through the lymphatic and venous routes to form high-grades. The most common form of malignant brain cancer is gliomas that derive from glial cells. One of the essential roles of glial cells is to develop a fatty layer of myelin sheath on nerves for insulation (Caponnetto *et al*., 2024).

Different types of brain cancers are illustrated in Supplementary Material 4. They are distinctive in their biology, risk factors, proliferation rate, prognosis, and treatment (Shreykumar *et al.,* 2021). Poor prognosis is experienced in individuals with high-grade glioma where the average five-year survival rate is 36%. The recurrence of lower-grade gliomas is between 52-62% within five years and can be bypassed to form malignant brain tumours where the estimated percentage rate is 80% within a decade.

Benign tumours are non-life-threatening tumour that remain in the primary site but can cause considerable uncertainty and distress amongst the patients. The most common benign entity is meningioma which arises in the meninges – please see Supplementary Material 4. Patients with benign and low-grade tumours are rendered ineligible for care services despite their potential risk of contributing to functional impairments (Ostrom *et al.,* 2018; Lion *et al*. 2023).

In contrast, high glioma cases require long-term integrated psychosocial support and management for symptom monitoring. Patients with cerebral metastases also exhibit supportive care (Maqbool *et al.,* 2017). Psychosocial support refers to spiritual, social, emotional, or practical interventions and psychoeducation based on the individual needs of brain cancer patients and their families (Randazzo and Peters, 2016; Goebel and Mehdorn, 2019; Maqbool *et al*., 2017; Renovanz *et al.,* 2020; Riba *et al.,* 2019, Singer *et al.,* 2018). The complexity of multimodal treatments for malignant cancer requires chemo-radiotherapy with subsequent cycles with chemotherapy whilst observations are made for benign tumours (Lion *et al*., 2023). This suggests how tumour characteristics can affect accessibility to health and social services and the need for an in-depth analysis on psychosocial practices in patients.

During the progression of disease, 20-40% of cancers have been diagnosed with a solid malignancy outside of the CNS (Cagney *et al.,*

2017). This may result in serious side effects predominantly paralysis, visual field defects, aphasia, paresis, personality changes and epilepsy (Fehrenbach *et al.,* 2021). The invasive character of neurological tumours has elevated predisposition towards difficulty in stabilising their coping mechanisms, posttraumatic stress symptomatology and cognitive impairments. This negatively influences adherence to treatment and clinical outcome in patients with intracranial neoplasia in comparison to patients with benign tumours (Halkett *et al.,* 2015; Randazzo and Peters, 2016; Fehrenbach *et al*., 2021). It is reported that 50% of brain cancer patients have experienced neglect in their psychological wellbeing post-surgery as the focal point is physical rehabilitation and drug treatment. This further raises the importance of collaboration between neurosurgeons and neuropsychologists to maximize the successive rates of patient recovery (Raffa, Quattropani, and Germano, 2019).

Thus, the present study explores regions and other multifactorial avenues that influence brain cancer prevalence, predominantly age, gender, and type of brain tumour. These potential risks alongside lifestyle factors and psychological status of patients and their respective families have created fluidity to bypass disciplinary boundaries - an inquiry of psych-oncological, sociological, political, and economic perspectives. Biological and social processes have shaped patients' perceptions and advocated changes in clinical practice, welfare policy, and the importance of respecting the rationality of patient experiences and decision-making (Kerr *et al.* 2018).

1.3 Sociology of brain cancer

In the last decade, there has been a corpus of sociological literature that is concentrated on qualitative research, patient, and their relative experiences with cancer through a narrative and inclusive approach (Kerr *et al*. 2018). Through the social constructivist lens, early works have been notable on experiences of illness and have been transformed to the most current Foucauldian perspective on lived experiences of body and chronic disease and how patients realigned personhood and the importance of individualization of risk and responsibility (Blaxter and Paterson, 1982; Bunton and Petersen, 2002). Medical sociologists such as Kerr *et al.* (2018) have broadly defined two major themes focused on the sociology of cancer: the social and biographical context of cancer identification and subjectivity and cancer and caring practice. Factors such as stigma, survivorship, surveillance, anomie, faith, decision-making, palliation, and physical manifestations are branched out from these themes.

From the functionalist lens, having good health stabilizes a society where illness is considered deviance. One of the fundamental functionalists, Talcott Parsons discussed the sick role where defined patterns are relayed to ensure appropriate behaviour and conduct is made for those who are sick and those who look after them (Parsons, 1951).

Physicians have a form of authoritarian role that certifies the illness based on physical examination and other testing. Patients would receive a response after several days or weeks if they were to call the physician initially. Conversely, if a physician contacts the patient and leaves a voicemail, the social normative act is for the patient to return the call. Physicians have fewer social norms but patients would like to explore and understand about their health (Puttman, n.d).

In contrast, conflict theorists consider money and power can biphasically increase one's importance in society and are able to make informed discussions in how the National Health Service works. Health disparities can effectively rise in healthcare institutions despite high bureaucracy because they are unable to serve all patients equally. People with low income are afflicted with poor diet, working conditions and are unable to challenge the healthcare system (Puttman, n.d.). Racism, ageism, sexism are other behavioural consequences. Conrad and Schneider (1992) have sociologically examined how the definition of deviances can be socially transformed from bad behaviour into sick behaviour where it is known as medicalisation of deviance and can also be demedicalized. A dual focus of these concepts can affect patient response.

The sociology of emotion is fundamental in exploring the three contrasting effects of brain cancer: feelings, emotional state, and affect during diagnosis and treatment. Feelings refer to the decline of physical drive, for instance, pain, tiredness, and appetite whilst emotional states resemble the non-verbal expressions in the face and body where they could correspond to positive emotions such as happiness, relief, hope, and contentment or are fuelled with negativity such as sadness, fear and anger. Such sentiments are socially constructed with culturally delineated forms of normativity and disciplinarity in demanding life situations and cancer survivorship (Broom and Kenny, 2021; Szot *et al*. 2021; Bell and Ristovski-Slijepcevic, 2011; Steinberg, 2015).

The social ethical order can inflect the resilience of an individual, with responsibility and willpower (Beck and Beck-Gernsheim, 1996; Foucault, 2008; Lemke, 2001; Thornton, 1999). Affect is the evaluation of liking the idea or process, for instance, treatment and other informed decisions (Szot *et al*. 2021).

During the initial phase of diagnosis, most brain cancer patients experience anxiety, depression, and despair after the continuum of worry and sadness (Loughan *et al.,* 2020). It was evidently observed in 48% of the population of malignant brain cancer patients. This highlights the degree of negative emotions that infer the impact of cancer at advanced stages on the patient's psychological well-being. It can further manifest into psychological distress which the National Comprehensive Cancer Network describes as influencing their resilience and unpleasure experience of a cancer diagnosis, its recurrence, and/or hospital stay where anxiety, impatience, distractibility, sleep difficulties, and other psychic symptoms may

arise and are consequently diagnosed as psychiatric disorders (Caponneto *et al*. 2024; Randazzo and Peters, 2016; Riba *et al.,* 2019; Randazzo and Peters, 2016; Ford *et al*., 2012; Dilek *et al.,* 2019; Singer *et al,* 2018; Carlson *et al.,* 2004; Kier *et al.,* 2008; Randazzo *et al.,* 2017).

Other reports have demonstrated how 79% of patients with malignant intracranial tumours experience such negative symptomatology (Fehrenbach *et al.,* 2021). Reduced QoL and therapy adherence can further decrease the success rate and a small fraction receive psychological assistance. This is somatically burdened amongst patients who are of young age (Goebel *et al*. 2019). Besides anxiety syndromes, this could be subjected to somatic symptoms where tachycardia, hypertension, sweating, gastrointestinal disturbance, and muscular vascularity are experienced (Caponneto *et al*., 2024).

Such trajectories largely depend on changing dynamics of survivorship, availability of curative treatments, uncertain prognosis, awareness of the scope and extent of therapy post-diagnosis and phenomenological experiences which draws into classical social theory (Loughan *et al.,* 2020; Fehrenbach *et a*l., 2021). Patients with high percentage of survival focus on disease and commitment to treatment. In contrast, patients with low survival rates experience mild cognitive deficits that negatively affect their ability to partake in daily tasks, loss of independence where they feel they are a burden to social relationships. Further analysis reveal a decline in leisure activities, decrease in cognitive functioning, loss of occupation and contemplating on the illness and its affliction (Mol, 1999; Szot *et al*. 2021; Keir *et al*., 2008; Riba *et al.,* 2019; Randazzo *et al.,* 2017; Ownsworth, 2016; Loughan *et al.,* 2021).

However, the degree of neurocognitive impairment varies by gender and community involvement. It is largely dissonated on the biological factors that are linked with the tumour. For instance, the extent of the malignancy and where the tumour is situated e.g. temporal, insular, or prefrontal, and the underlying lesion of CNS. This influences its treatment modalities where single or combined therapy is applied that can cause psychological factors that comprise mood disorders and the revealing force of unruly emotions and disruption of productivity and survivorship (Lawrie *et al.,*2019; Pertz, Schlegel and Thoma, 2022; McDonald and Genova, 2021; Kendall, 1996, Cassel *et al.* 2016; Broom and Kenny, 2020).

For exemption, coping resources, emotional regulation, metacognitive abilities, and the buffering capacity of social support from family, friends, and other caregivers can positively influence the psychosocial functioning of brain cancer patients (Cobb, 1976; House, Landis and Umberson, 1988; Keyes, 1998; Shah *et al*., 2023). Love, respect, compassion, watching comedy and delving in healthy activities collectively helped to overcome and distract patients from the disease (Shah *et al.,* 2023).

Strong practice of faith and prayer can also alleviate psychological stress and elements of gratitude to the creator. This helps increase courage and peace during such life challenges (Shah *et al.,* 2023). It also emphasizes how sociocognitive functioning can tentatively influence QoL and outcome and the quantity of published literature on psychosocial outcomes of brain cancer patients has significantly increased through broader ontological consequences (Pertz, Schlegel and Thoma, 2022; Boyd *et al.,* 2021; Blackman, 2008; Broom and Kenny, 2020).

Shah *et al.* (2023) performed a qualitative enquiry into the patient-physician relationship and discovered the important of appropriate information and comprehension in patients with high-grade glioma when discussing their care plan and whether surgery should be opted. Participants in their study emphasised on careful selection of wording and a friendly character was needed during consultation. Humility, patience, and compassion upon answering questions and this decreased their anxiety levels and improve their overall wellbeing (Southam-Gerow *et al.*, 2011; Shah *et al*. 2023). However, Besnard *et al.,* (2023) reported that Theory of Mind (ToM) deficits post-treatment for several years in adult patients with primary brain tumours which limits QoL socially and emotionally and follow-up is need to master it.

1.4 Factors that affect brain cancer incidence

This section aims to examine the current research on the important windows of tumour development and interplay of the following factors.

Age

Several reports have discovered that the largest age-standardized incidence rate of neurological cancers in the UK was amongst female and male patients aged 84 years and above, particularly between the range of 85-89 years (Cancer Research UK, n.d.). It is estimated 24% of all new cases of brain tumours in the UK are diagnosed in patients aged 75 years and over. It is the 7th most common cancer amongst female populations with 6,700 new annual cases whereas it is the 11th most common cancer with 6,100 new cases annually in male patients between the years 2017-2019 (Cancer Research UK, n.d.). Though, the incidence rates will be decreased in the UK between the respective year ranges 2023-2025 and 2038-2040. In the latter, it is predicted there would be 13600 new neurological tumours.

A US population study discovered the major histological group of primary brain cancers in children aged 0-14 years (n=14846) was pilocytic astrocytoma with a 17.7% incidence rate. Pilocytic astrocytoma is a WHO Grade I cancer that is slow-growing and localized with an infiltrative pattern (O'Neill *et al.,*2017). Glioblastoma had an incidence rate of 2.6% but

the lowest incidence was found in patients with lymphoma (0.3%) and oligoastrocytic tumours (0.6%) (O'Neill *et al*., 2017).

Lymphoma is a rare brain tumour of haematopoietic origin with large lymph nodes. It is confined to the brain, leptomeninges, eyes, and spinal cord. It is distinctive to other forms of non-Hodgkin lymphoma (Batchelor *et al*., 2017). Oligoastrocytic tumours contain two morphological cell types: neoplastic astrocytes and oligodendrocytes (O'Neill *et al.,* 2017).

However, paediatric patients aged 15-19 years (5863) had a two-fold higher incidence rate for glioblastoma (3%). In this age range, tumours of the pituitary had the highest incidence (23.2%) and lymphoma and oligoastrocytic tumours remain tumours of the lowest incidence (O'Neill *et al.,* 2023).

Tumours of the pituitary remain the highest incidence in young adults aged 20-34 years by the site (30.6%) and histology (28.6%). They are confined in the pituitary gland pictured in Supplementary Material 4. The lowest incidence rates were found in patients with neuroepithelial tumours (0.1%). Simultaneous results were found for patients with intracranial germ cell tumours and lymphoma (1.3%). Germ cells are primordial embryonic cells that develop into sex cells (Alapetite, Yanagisawa, and Nishikawa, 2017). This signifies that brain tumours that develop in young adults differ in children and have a higher incidence. There are 10.4 cases per 100,000 in young adults aged 15-39 years and 7.1 cases per 100,000 for 34-39 years in comparison to 5.26 cases per 100,000 in children aged 0-14 years (Monterroso *et al.,* 2022; Ostrom *et al.,* 2014; Ostrom *et al.,*2020; Shelton *et al*., 2024).

These stimulating outcomes contradict Ostrom *et al.'s* (2020) findings that malignant brain tumours in children are risen from embryonical cell types such as medulloblastoma, whereas young adults predominantly have oligodendroglioma and glioblastoma.

Recent studies by Fitzmaurice *et al.* (2019) on Global Burden Disease (GBD) detected a higher downward trend in the annual brain cancer incidence in male patients aged 0-14 years (0.6%) than in females (0.4%). This is concurrent with the declining rate of mortality of both sexes to 1.4% per year (Ilic and Ilic, 2023). Further results from the GBD detected that the male annual percentage increase in incidence and mortality was 2.5% and 1.7% respectively for patients aged 85 years and above. On the other hand, the female annual incidence and mortality rates rose by 2.5% and 1.5% respectively (Ilic and Ilic, 2023).

Gender

Ilic and Ilic (2023) further reported from the GBD study that in most of the WHO regions there was a marked increase in both sexes, those that identify themselves as female and male, especially in Cuba where the average annual percentage change (AAPC) was 5.7% in males and 5.4% in females. However, an anomalous result was found amongst the male populations in South-East Asia where the AAPC was low (AAPC = −0.1%, 95% CI = −0.1 to

−0.0). In general, mortality rates of brain cancer had an increasing trend in female patients than male patients.

Conversely, both sexes had a significant decrease in mortality rates in the Western Pacific (Ilic and Ilic, 2023). Hormonal, immune, and epigenetic regulation is a possible biological explanation for this result (Sun *et al.,* 2015, Williams *et al.,* 2019; Klein and Flanagan, 2016). In the UK, brain cancer incidence increased for both sexes but the AAPC of female patients was largely noted for liver cancer (3.9%) than brain cancer (1.8%) (Shelton *et al.,* 2024). A plausible reason for the disparities in the West Pacific and the UK could be associated with the inhomogeneous distribution of exogenous and endogenous factors in Western countries and less industrialized countries.

Low physical activity and a high-calorie diet are common risk factors for cancer. There is a high frequency of the female population having visceral obesity rather than subcutaneous adipose tissue. This positively correlates with the development of insulin resistance and diabetes mellitus (T2DM). Researchers have considered these metabolic conditions as the real pandemic of the third millennium more than COVID-19 (Nevola *et al*., 2023).

Moreover, there is an idiosyncratic risk factor between brain and liver cancer which is associated with the levels of androgen and oestrogen hormones. The liver is an oestrogen-sensitive organ with recognised sexual dysmorphism. This increases the modulation of the liver and hormonal actions. Remarkably, oestrogen regulates lipid and glucose metabolism and has protective measures against inflammation and fibrosis.

Comparatively, the risk of liver cancer is estimated to be two to three-fold higher in male than female patients. It is related to the abundance of androgens (testosterone) and lifestyle behaviours that intersect with age. A retrospective analysis of 1110 liver cases where 23.5% were female, discovered a higher proportion of younger male patients developed tumours than female subjects (59.2 vs. 62.5 years, $p < 0.001$) (Rich *et al*., 2020). There was also a higher incidence of early-staged liver tumours in females at diagnosis compared to male patients. This can significantly influence the carcinogenic power to develop liver cancer than brain cancer. It can also impact the effectiveness of surveillance programmes that contribute to the late diagnosis of liver cancer (Nevola *et al.,* 2023).

Region

The age-standardized incidence rates (ASR) for glioma in England were consistent by region between the years 2006 – 2010 (Sehmer *et al*., 2014). There were 435 cases of Grade II to IV in Lancashire and Cumbria where 65% were male patients (281) and 35% were female patients (154). 61% of the study population were within the range of 60-79 years. The ASR was 7.10 per 100,000 (95% CI, 6.47–7.80) whereas the North West region was 7.19 per 100 000 (95% CI, 6.89–7.50) and England collectively at 6.93 per 100 000 (95% CI, 6.82–

7.04) (Sehmer *et al.*, 2014). The variation in cancer incidence within the UK regions is attributed to the socioeconomic status and unbalanced lifestyle that contribute to the prevalence of neurological tumours.

Level of income

Globally, countries with high HDI have the highest brain cancer incidence (Lin *et al.*, 2021). The incidence rate was three-fold higher in Central Europe than in Asia Pacific and the variability is caused by environmental risk factors, particularly exposure to the carcinogenic agent, Gamma radiation (Khazaei *et al.*, 2020; World Health Organisation International Agency for Research on Cancer, 2024). Countries that have similar HDI with varied brain cancer incidence could be explained by differences in the proportion of glioma patients with genetic susceptibilities (Kinnersley *et al.*, 2015).

In contrast, this contradicts Ilic and Ilic (2023) findings where high levels of income negatively correlate with age-standardized rates (ASR) of incidence and mortality of brain cancer. For example, Europe and America have the highest incidence rates than Africa in both sexes. In addition, South-East Asia had a significantly downward trend in brain cancer amongst the male population whilst other regions had a significant rise in both sexes (Ilic and Ilic, 2023).

Recent reports by Cancer Research UK (n.d.) detected similar scores in female patients who resided in England between 2013 and 2017 regardless of the level of deprivation. However, males had *ca*. 8% lower incidence rates in most deprived areas than in the least deprived areas. It is estimated that *ca*. 190 cases in male patients are associated with high levels of deprivation. Thus, there is consistency in reporting cancer-associated pain with lower socio-economic status (AuBuchon *et al.*, 2024). Similar results were indicated in earlier population-based studies between 1996-2013 in England where a deprivation gap was indicated in men (Exarchakou *et al.,* 2018).

Further reports revealed that between the years 2015-2019, 14.8% of cases of brain cancer reside in the least deprived areas whereas 20.1% of people in most deprived locations in England have survived for a minimum of five years or more (Cancer Research UK, n.d.). To date, brain cancer screening is unavailable (Ilic and Ilic, 2023; Schüz *et al*. 2015).

The identification of regions in England that are most deprived is associated with persistence in low income. Before housing costs during the period 2018 to 2022, Yorkshire and the Humber and the East Midlands had the highest percentage rate with 11% (Francis-Devine, 2024). London and South West England had the lowest percentage rate with 7%. However, regarding post-housing costs, there were regional differences where London in addition to Yorkshire and the Humber had the highest rate (14%) whereas, South West England had the lowest percentage score of people with persistence in low income (Francis-Devine, 2024).

Alternatively, in the most recent epidemiological data between 2020 and 2023, the region that had relatively low income before and post-housing costs was West Midlands with a percentage rate of 22% and 27% respectively. This varied with age because the percentage rate in children (30%) was 1.36-fold higher than all residents in England (22%) before housing costs (Francis-Devine, 2024). South East England had the lowest persistence income for children alone (14%) and this was 1.08-fold higher than adults in general with 13% before housing costs (Francis-Devine, 2024). Multiple regions had analogous percentage rates in people in general before housing costs, for example, London and East of England with 14%. Another pair group was North West and Yorkshire and Humber with 20%. North East and East Midlands also had simultaneous results with 18% (Francis-Devine, 2024).

Nonetheless, after housing costs, West Midlands had a higher percentage of children 39% and this was 1.44-fold higher than people in general (27%). East of England was the sole geographical region with persistent low income for children and people in general with 23 and 18% respectively. Parallel results were found in people in general in South East and South West England with 19% (Francis-Devine, 2024).

Amongst the indicators announced by the UK government that are associated with the variability in the regions in England with relative poverty post-housing costs was predominantly lone parenthood (58%) (Francis-Devine, 2024). This was subsequently followed by a fall in household earnings (26%) and a change in tenure (20%). Simultaneous results were found with a transition from a working to a workless household and a fall in benefit income (16%) (Francis-Devine, 2024). Other disadvantages that occur in people living in the most deprived areas are parental conflict where there is a change from couple to single to person household, occupational pension income, and a fall in investment income (10%). The least causal factor for low income was the rise in housing costs by 9% (Francis-Devine, 2024). Other potential roots of deprivation are dependency on drugs, alcohol, poor diet, and other lifestyle factors (Francis-Devine, 2024). This suggests how level of deprivation is associated with poor clinical outcomes.

1.5 Routes of diagnosis

The UK healthcare policy aims to decrease brain cancer incidence rates that vary geographically with referral patterns by creating an inclusive health environment where all patients are treated correspondingly minimizing social inequality. McPhail *et al.*, (2015) emphasized how the cancer stage and survival rates are strongly connected with increased deprivation. To date, brain cancer screening is unavailable, however, Cancer Waiting Times (CWT) standards have been developed by the National Health Service (NHS) to efficiently improve diagnosis and survival rates of neurological cancers (Ilic and Ilic, 2023; Schüz *et al.* 2015; Cancer Research UK, n.d). The time intervals for referral for suspected cancer, diagnosis, and starting treatment and

associated targets vary per different UK nations due to the decentralized nature of UK health policy (Cancer Research UK, n.d.; Office for National Statistics, 2024). Upon diagnosis, there are elevated scores of anxieties and psychological stress in patients and their families especially women under the age of 40 years. However, female patients above the age of 80 years and above are subjected to lower levels of anxiety (Rowlands *et al.,* 2022). A statistically significant difference was discovered in the cause of the worry (p=0.02). There was *ca*. 67% of patient cases reported to be linked to the cancer diagnosis, whereas, other patients (22%) had alternative reasons for worry (Rowland *et al*., 2022).

The NHS England has three respective standards for cancer care: The 28-Day Faster Diagnosis Standard (FDS) was established as part of the NHS Long Term plan in 2015 but was only applied since October 2021 and aims for patients to receive a diagnosis or all-clear within 28 days from urgent referral. Urgent referrals to a cancer specialist or for further investigations are performed by healthcare professionals in primary care, namely, general practitioners (GP), optometrists, or dentists using the FDS and National Institute for Health and Care Excellence (NICE) guidelines (Cancer Research UK, n.d.; Rowlands *et al*., 2022; Yorkshire Cancer Research, 2024). The NICE guidelines were updated in 2015 where instructions and advice are given on prioritizing symptoms for urgent action (Cancer Research UK, n.d.; Rowlands *et al*., 2022; Yorkshire Cancer Research, 2024). For example, suspected leukaemia would need to be referred within several hours or days, alternatively, a radiological examination for suspected lung cancer can be performed within two weeks to determine the stage of cancer. This suggests how thorough the diagnostic procedure and administrative systems aim to improve patient care.

The key objective of the 31-day standard is to initiate treatment within 31 days after consultation with the patient. During the meeting, results are explained, and a point of decision-making on whether cancer treatment should be pursued; this is known as the 'clock start' moment (Cancer Research UK, n.d; Yorkshire Cancer Research, 2024). An agreed course of treatment plan commonly involves a multidisciplinary team (MDT) where chemotherapy, radiotherapy, surgery, active monitoring, or palliative care are planned depending on the stage and grade of cancer. Specialised tests are accessible in larger hospitals which may increase the length of time for the referral to be executed and this pauses or stops the clock in certain regions.

The 62-day standards consist of treating patients within 62 days from an urgent referral but vary per UK nation (Cancer Research UK, n.d.). In England, Scotland, and Northern Ireland, the clock starts when the cancer referral is received whereas in Wales it is perceived as the point of suspicion (Cancer Research UK, n.d.; Yorkshire Cancer Research, 2024). The clock stops for both 31-day and 62-day CWT when the patient initiates

their treatment. This helps decrease variation in referral patterns, lower social inequalities and improve clinical outcomes (Rachet *et al*., 2020).

Similarities with other UK nations have a general standard and set its targets for compliance with the 31 and 62 days from cancer referral to 'decision to treat'. The percentage number of patients waiting more than 31 days has increased over the 12 years in England, Northern Ireland, and Scotland (Office for National Statistics, 2024). Records from the past five years indicate Wales have broadly increased. However, the percentage of patients waiting more than 62 days to initiate treatment has relatively increased during the coronavirus (COVID-19) pandemic due to lockdown since March 2021 (Office for National Statistics, 2024). The highest target rate achieved for the 31-day standard was 96% and 95% in England and Scotland respectively. In contrast, Northern Ireland has surpassed this rate with 98%. Previously, there was no 31-day CWT in Wales before changes were made in 2019 and data are not publicly available (Office for National Statistics, 2024).

Conversely, there have been recent reports that the number of patient cases awaiting their initial consultant-led appointment following their GP referral in Northern Ireland has risen from 210,738 in June 2023 to 230,530 in June 2024 (Factcheck NI, 2024). The 9.4% increase is reflective of the Northern, Southern, and Western trusts in Northern Ireland whereas, Belfast and South Eastern Trust has been exempt. These alarming statistics are proportionately much higher than other UK nations and verified by the Department of Health and the Northern Ireland Statistics and Research Agency (NISRA). In defense, the Department of Health explained that the incomplete evaluation of Belfast and South Eastern Trust is caused by considerable challenges faced when collating information during the staggered moments of its new electronic records system (FactcheckNI, 2024). This highlights the critical need to improve the management of risks and the healthcare system nationally which is governed by sophisticated technologies that terrain patient care and systems of social control. Metaphorically, Foucault's concept of panopticon surveillance within healthcare is a replicable apparatus of power, knowledge, and disciplinary function to improve performance in public health (Dillard-Wright, 2019).

Moreover, despite its impact and robust standardized methods, the FDS is not the fundamental target in how timely diagnosis is discussed. Before the use of FDS, Yorkshire Cancer Research (2024) revealed that 83.2% and 68% of patients who reside in Yorkshire and Leeds respectively are seen by a specialist within two weeks with suspected malignancy where the former rate surpassed the percentage number of people in all of England (75.6%). The two-week cancer pathway is a well-established mechanism that aims to shorten the referral time for cancer diagnosis and treatment (Sheridan *et al.,* 2019). Alternatively, it remains below the national target of 93% since May 2020 partially due to

the COVID-19 pandemic (National Health Service, 2000).

Upon the application of the 28-day target for suspected cancer or cancer screening, there was significant improvement in the clinical outcomes allowing innovative diagnostic techniques to improve time efficiency and to tackle long waiting lists. This minimizes delay in diagnosis in patients with visible symptoms that could indicate an underlying neoplasia. It is estimated that more than 90% of urgent referrals have an all-clear diagnosis (National Health Service, 2000).

Furthermore, there are challenges made in case recognition and only 1% of brain tumours go through the NHS Cancer Plan – a two-week wait pathway and are then urgently seen by emergency doctors and neurologists with symptoms of focal deficits or seizure presentations are referred early. On the other hand, clinical presentations of headache, cognition, fluctuations in personality traits, or visual symptoms are difficult to identify to be referred which is the prominent reason for delayed diagnosis when performed individually (National Cancer Research Institute, 2023).

Nevertheless, when more than one symptom appears especially in combination, it increases the likelihood of detecting brain tumours (National Cancer Research Institute, 2023). It is advised as part of the NICE guidelines to observe for papilloedema which is the swelling of the optic disc when chronic headaches are suspected. Other disciplines such as optometrists have been trained to identify field defects and other examination findings and when to refer for papilloedema. For example, radiological examination using Magnetic Resonance Imaging (MRI) is directly accessible in secondary care services i.e. hospitals (National Cancer Research Institute, 2023). Waiting and reporting times are also increasing which further adds pressure on meeting the target.

A qualitative study was conducted in England where 2000 people and then 1825 were later interviewed but responses of 385 adults who were referred or expected to be referred were analysed. From the sample population, 334 people responded and 45% were not referred for suspected cancer in their appointment (Healthwatch, 2023). One in four (28%) waited for a month before they were referred for their first appointment. One in six (16%) waited more than a month. One in seven (14%) are still pending a confirmation appointment for a referral for more than a month (Healthwatch, 2023). This presents the diverse statuses of urgent referrals and among the explanations for these results are projected, hospital appointments were not booked, lost, stalled, or rejected (Healthwatch, 2023).

Further reports by the Official NHS data presented a high proportion of people not attending their first hospital appointment since May 2021; the target to start their first treatment within two months was missed before December 2015. Thus, this suggests that referral for suspected cancer was delayed before the COVID-19 pandemic. There are

other reasons in the bigger picture where the psychological well-being and response of the patient varies.

Furthermore, other explanations for referral delay were the GP wanting to try alternative treatment and medications initially, patients expressing how the appointment was too rushed, miscommunication between NHS teams, poor administrative systems, and a lack of specialized knowledge in primary care especially on the signs and symptoms of cancer (Healthwatch, 2023). Alternative routes for referral were also explored by every three in four patients who changed their GP, hospital, NHS 111, Accident and Emergency (A and E) out of hours, and pharmacy (Healthwatch, 2023).

Another study by Sheridan *et al*. (2019) was performed at Leeds NHS Trust Hospital, a tertiary cancer care setting in a large city composed of people from different socioeconomic statuses and ethnic groups. The researchers discovered that 5.2% of patients (n=5673) did not attend their appointments and 68.6% (n=3893) were scheduled for outpatient appointments. It is largely predicted by socio-demographic factors: young (18-29 years) and older (above the age of 85 years) male patients with greater deprivation who live far away from the hospital with a mean distance of 8.1 km. They also have a suspected cancer site and had an earlier year referral, collectively, these factors mainly contribute to diagnosis than practice factors, for instance, low detected rate of cancer, lower cancer conversion rate, and lower Quality and Outcomes Framework score (Sheridan *et al*., 2019). 9.6% of patients (n=10360) were diagnosed within six months of referral where 9.8% of the proportion of patients attended their appointment and 5.6% of patients were classified as non-attending patients. This affected the risk of mortality rate where those who attended had 19.2% early mortality outcomes whereas, those who did not attend had 31.3%. Additional results suggested 19.6% of patients were deceased within 12 months of diagnosis. This contradicts Rowlands *et al*., (2022) findings which proclaimed that female was suspected to have more psychological stress than male patients.

The prominent reasons for non-attendance were cancellation (40.6%), did not attend (31.4%), or a combination of both reasons (14.9%). Similar to findings by Healthwatch (2023), some patients were seeking private healthcare or were seen at another hospital (1.2%; n=1267). This was anecdotally observed in other trusts and contributed to the NHS financial crisis where there was a waste of resources, services, and screening (Ellis *et al*., 2017; Williamson *et al*., 2017; Campbell *et al*., 2015). This emphasizes that the NHS should not be penalized for delayed diagnosis. The 93% national standard is affected by combinatorial factors such as non-attendance of symptomatic patients in both sexes (NHS England, 2018a; Sheridan *et al.,* 2019).

Amongst the recommendations suggested by Healthwatch (2023) is for the UK Government, NHS England, and Integrated Care Systems

(ICS) to support GPs and hospitals with timely referral processes through training and patient assurance through communication and understanding. Involving the patients in appointment selection and their ability to access information about their health status through online referral trackers will help alleviate this clinical concern of attendance behaviour because initial absence can cumulatively lead to early disease progression and poor survival rates.

2. THE AIM, OBJECTIVES AND RESEARCH QUESTIONS

The aim of this research paper is to assess the sociodemographic factors that influence brain cancer incidence and is divided into three phases. The first phase is a review the national brain cancer cases per type of tumour: malignant, non-malignant, benign endocrine and non-benign endocrine tumours between years: 2013 to 2020. Non-malignant brain tumours have a benign nature but still contribute to the mortality rate due to the cancer sites and histology in the cranial cavity (Shelton *et al*., 2024).

The subsequent phase involves evaluating factors that influence the prevalence of non-malignant and malignant brain tumours per region, age, and gender across England United Kingdom. This was then extended to explore the variability of the incidence rates in routes of diagnosis. The nature of this epidemiological study will provide a sociological explanation of cancer and help to further improve and shape clinical and organisational practice in primary and secondary care settings and the burgeoning field of cancer research.

3. METHODS

3.1 Study design

The descriptive epidemiology observational study aims to analyze the cancer incidence of patients with Brain, meningeal, and other primary Central Nervous Systems (CNS). The data was retrieved from the National Health Service (NHS) Get Data Out database of patients diagnosed with neurological tumours between the years 2013 and 2020. They are residents in England, United Kingdom, and registered with a general practitioner (GP) (Vernon, 2023; National Disease Registration Service, n.d; Shelton *et al.*, 2024). The year 2013 was when the National Cancer Registration and Analysis Service (NCRAS) initially collated data in a single system with high quality, precision, and consistency (National Disease Registration Service, n.d). It integrates clinically relevant data on patient sociodemographic factors: age at index referral, gender, region, deprivation, year of diagnosis and publishes information on incidence, routes of diagnosis, treatment regimens and survival rates after diagnosis at 3, 6, 9, 12, 24, 36, 48, 60, 72, 84 and 96 months with upper and lower confidence interval limits at 95% (Sheridan *et al.*, 2019; Vernon, 2023; National Disease Registration Service, n.d; Cancer Research UK, 2014).

Eligible patients with a specific type of cancer and the same characteristics were recruited

into small patient groups that have an estimated 100 patients. There are four main types of cancers established in the data and are dependent on their tumour malignancy status: malignant, non-malignant, benign endocrine, and non-benign endocrine tumours (Ilić and Ilić, 2023; Fehrenbach *et al*. 2021). The study participants in the cohort had either brain, meninges, or endocrine glands within the brain (pituitary gland, craniopharyngeal gland, and pineal gland) (Vernon, 2023; National Disease Registration Service, n.d). It does not include secondary brain tumours, lymphomas of the brain, or bone tumours of the skull (Vernon, 2023; National Disease Registration Service, n.d) The International Classification of Disease (ICD)-10 codes were used to classify the type and site of the cancer diagnosis: malignant brain tumour (C700, C700, C709-C729), non-benign endocrine (C751-C753, D443-D445), non-malignant brain tumour (D320, D321, D329-D334, D337, D339, D420-D421, D429-D434, D437, D439), benign endocrine (D352-D354). The behavioural changes of the brain tumour were coded in ICD-O-2 (National Disease Registration Service, n.d).

The initial comparative study focused on cancer incidence per type of tumour between 2013 and 2020. Further exploratory analysis aimed to discuss whether age was a potential factor in causing brain cancer over time. The age group varied per patient group – please see Table 1. A comprehensive examination of cancer incidence was conducted on malignant and non-malignant groups where patients aged 0-19 years and 70+ age group at two specific year periods 2013 and 2021 were analyzed based on gender, region, age, and routes of diagnosis on cancer incidence. Non-malignant brain cancer patients were integrated because the cancer sites in the cranial cavity can increase mortality rates (Shelton *et al.,* 2024; Ilić and Ilić, 2023). This would help improve the primary outcomes for cancer patients with better diagnosis, and treatment and induce policy changes.

The sex of the groups and regions were reported at the time of their diagnosis. There were four regions: North of England, South of England, Midlands and East of England, and London. The main routes of diagnosis (Two-week wait, GP referral, another outer patient, inpatient elective, emergency presentation) were analyzed to determine how the sequence of interaction between brain cancer patients and the NHS is set for diagnosis and referral route to secondary care (Shelton *et al*., 2024).

Table 1: The age of the patients in the Cohort collected by the NHS (Vernon, 2023)

Age groups (in years) per type of tumour		
Malignant brain	**Non-malignant brain**	**Benign endocrine**
0-4	**0-19**	**0-39**
5-9	**20-29**	**40-49**
10-19	**30-49**	**50-59**
20-29	**50-69**	**60-69**
30-49	**70+**	**70+**
50-69		
70+		

Statistical analysis

Data was analyzed using the Minitab Version 22.1 (64-bit) 2024 software. A generalized linear regression model with Poisson link function was performed to assess the trend of brain cancer incidence between the years 2013 to 2020 for malignant, non-malignant, and benign endocrine tumours because overdispersion can commonly occur in modeling rates and count (Shelton *et al.,* 2019). Residual plots were constructed as a standard measure for assessing the model fit. Graphical presentation using time-series plots and bar charts was applied to visually interpret the data.

The 95% confidence interval (95% CI) was applied. Confidence intervals are expressed as a percentage to determine the reliability of the estimate and whether there is a significant difference between two types of cancers or periods (UK Government, n.d.; Cancer Research UK, 2014). An overlap between the range of two sets of confidence intervals suggests there is a significant difference (Cancer Research UK, 2014).

The 95% confidence interval is presented as brackets (lower confidence interval – upper confidence interval). This refers that one is assured that 95 out of 100 times the estimate will fall between these values specified by the confidence interval. It is a measure of precision – the narrower the confidence interval, the more precise. It also holds clinical significance when making informed decisions.

The cancer incidence rate was calculated by dividing the incidence value which refers to the number of newly diagnosed cancer cases by the population. The outcome is then multiplied by 100,000 to obtain population by year. Chi-squared was applied for bivariate analysis for the brain cancer incidence of patients aged 0-19 years on two variables: year and type of tumour to determine whether there is an association and decide whether to accept or reject the null hypothesis.

Further exploratory analysis was graphically presented using bar charts, residual plots, pie charts, and heat maps to visually determine the association between factors.

Two-way ANOVA was applied for multivariate analysis to determine their association between year and individual factors: age, gender, region, and type of tumour influence brain cancer incidence and routes of diagnosis to determine whether there is a significant difference. A p-value that is less than 0.05 ($p < 0.05$) is considered statistically significant (Sheridan *et al.*, 2019).

Ethical considerations

Sociodemographic and clinical data was collected by the NHS after patient informed consent (Fehrenbach *et al.*, 2021; National Disease Registration Service, n.d). The data is quality assured by the National Cancer Registration and Analysis Service, part of NHS England (NHSE) (National Disease Registration Service, n.d). The data was publicly available to utilize for educational and research purposes. Ethnicity, type, and stage of cancer were not among the indicated variables to maintain patient confidentiality in line with Caldicott's principles.

Analysis was further supported by the NHS's Open Government Licence and sections 254(1) and 254(6) of the Health and Social Care Act 2012 and UK Policy Framework for Health and Social Care Research (National Disease Registration Service, n.d; Shelton *et al.*, 2024). The anonymity of the patients was maintained by grouping patients to lower the risks of patient confidentiality. Further steps were applied where data for all endocrine tumours of the brain for a particular year or routes of diagnosis for all genders were also not publicly available (National Disease Registration Service, n.d).

4. RESULTS

There are two fundamental objectives for this epidemiological study: to explore the effect of the sociodemographic factors on brain, meningeal, and other primary CNS tumours incidence and routes to diagnosis across England primarily: age, region, gender and whether this varies by year of diagnosis and type of brain tumour. The latest recorded data in the Get Data Out database was published by the National Health Service in 2020 (Vernon, 2023). There were 9,247 new cases of brain cancer identified from a population of 56,550,138 in England. The incidence rate (IR) was calculated to be 16.35 per 100,000 people. In descending order, 4585 patients were diagnosed with malignant brain tumours (IR, 8.12), 3866 for non-malignant tumours (IR, 6.84), 640 for benign endocrine tumours (IR, 1.13), and 156 for non-benign endocrine tumours (IR, 0.28).

4.1 An overview of the brain cancer incidence across England between 2013-2020.

The initial investigation was to explore the general trend of brain cancer incidence. Figure 1 presents a graphical presentation of the number of new patient cases diagnosed with brain cancer across England in 2013-2020 for both sexes combined. The minimal incidence of

brain cancer affected 9,247 patients (2020) and the maximum incidence is 10,738 patients (2017). There was a steady increase from 2013 to 2014 in the number of patients diagnosed with brain cancer, however, between 2014 (n=10,006) and 2017 (n=10,738), there was a substantial rise of 7.32%. This was followed by a declining trend post-2017 where in 2018, the number of patients observed decreased to 10,466. The largest percentage change was indicated between 2019 (n= 10,441) and 2020 (n= 9,247) where there was an 11.44% deduction. This is reflected in the incidence rates listed in Table 2 alongside their respective 95% upper and lower confidence levels (CI). The highest brain cancer incidence was indicated in 2016 (0.019). In 2016, the lower and upper confidence intervals for the brain cancer incidence rate per 100,000 were 18.61 and 19.34 respectively; this is a 0.73 difference. In contrast, the lowest cancer incidence was observed in 2020 (0.016).

In 2020, the lower and upper confidence level was 18.195-18.91; this is a 0.72 difference. Associatively, there is a 95% confidence level that this interval refers to greater certainty in the estimate and will contain the true population proportion. A large number of cancer patients being diagnosed and those who could not make it (mortality), the random variability is seemingly probable to be narrow. This is 18.88 and 16.35 per 100,000 in 2016 and 2020 respectively. The negative skewness value (-1.39) indicates a left-skewed distribution where there is an extension towards more negative values (Bobbitt, 2022). The kurtosis value (2.17) suggests a platykurtic thin-tailed, uniform distribution and low frequency of outliers (Turney, 2024).

Figure 1: A time series plot presenting the brain cancer incidence across England between years 2013-2020.

These data were obtained from Get Data Out from the National Health Service.

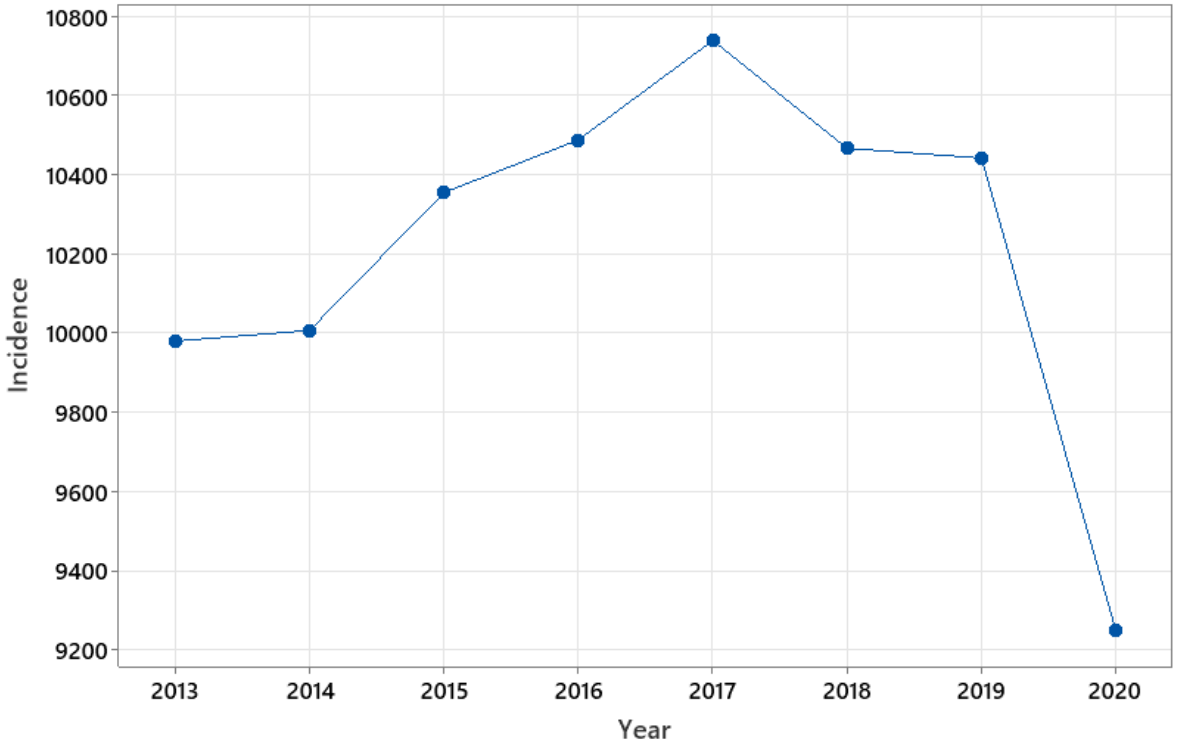


Table 2: Annual brain cancer incidence rates between 2013-2020 across England.

This data is from The Get Data Out from the National Health Service. It corresponds to all sexes, ages, level of deprivation, types of tumour and regions.

Year	Brain Cancer incidence (Incidence/Population)	Brain cancer Incidence rate per 100,000 (95% CI)
2013	0.0185	18.53 (18.16-18.89)
2014	0.0184	18.42 (18.06-18.79)
2015	0.0189	18.899 (18.54-19.27)
2016	0.01898	18.98 (18.61-19.34)
2017	0.0193	19.31 (18.94-19.68)
2018	0.0187	18.697 (18.34-19.06)
2019	0.0186	18.55 (18.195-18.91)
2020	0.0164	16.35 (16.02-16.69)

4.2 Distribution of cases by types of brain tumours

For a more comprehensive analysis, the incidence rates per type of tumour were explored across England between the years 2013-2020 as presented in Figure 2, the lowest incidence rate was relatively stable for benign endocrine tumours over the years. The increase in incidence rate was predominantly driven by patients with malignant brain tumours than other tumour types. The trend analysis does not show a decreasing trend in non-malignant tumours, benign and non-benign endocrine tumours, rather there was decrease in all three types in year 2020 only.

The highest incidence rate for malignant melanoma was found in 2015 with 8.87 per 100,000 people (95% CI =8.62 – 9.12). In contrast, the highest incidence rate for non-malignant melanoma was found in 2017 with 8.41 per 100,000 people (95% CI =8.17 – 8.66). The peak incidence rates for benign and non-benign endocrine tumours were significantly lower in the cohort, at 1.89 and 0.39 per 100,000 people in 2014 and 2013, respectively.

The Two-way analysis of variance (ANOVA) results determined the interaction between the two independent variables, year, and type of tumour and whether they affect the continuous dependent variable (brain cancer incidence) (Bevans, 2023; Bobbitt, 2021; Minitab Support, 2024).

The F-test compares the variance in each group to the overall variance in the

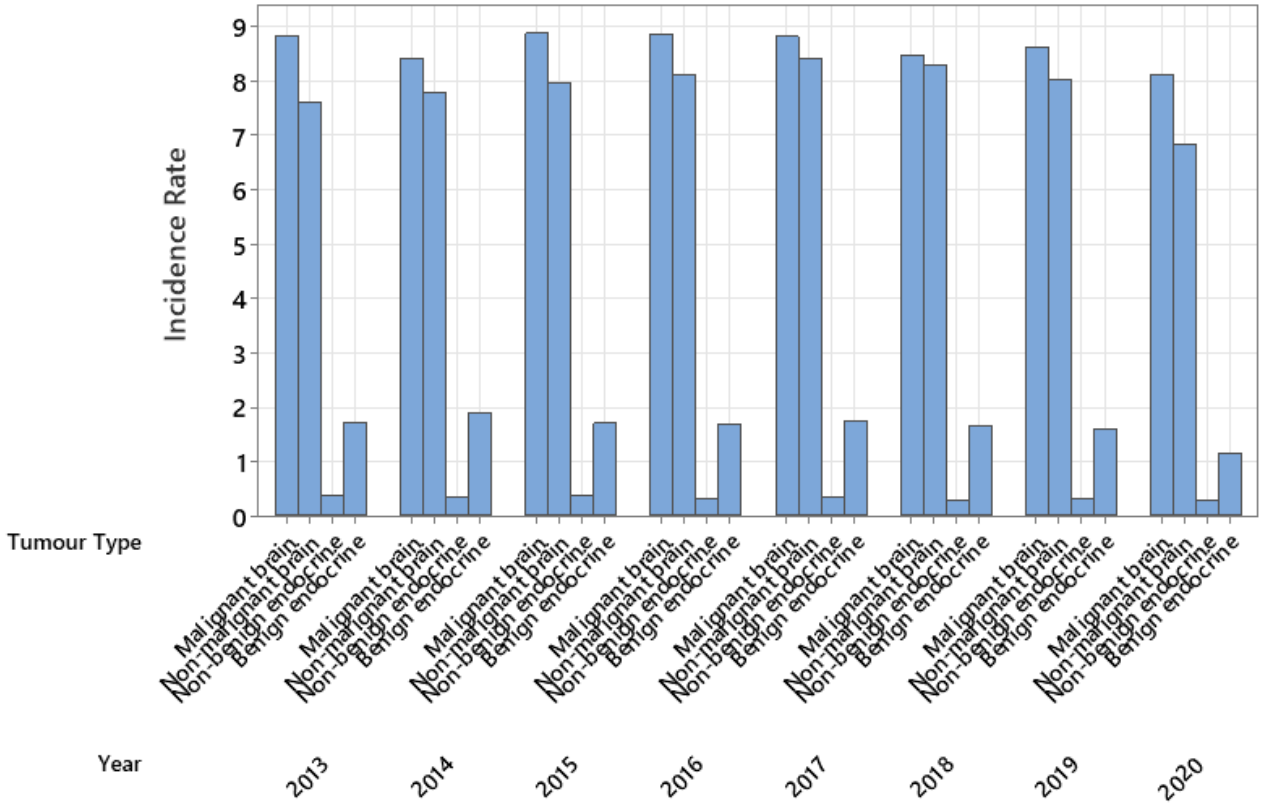
dependent variable. A higher F value suggest there is a higher chance that differences observed is real and independent from chance (Bevans, 2023). The year ($F(7) = 3.65$, $p = 0.010$) and type of tumour ($F(3) = 2563.37$, $p = 0.000$) present there is significant difference in brain cancer incidence.

In spite of this, the interaction between these subject factors (year and type of tumour) is not significant.

The high predicted R^2 (99.37%) indicates that the model forms precise predictions for new observations due to the sample size (Minitab Support, 2024).

Figure 2: The incidence rate of patients diagnosed with brain cancer across England between years 2013-2020.

This data is from The Get Out Data from the National Health Service. It corresponds to the trends of incidence for four classes of brain cancer: malignant tumour, non-malignant tumour, non-benign endocrine and benign endocrine tumours across all genders and regions in England, United Kingdom.



4.3 The effect of age incidence on type of brain tumour

The following analysis explored age as a potential risk factor per type of tumour: malignant, non-malignant, and benign endocrine tumours. All patients aged 0 to 70+ living in regions in England and were diagnosed and histologically confirmed between 2013 and 2020 were ascertained.

Age and malignant tumours

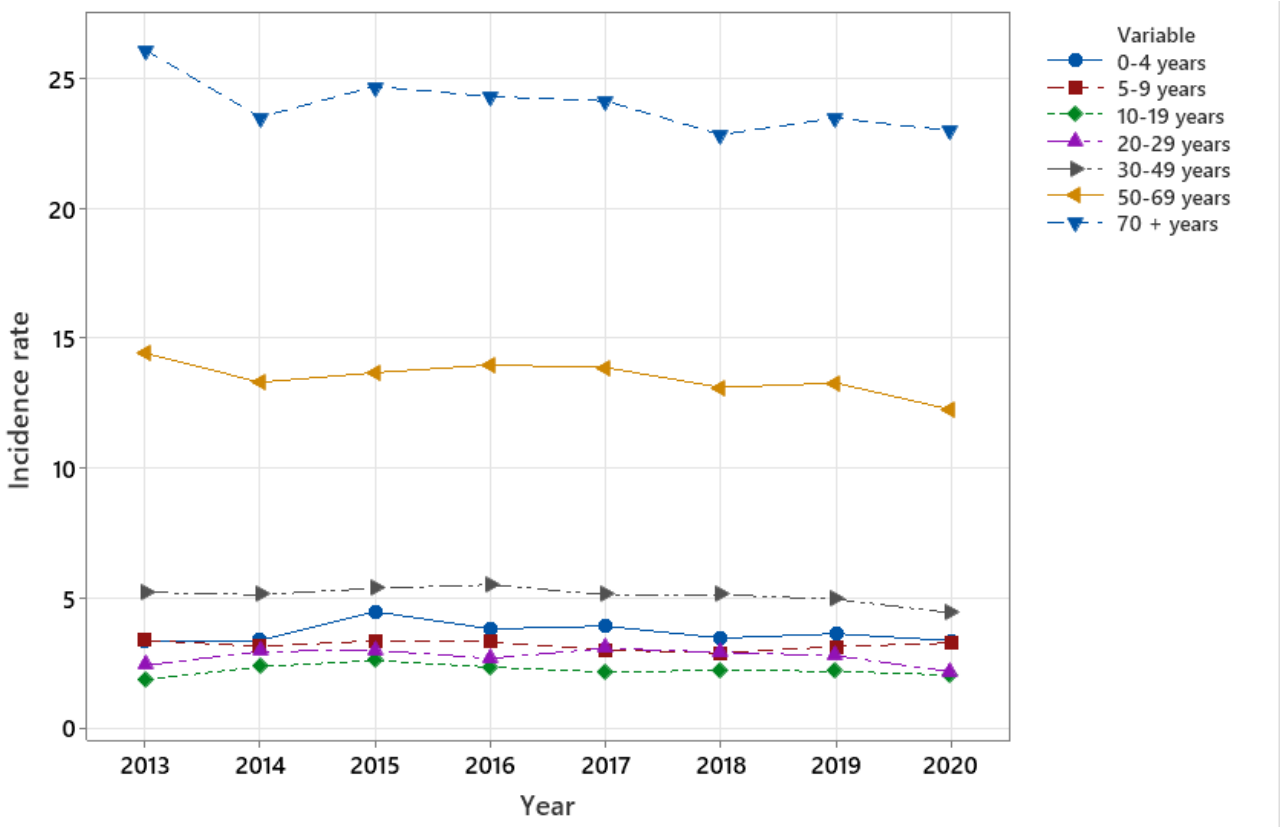
Approximately a quarter of patients diagnosed with malignant brain cancer were aged 70 years and older with an annual incidence rate within the range of 16.893 to 35.063 per 100,000. The age group with the least potential risk for malignant brain tumours was aged between 10 – 19 years with an annual incidence rate within the range of 1.84 and 2.58 per 100,000 as presented in Figure 3. There has been a slight reduction in the yearly incidence rate reported in 2014 for patients aged 50 to 69 and 70+ years, whereas, there was minimal growth in the annual incidence rate for patients aged 0-4 years till 10-19 years. In contrast, there was a steady incidence rate for patients aged 30-49 years from 2013-2020.

In 2018, there was another declining trend in the incidence rates for patients with malignant brain tumours in two respective age groups: 50-69 years and 70 and above years. Patients aged 50-69 years decreased from 0.014 (1836 cases; 95% CI =13.22 - 14.495) in 2017 to 0.013 (1747 cases; 95% CI =12.47-13.71) in 2018. This is 13.85 to 13.08 per 100,000 people in all of England. The lower and upper confidence interval differences are > 1 but < 2 in both cases. This modest wide interval is subject to probable causal factors of variability. Possible uncertainties have risen: the period or when the cancer diagnosis took place, when a death about cancer, and data sent to the NRDS. There is a 95% confidence level that this interval may not fully contain the true population proportion (Centre for Disease Control, 2025).

Further decline of incidence was found in patients aged 70 years and above with malignant brain cancer. There was a 1.295% difference in the incidence rates, in 2017, it was 0.024 (1721 cases; 95% CI =22.98-25.27), and in 2018, it was 0.023 (1678 cases; 95% CI =21.73 – 23.93). This was 24.10 and 22.81 per 100,000 people correspondingly. The differences between the lower and upper limits are between two and three. A slight downward trend was indicated in patients aged 0 – 4 years. Minimal changes were observed in the remaining age groups within the cohort.

Figure 3: The annual age incidence rates per 100,000 with 95% confidence intervals of malignant brain tumours between years 2013-2020.

These data were obtained from Get Data Out from the National Health Service.



The data for age versus malignant brain cancer incidence follows the Poisson distribution because the residual plots fall closely along the line (Minitab, 2024b). There was no significant change in the trend in rates of malignant brain cancer incidence with year as the regression variable (0.893; $p > 0.05$).

Contrarywise, there was substantial difference with age where patients aged 20-29, 30-39, 50-69, and 70+ years (0.000; $p < 0.05$) had more significance than patients aged 5 to 9 years (0.005; $p < 0.05$) and 10 to 19 years (0.007; $p < 0.05$). The continuous predictor was year and the categorical data was age and this suggests the continuous predictor is not significant and the coefficient for the predictor is similar to zero. However, the categorical predictor was significant which emphasizes not all events have the same mean number of events at the statistically significant level (0.05). This may indicate changes in the response variables.

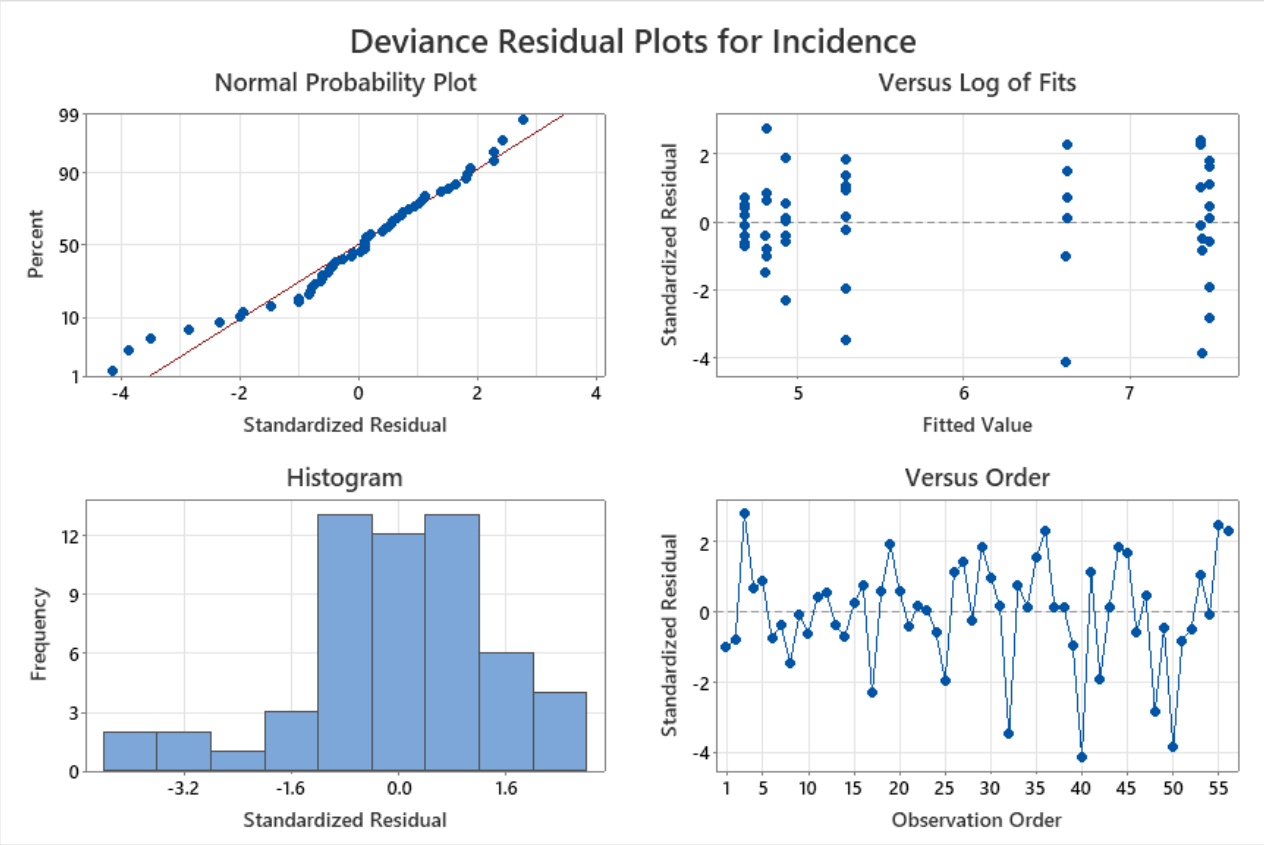
The coefficient and number of events depend on the link function, and reference levels of categorical predictors. A positive coefficient was shown for patients aged 10-19 (0.1186 ± 0.0438), 20-29 years (0.4814 ± 0.0405), 39-49 years (1.8049 ± 0.0344), 50-69 years (2.6660 ± 0.0330) and 70+ (2.6145 ± 0.0330) and this may indicate an even more likely cost at the level of predictor rather than the reference level of the factor. A negative coefficient was shown in 5 to 9 years (-0.1311 ± 0.0466) and year (-0.00030 ± 0.00223) where events are less likely to occur. The estimated coefficient near zero suggests the effect of the predicted term is small or non-existent. The higher coefficient is associated with lower response values (Minitab Support, 2024c).

The goodness-of-fit tests determine whether there is a deviation between the predicted number of events and the observed number of events. The goodness of fit data for malignant melanoma is 0.000, and the usual significance level is 0.05. It helps assess how well the model fits the data. The smaller the value, the better the interaction (Minitab Support, 2024c).

The overall goodness of the data is based on the R squared value (99.73%). The Akaike's Information Criterion (AIC), corrected Akaike's Information Criterion (AICc), and the Bayesian Information Criterion (BIC) assess the relative quality of the data that fits the model. AICc performs better than AIC when the sample is small. To yield a better model, the AICc and BIC add a penalty by adding terms to prevent overfitting of the model to data (Minitab Support, 2024d). The Akaike's Information Criterion (AIC) value for age versus malignant brain tumour is 553.09. The corrected Akaike's Information Criterion (AICc) is 556.15. The Bayesian Information Criterion (BIC) is 569.29.

There are four deviance residual plots for incidence presented in Figure 4 related to malignant brain cancer to assess adequacy: normal probability, versus log of fits, histograms, and versus order. The Normal Probability Plot presents a straight line where most points are presented on the line or in proximity and reflects the normal distribution of error. A slight bell-shaped curve was observed in the histogram which reflects the skewness and number of outliers. There is no evidence of non- constant variance in the log of fits for standard Poisson regression. Residual versus order plot drives in a random pattern where there is no evidence of fitting the data adequately (Abbasi and Husseinlou, 2019).

Figure 4 Residual plots for malignant brain tumours.

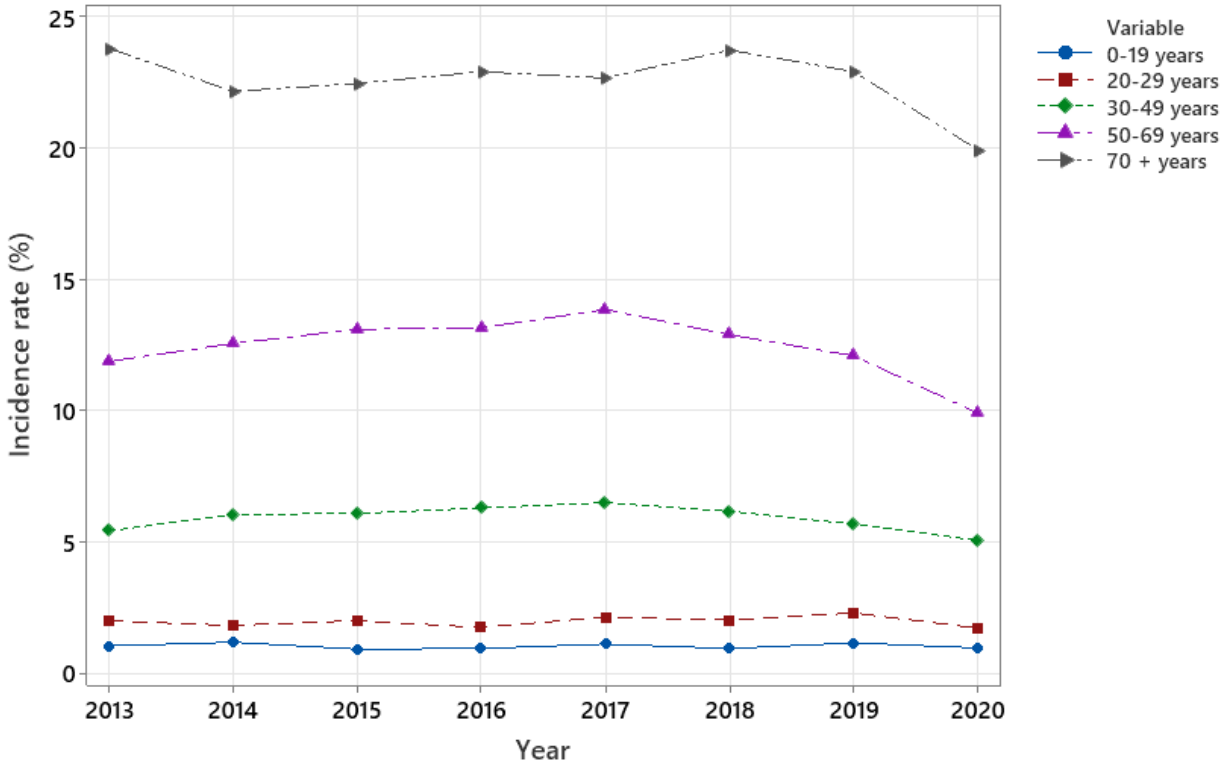


Age and Non-malignant tumours

Simultaneous results were found for the effect of age on the incidence attributed for non-malignant brain cancer indicated in Figure 5. Patients aged 70 and over had the highest annual incidence rate ranging from 0.016 to 0.029%. In descending order, 50-69 years (0.0799 – 0.016%), 30 to 49 years (0.037 – 0.078%), 20-29 years (0.017 – 0.023%) and 0 to 19 years (0.009 – 0.012%). Thus, the lowest age non-malignant brain cancer was between 0 to 19 years.

Figure 5: The annual age incidence rates with 95% confidence intervals of non- malignant brain tumours between years 2013-2020.

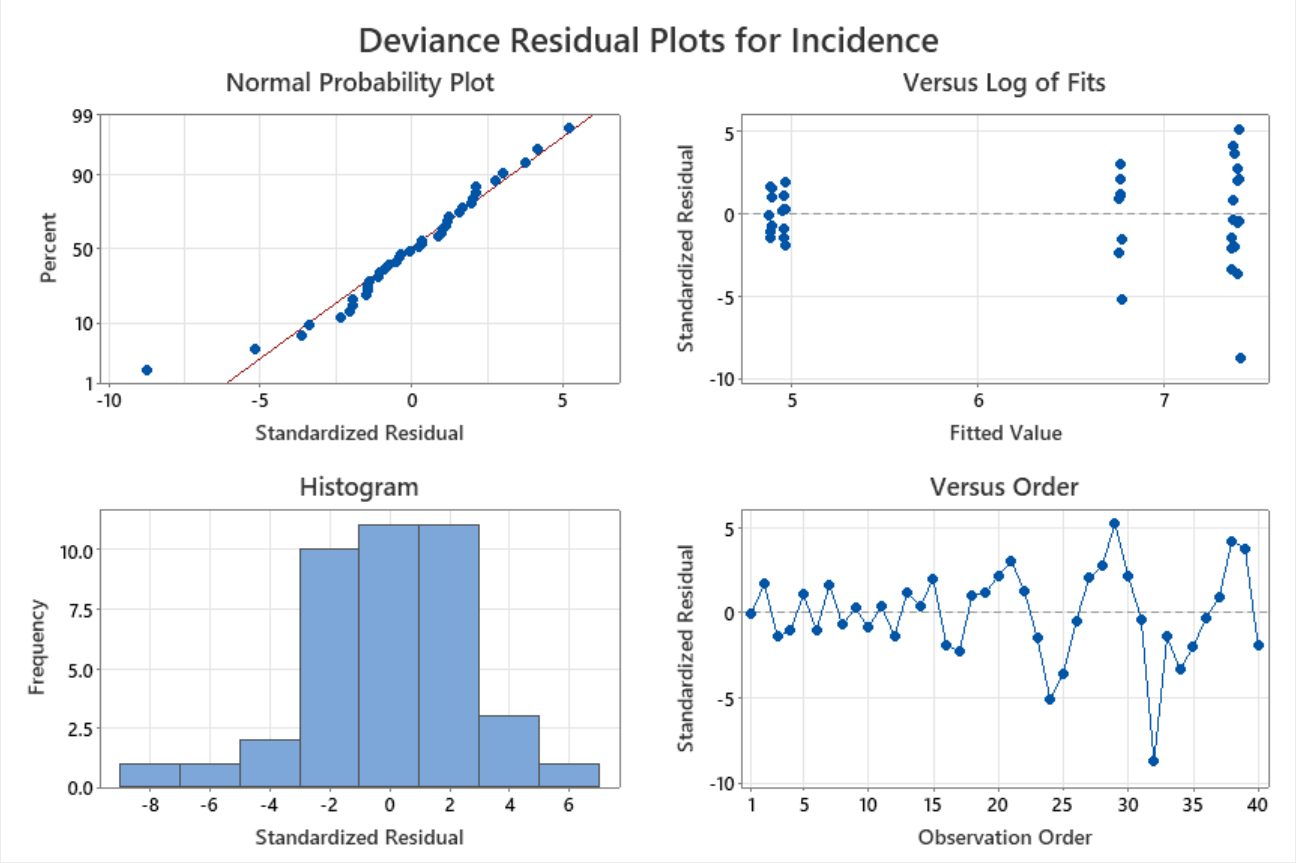
These data were obtained from Get Out Data from the National Health Service.



The regression analysis linked with the Poisson function presents no significant variation between the independent variable age and the incidence rate (p-value < 0.287). This was also apparent for patients aged 20-29 (0.092; p > 0.05). However, there was a significant difference for patients aged 30-49 years, 50 – 69 years, and 70 years and above (0.000; p < 0.05). The AIC value (551.02), AICc (553.57), and BIC (561.15) present less interaction effect. The Goodness-of-Fit test indicated a deviance value of 0.0000 (Minitab Support, 2024d).

The residual plots for non-malignant tumour incidence are illustrated in Figure 6. The normal probability plot is more clustered and *ca*. 99% of the data points are on a straight line more than what was observed in the normal probability plot for malignant tumours shown in Figure 4. There is less scattering of data points in the Versus Log of Fits and they are around zero. The histogram has a bell-shaped distribution and the versus order plot shows fluctuation (Minitab Support, 2024d).

Figure 6: The residual plots for non-malignant tumours.



Age and Benign endocrine tumours.

There is consensual agreement that the age group that are at most risk of brain tumour are patients aged 70 years and above. On the other hand, the age group that are at least risk vary based on type of tumour where patients aged between 0 to 39 years have the lowest incidence for benign endocrine cancers between years 2013 and 2020. There is an overlapping trend between the variables presented in Figure 7 for patients with benign endocrine tumours rather than a clear relationship that was presented in malignant and non-malignant tumours. For instance, in 2014, the cancer incidence rate for benign endocrine tumour for patients aged 60 to 69 years was 0.038 (225; 95% CI =3.34-4.35%) and this is higher than those aged 70 years and above in the same year, 0.035 (228; 95% CI =3.04-3.96%). As an expression of a population of 100,000 people, this is 3.82 and 3.47 respectively.

Though, in 2015, an opposing effect took place where the incidence rates for patients aged 70 and above per 100,000 people, 3.36

(225; 95% CI =2.94 – 3.83%) surpassed the incidence rates for patients aged 60 – 69 years with 3.21 (190; 95% CI =2.7 7– 3.699%) and other age groups 50-59 years with 2.43 (172; 95% CI =2.077-2.82%) and 40-49 years with 1.95 (147; 95% CI =1.65-2.296).

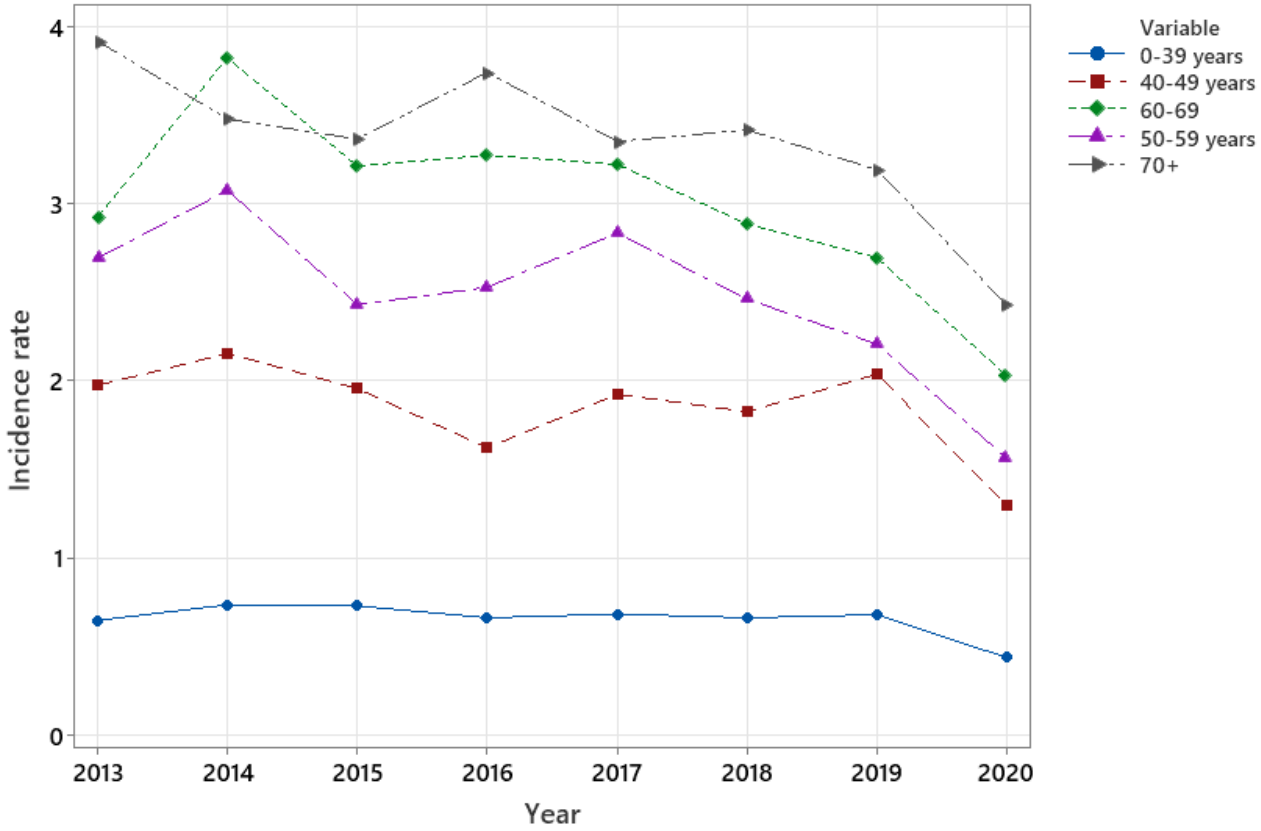
In 2017, another contrasting result took place where the brain cancer incidence decreased for both age groups 70 and above (239 cases) and 60 to 69 years (189 cases). This is 3.35 (95% CI =2.94-3.8) and 3.22 (95% CI =2.78-3.71) per 100,000 people. Alternatively, the rise in incidence was predominantly driven by patients aged 50-59 years with 0.0028 (209 cases), and those aged 40-49 years with 0.0019 (140 cases). This is 2.83 per 100,000 (95% CI =2.46-3.24) and 1.92 per 100,000 (95% CI =1.62-2.27).

In 2018, a declining trend in incidence rates for benign endocrine cancers was observed in the following order, 60-69 years (0.0029; 169 cases), 50-59 years (0.0025; 184 cases) and 40-49 years (0.0018; 131 cases) and 0 – 39 years (0.00066; 185 cases) with exception of patients aged 70 years and above where there was an increase (0.0034; 251 cases) recorded. This is 2.88 (95% CI =2.46-3.35), 2.46 (95% CI =2.12-2.84), 1.82 (95% CI =1.52-2.16), 0.66 (95% CI =0.57-0.76) and 3.41 (95% CI =3.00-3.86) per 100,000 people respectively.

Conversely, in 2019, there was a downward trend for patients aged 70 years and above (0.0032; 241 cases). 60-69 years (0.0027;159 cases) and 50-59 years (0.0022, 167 cases). This was 3.19 (95% CI =2.799-3.62), 2.69 (95% CI =2.29-3.14) and 2.20 (1.88-2.56) per 100,000 people respectively. There was a slight increase for 0-39 years (0.00068;190 cases) but this was more apparent for patients aged 40-49 years (0.0020; 145 cases). This was 0.68 (95% CI =0.58-0.78) and 2.03 (95% CI =1.72-2.39) per 100,000 people. Nevertheless, in the subsequent year, the latest published data presented all five patient age groups had a downward trend.

Figure 7: The effect of age on the incidence rate per 100,000 for benign endocrine tumours (2013-2020)

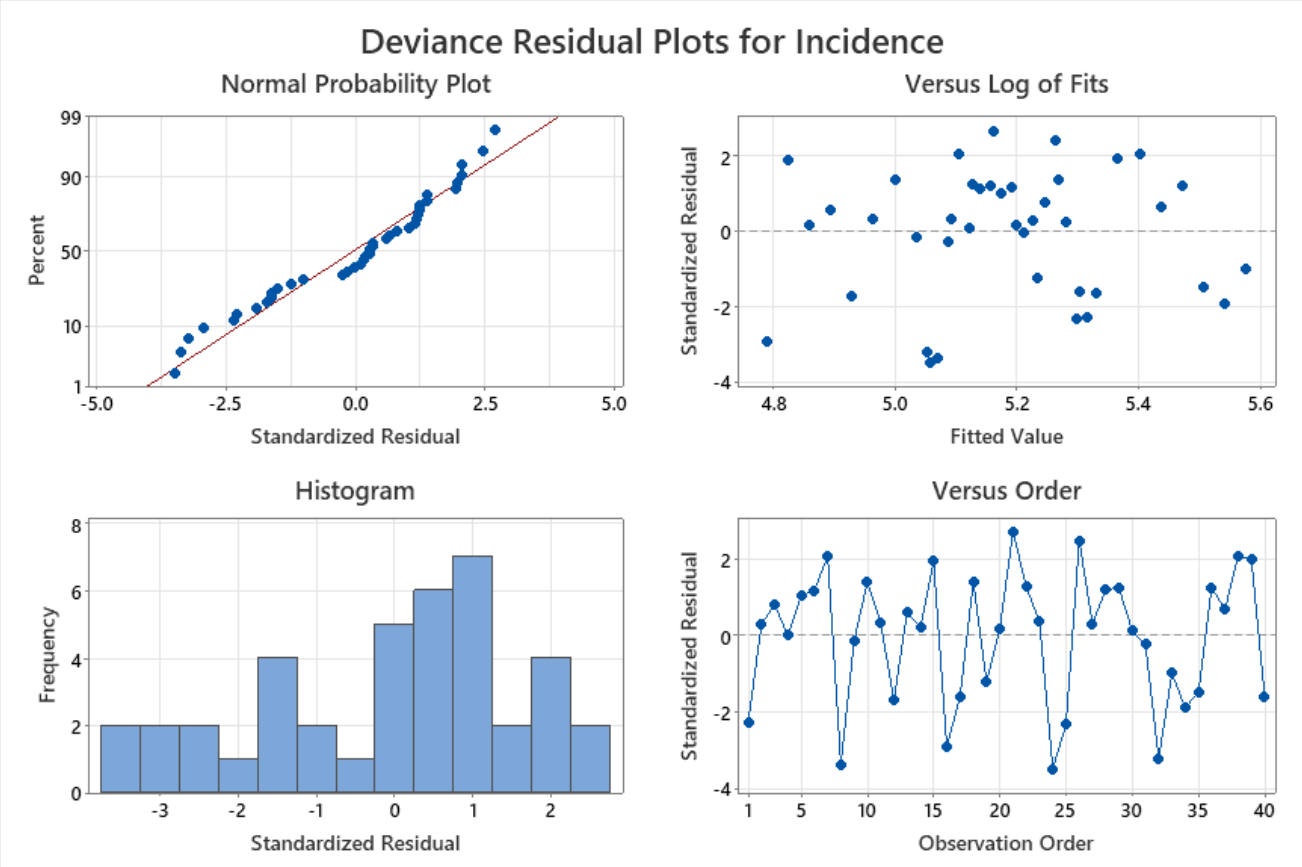
These data were obtained from Get Data Out from the National Health Service.



In comparison to malignant and non-malignant brain tumours, the Poisson regression analysis for benign endocrine tumours suggests there is a significance difference between the variables: year and cancer incidence (0.000; $p < 0.05$). Some of the corresponding age groups in the Cohort had a significant variation, for instance, 40 to 49 years and 70 years and above had a p value of 0.000 whereas patients aged 50-59 years (0.737; $p > 0.05$) and 60-69 years (0.627; $p > 0.05$) have shown no significant difference but in general, it is 0.000 according to Wald test. The deviance R-squared value is 73.16%, AIC (387.81), AICc (390.36) and BIC (397.95) which suggests a better fit for the model. The deviance p value is 0.000.

The residual plots for Poisson regression analysis are displayed in Figure 8 and it shows a left-skewed distributed histogram. This suggests the mean is less than the median due to the high frequency situated on the right side. There are also data points clustered on a straight line for the Normal Probability Plot. This emphasises the normality assumption is satisfied and there is no clear evidence of correlation between the fitted value and standardized residual for the Versus Log of Fits.

Figure 8: The residual plots for benign endocrine tumours.



4.4 Comparative study on determining the age group (0-19 and 70+) that is at risk of obtaining malignant and non-malignant tumours in 2013 and 2020.

Cancer can occur at any age, however, increasing age is considered a potential risk factor. Cancer Research UK (2024) has estimated that patients aged between 85 to 89 years are at the most risk and wanted to determine whether the evidence supports this by comparing the youngest (0-19 years) and eldest age groups (70+) in the cohort study for malignant and non-malignant brain tumours at two-time points 2013 and the latest record available 2020 as displayed in Figure 9.

In general, there is a greater magnitude of patients diagnosed with brain cancer at the age of 70 and above than those between 0 and 19 years. Bar chart presentation shown in Figures 9a and 9b are for 0 to 19 years and 70 years and above respectively. In Figure 9a, there was a 2.55-fold difference between the number of patients diagnosed with non-malignant brain tumours of age 0 to 19 in 2013 (n= 131) and malignant brain tumours (n= 334). In 2020, there was a 2.82-fold

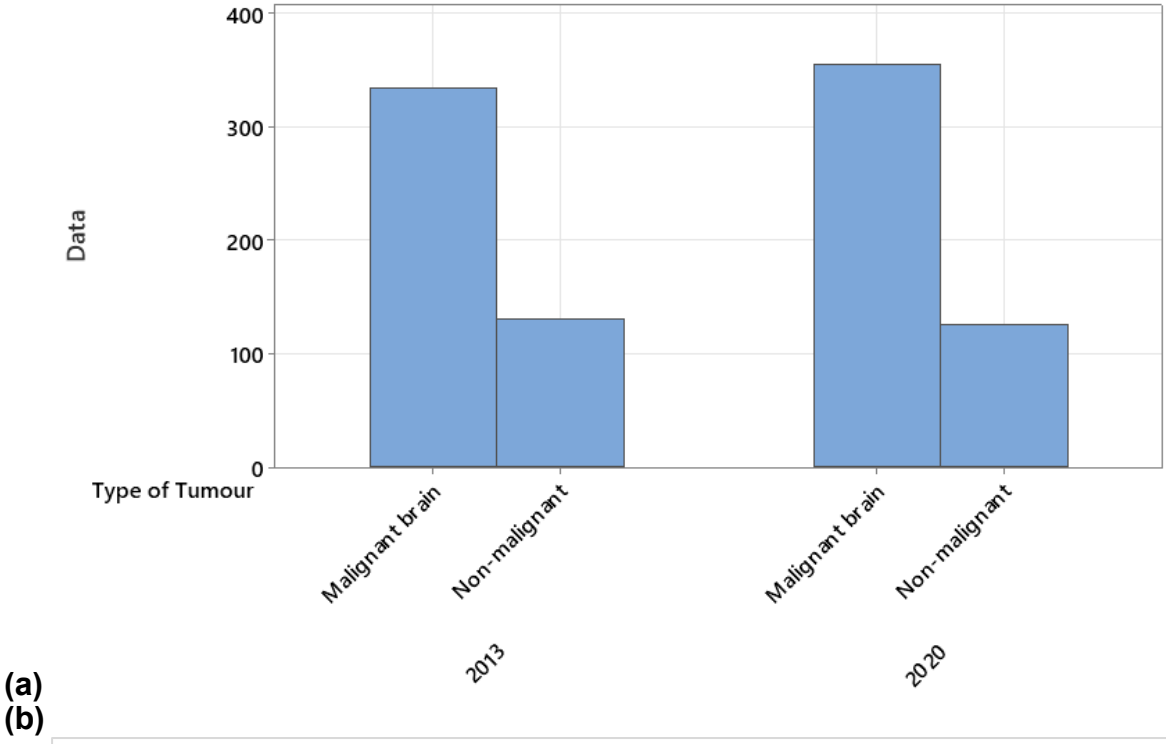
difference between non-malignant (n= 126) and malignant (n= 355). However, when comparing the same-sub groups, 2013 and 2020, there is a 1.06-fold difference between malignant brain tumours (6.28743% increase) and a 1.04-fold difference in non-malignant brain tumours (3.81679% decrease).

On the other hand, in 2013, there was a 0.945-fold difference between patients diagnosed with malignant brain tumours age 70+ (n=1666) and non-malignant brain tumours (n=1520). In contrast, there was a 0.933-fold difference in 2020, with 1763 patients diagnosed with malignant brain cancer compared with 1530 patients with non-malignant brain tumours. This suggests variation has been determined. However, there was an 5.82% increase between malignant brain cancers in both respective years and a negligible 0.067% upward trend between 2013 and 2020 for non-malignant brain cancer.

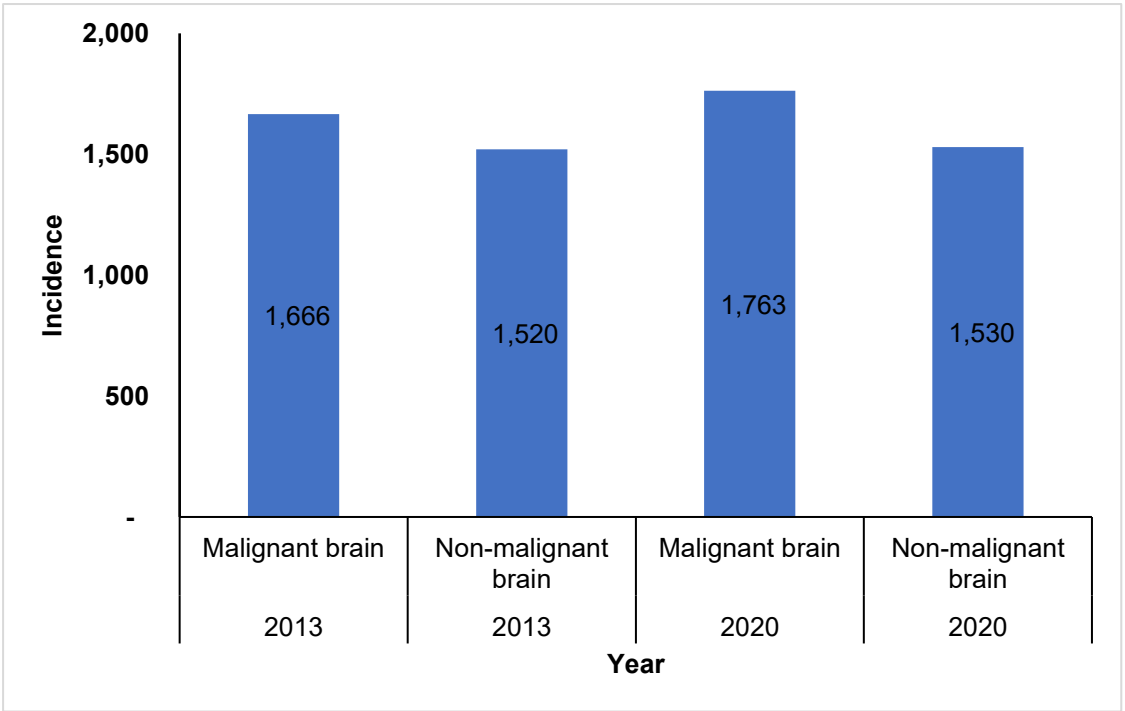
Bivariate analysis using a Chi-squared test on year and type of tumour with the cancer incidence was assessed to determine whether there is an association between the variables. No significant difference was found in patients aged 0-19 years (0.494; $p > 0.05$), and a similar case was found for patients aged 70 years and above (0.315; $p > 0.05$). Therefore, the null hypothesis is accepted in this analysis.

Figure 9 Clustered bar chart presenting brain cancer patients per tumour type in 2013 and 2020.

It reflects the proportion of the total number of cases of malignant and non-malignant brain cancers for all genders and regions of patients aged a) 0-19 years. b) 70 years and above. These data were obtained from Get Out Data from the National Health Service.



(a)
(b)



4.5 The effect of gender and region for patients diagnosed with malignant brain tumours aged 50-69 years and 70+ in 2013 and 2020.

Further investigation reviewed the effect of social determinants (region, gender, age) of patients with the cancer incidence of malignant and non-malignant tumours at two-time intervals: 2013 and 2021. The Cohort study is partitioned into four regions: North of England, South of England, London and Midlands and East of England where patients are assigned based upon their postcode at diagnosis and the National Statistics Postcode Lookup (Vernon, 2023) The two age-groups explored was 70+ years and 50-69 years. There are three types of sexes explored: male, female and persons where the latter combines both sexes together. Multivariate analysis using the general linear model data for analysis of variance for malignant tumours in 2013 was performed. There was no significant difference per region (0.084; $p > 0.05$) but there were significant variations by age, year, and gender [females, males, all persons] (0.000; $p < 0.05$). The coefficient p-values for the respective regions are as follows shows no significant difference: North of England (0.583), London (0.056), and Midlands and East of England (0.996).

Table 3 presents the data for malignant cancer incidence per region, gender, and age in 2013 and 2021. In 2013, male patients aged 50-69 years were at the most risk in every region except London [blue], where there is no identification of sex within the Get Data Out (GDO). The smallest incidence rate of the newly registered malignant brain cancer cases in both sexes was recorded in London with 13.24 (202; 95% CI =11.473-15.192%) [blue].

In 2013, male patients aged 50-69 years residing in the Midlands and East of England [red] had the highest incidence rate of 0.019 (369 cases) whereas, South of England [green] had the lowest incidence for the male population with 0.016 (264 cases). This is 19.03 (95% CI =17.14-21.08%) and 15.64 (95% CI =13.81-17.64) per 100,000 people respectively.

Similarly, the highest incidence rate for female patients was found in Midlands and East of England with incidences up to 235 cases. This is 11.81 per 100,000 (95% CI =10.35-13.42%). Research has shown the South of England to be highly populated and more ethnically diverse. The lowest incidence for female patients was found in the South of England where with 12.03% (211; 95% CI =10.463-13.77%).

On the contrary, there was a conflicting result in 2020 for the male patients aged 50-69 years diagnosed with malignant tumours to their earlier outcome in 2013. This time, the highest incidence was discovered in the South of England [green] with 0.017 (309 cases). The region where male patients had the lowest incidence was the Midlands and East of England [red] with 0.015 (307 cases). This is

17.06 (95% CI =15.21-19.07) and 14.83 (95% CI =13.22-16.59) per 100,000 people. In descending order from highest to lowest was observed for male patients in 2020: South of England, North of England and Midlands and East of England.

Simultaneous results for female patients aged 50-69 years were discovered for malignant brain cancers in 2020. The highest incidence was identified in the South of England [green] like 2013. However, the incidence rate decreased to 0.0099 (186 cases). This is 9.87 per 100,000 (95% CI = 8.50-11.39). Another variation for female patients was the region with the least incidence where in 2020, it was indicated in Midlands and East of England [red] with 0.0086 (184 cases). This is 8.60 per 100,000 people (95% CI =7.40-9.94).

In general, the South of England had the highest incidence of cases (0.013, 495 cases) and London had the lowest (0.012, 194 cases) for both sexes combined (Persons) aged 50-69 years in 2020. This is 13.39 (95% CI =12.24-14.63) and 10.76 (95% CI =9.30-12.39) per 100,000.

Upon assessment of the 2013 data, male patients aged 70 years and above diagnosed with malignant brain tumour residing in the South of England had a 0.035 incidence rate (282 cases) whereas, the lowest incidence rate was indicated in the Midlands and East of England with 0.032 (282 cases). This is *ca.* 2.59-fold difference between the years. As an expression per 100,000 people, it is 35.06 (95% CI =31.09-39.40) and 31.86 (95% CI =28.25-35.81) correspondingly.

Alternatively, the lowest incidence in 2013 for female patients aged 70 years and above was observed in the Midlands and East of England at 0.019 (214 cases). This is 18.78 per 100,000 (95% CI =16.35-21.47). The highest incidence rate was identified in the South of England for female subjects with 0.022 (233 cases). This is 22.21 per 100,000 (95% CI =19.45-25.25%).

Moreover, the South of England had the highest incidence for both sexes with 0.0278 (515 cases). This is 27.79 per 100,000 people (95% CI =25.44-30.295). The lowest incidence was found in the London for patients aged 70 years and over with 0.025 (163 cases). This is 24.47 per 100,000 (95% CI =20.86- 28.53).

In 2020, there were conflicting results between male and female patients aged 70 years and above with malignant brain cancer. South of England was the region with the highest incidence for male patients 0.032 (323 cases) but was the lowest incidence for female patients 0.019 (232 cases). This is 31.79 (95% CI =28.42-35.45) and 18.56 (95% CI =16.25-21.11) per 100,000 people.

On the other hand, North of England had the lowest incidence for male patients with 0.025 (244 cases) but the highest incidence for female patients with 0.020 (242 cases). This is

24.91 (95% CI =21.88-28.24%) and 20.11 (95% CI =17.65-22.81) per 100,000.

The same regions were also discovered when analysing the cancer incidence for both sexes together. South of England had the highest incidence with 0.0245 (555 cases) whereas London had the lowest cancer incidence with 0.0199 (156 cases). This is 24.495 (95% CI =22.499-26.62) and 19.99 (95% CI =16.98-23.39) per 100,000 respectively. In the declining trend, from highest to lowest rates, South of England, Midlands and East of England, North of England and then London.

Table 3: Incidence rates and characteristics of patients aged 50-69 years and 70+ cohorts diagnosed with malignant brain tumours per gender and region in 2013 and 2020

Age	Region	Gender	2013			2020		
			Incidence	Population	Incidence rate per 100,000 (95% CI)	Incidence	Population	Incidence rate per 100,000 (95% CI)
50-69 years	London	Persons	202	1,526,209	13.24 (11.47-15.19)	194	1,802,378	10.76 (9.30 – 12.39)
	Midlands and East of England	Persons	604	3,928,347	15.38 (14.17-19.65)	491	4,209,205	11.67 (10.66-12.74)
	Midlands and East of England	Female	235	1,989,433	11.81 (10.35-13.42)	184	2,139,068	8.60 (7.40-9.94)
	Midlands and East of England	Male	369	1,938,914	19.03 (17.14-21.08)	307	2,070,137	14.83 (13.22-16.59)
	North of England	Persons	533	3,692,602	14.43 (13.24-15.71)	485	3,910,496	12.40 (11.32-13.56)
	North of England	Female	220	1,870,023	11.77 (10.26-13.43)	176	1,992,446	8.83 (7.58-10.24)
	North of England	Male	313	1,822,579	17.17 (14.32-19.19)	309	1,918,050	16.11 (14.36-18.01)
	South of England	Persons	475	3,442,149	13.8 (12.59-15.098)	495	3,696,167	13.39 (12.24-13.63)
	South of England	Female	211	1,753,654	12.03 (10.46-13.77)	186	1,884,853	9.87 (8.50-11.39)
	South of England	Male	264	1,688,495	15.64 (13.81-17.64)	309	1,811,314	17.06 (15.21-19.07)
70+ years	London	Persons	163	666,092	24.47 (20.86-28.53)	156	780,311	19.99 (16.98-23.39)
	Midlands and East of England	Persons	496	2,024,408	24.50 (22.39-26.76)	566	2,450,301	23.099 (21.24-25.08)
	Midlands and East of England	Female	214	1,139,381	18.78 (16.35-21.47)	262	1,344,341	19.49 (17.2-21.998)
	Midlands and East of England	Male	282	885,027	31.86 (28.25-35.81)	304	1,105,960	27.49 (24.48-30.76)
	North of England	Persons	492	1,843,556	26.69 (24.38-29.15)	486	2,183,326	22.26 (20.32-24.33)
	North of England	Female	223	1,051,373	21.21 (18.52-24.19)	242	1,203,659	20.11 (17.65-22.81)
	North of England	Male	269	792,183	33.96 (30.02-38.27)	244	979,667	24.90 (21.88-28.24)
	South of England	Persons	515	1,853,324	27.79 (25.44-30.295)	555	2,265,781	24.495 (22.499-26.62)
	South of England	Female	233	1,049,055	22.21 (19.45-25.25)	232	1,249,740	18.56 (16.25-21.11)
	South of England	Male	282	804,269	35.06 (31.09-39.40)	323	1,016,041	31.79 (28.42-35.45)

4.6 The effect of gender and region for patients diagnosed with non-malignant brain tumours aged 50-69 years and 70+ in 2013 and 2020.

In 2013, the region with the highest incidence for male and female patients aged 50-69 years diagnosed with non-malignant brain tumours was South of England [green] with 0.010 (172 cases) and 0.017 (295 cases) respectively. This is presented in Table 4. Midlands and East of England [red] had the lowest incidence rates for male and female patients with 0.0086 (166 cases). and 0.014 (269 cases) respectively. This is expressed as 10.19 (95% CI =8.72-11.83), 16.82 (95% CI =14.96-18.86), 8.56 (95% CI =7.31-9.97), 13.5 (95% CI =11.95-15.24) per 100,000.

For both sexes (persons), the highest brain cancer incidence was in South of England [green] 0.014 (467; 95% CI =12.36-14.86%), whereas, the lowest brain cancer incidence was in London [blue] 0.0097 (148 cases; 95% CI =8.198-11.39%). It is expressed as 13.57 and 9.697 per 100,000 people.

Similar results were mirrored in male and female patients aged 70 years and above within the same year (2013) but at a higher incidence rate. Both male and female subjects were predominantly found in the South of England [green] with 0.020 (163 cases; 95% CI =17.28-23.63) and 0.032 (330 cases; 95% CI =28.15-35.04). This is 20.27 and 31.46 per 100,000 people. This gives a total incidence rate for both sexes to be 0.027 (493 cases; 95% CI =24.30-29.06%). This is 26.60 per 100,000 people.

The region with the lowest incidence rates for male and female subjects was North of England with 0.0153 (121 cases) and 0.0244 (257 cases) respectively. This is 15.27 (95% CI =12.67-18.25) and 24.44 (95% CI =21.55-27.62) per 100,000 people accordingly. However, when combining both sexes (persons), London had the lowest incidence rate for non-malignant cancers with 0.019% (127 cases). This is 19.07 per 100,000 people (95% CI =15.895-22.69).

In 2020, male and female patients aged 50 to 69 years with non-malignant brain cancers had the highest incidence of non-malignant brain cancers in North of England with 0.0078 (150 cases) and 0.016 (311 cases) respectively; female subjects had a higher incidence rate. As an expression per 100,000 people, it is 7.82 (95% CI =6.62-9.18) and 15.60 (95% CI =4.99-7.32%) accordingly.

The region with the lowest incidence rates for female and male subjects was concurrent with each other, South of England where there was an incidence rate of 0.0116 (219 cases) for female patients and is 11.62 per 100,000 people (95% CI =10.13-13.26). For male subjects, the incidence rate was 0.00607 (110 cases) and this is 6.07 per 100,000 (95% CI =4.991-7.32%). However, when combining both sexes, the North of England and London had the highest and lowest incidence rate with

0.0118 (461 cases) and 0.00799 (144 cases) respectively. As an expression of per 100,000 people, this is 11.79 (95% CI =10.74-12.92) and 7.99 (95% CI =6.74-9.41) accordingly.

Similarly, male, and female patients aged 70 years and above had the highest incidence rates in the North of England with 0.018 (174 cases) and 0.028 (335 cases) respectively. This is 17.76 (95% CI =15.22-20.61) and 27.83 (95% CI =24.93-30.98%) per 100,000 correspondingly.

However, the region that had the least incidence varied between the genders. The lowest incidence for male subjects was Midlands and East of England with 0.014 (154 cases). This is 13.93 per 100,000 people (95% CI =11.81-16.31%) whereas, for female subjects it was South of England with 0.021 (258 cases). This is 20.64 per 100,000 (95% CI = 18.20-23.32).

Upon the combination of both sexes together, North of England was the region with the highest incidence of non-malignant brain cancer with 0.023 (509 cases). This is 23.31 per 100,000 people (95% CI = 21.33-25.43). In contrast, the lowest incidence of all persons was discovered in London with 0.0177 (138 cases). This is 17.69 per 100,000 people (95% CI =14.86-20.89).

Multivariate analysis of variance using the Poisson function was applied and presents no significant difference between incidence for non-malignant cancer with the region (0.119; p-value> 0.05). However, there were significant variations for age and gender (0.000; p-value < 0.05) and year (0.001; 0.000; p-value < 0.05). The coefficient values present a significant difference for the London region (0.026; p-value < 0.05). The Midlands East of England and North of England present no significant difference where the p-values were 0.648 and 0.157 (p-value> 0.05) respectively.

Table 4: Incidence rates of patients aged 50-69 years and 70+ cohorts diagnosed with non-malignant brain tumours per gender and region in 2013 and 2020

Age	Region	Gender	2013			2020		
			Incidence	Population	Incidence rate per 100,000 (95% CI)	Incidence	Population	Incidence rate per 100,000 (95% CI)
50- 69 years	London	Persons	148	1,526,209	9.697 (8.198-11.39)	144	1,802,378	7.99 (6.74-9.41)
	Midlands and East of England	Persons	435	3,928,347	11.07 (10.06 – 12.17)	413	4,209,205	9.81 (8.89-10.81)
	Midlands and East of England	Female	269	1,989,433	13.52 (11.95-15.24)	265	2,139,068	12.39 (10.94-13.97)
	Midlands and East of England	Male	166	1,938,914	8.57 (7.31-9.97)	148	2,070,137	7.15 (6.04-8.398)
	North of England	Persons	443	3,692,602	11.997 (10.91-13.17)	461	3,910,496	11.79 (10.74 – 12.92)
	North of England	Female	268	1,870,023	14.33 (12.67-16.15)	311	1,992,446	15.61 (13.92- 17.44)
	North of England	Male	175	1,822,579	9.60 (8.23-11.14)	150	1,918,050	7.82 (6.62-9.18)
	South of England	Persons	467	3,442,149	13.57 (12.36-14.86)	329	3,696,167	8.90 (7.97-9.92)
	South of England	Female	295	1,753,654	16.82 (14.96-18.86)	219	1,884,853	11.62 (10.13-13.26)
	South of England	Male	172	1,688,495	10.19 (8.72- 11.83)	110	1,811,314	6.07 (4.99-7.32)
70+ years	London	Persons	127	666,092	19.07 (15.895 – 22.69)	138	780,311	17.69 (14.86-20.89)
	Midlands and East of England	Persons	522	2,024,408	25.79 (23.62-28.095)	449	2,450,301	18.32 (16.67-20.1)
	Midlands and East of England	Female	348	1,139,381	30.54 (27.42-33.93)	295	1,344,341	21.94 (19.51-24.596)
	Midlands and East of England	Male	174	885,027	19.66 (16.85 – 22.81)	154	1,105,960	13.93 (11.81-16.31)
	North of England	Persons	378	1,843,556	20.50 (18.49-22.68)	509	2,183,326	23.31 (21.33-25.43)
	North of England	Female	257	1,051,373	24.44 (21.55-27.62)	335	1,203,659	27.83 (24.93-30.98)
	North of England	Male	121	792,183	15.27 (12.67-18.25)	174	979,667	17.76 (15.22-20.61)
	South of England	Persons	493	1,853,324	26.60 (24.30-29.06)	434	2,265,781	19.16 (17.395-21.04)
	South of England	Female	330	1,049,055	31.46 (28.15-35.04)	258	1,249,740	20.64 (18.20-23.32)
	South of England	Male	163	804,269	20.27 (17.28-23.63)	176	1,016,041	17.32 (14.86-20.08)

4.7 The effect of socio-demographic factors on the number of brain cancer cases and patient access to the routes of diagnosis across England 2013-2020

The last segment of this analysis investigates the interaction between social factors and diagnosis routes for brain cancer patients. This will help indicate and evaluate the timely diagnosis in cancer pathways to improve cancer survival. The National Disease Registration Service (2024) have confirmed eight routes that leads to a patient's diagnosis of cancer where data on two-week wait, GP referral, other outpatient, inpatient elective, emergency presentation, death certificate only, unknown and unclassified. Other routes include screen detection, and urgent suspected cancer referral (National Disease Registration Service, 2024). Figure 10 presents a bar chart displaying the percentage rate of patients diagnosed with malignant, and non-malignant cancers and all brain cancers in 2013. No data was available for the years 2019 and 2020. The routes population for all brain cancers, malignant and non-malignant cancers was 9942, 4755, and 4059 respectively.

A total of 87 patients from the routes population (9942) attended their index two week wait (2WW) referral of whom the percentage rate for patients with malignant brain cancer was 1.33% (63 cases; 95% CI=1.04-1.68%) whereas, for non-malignant brain tumours, it was 0.49% (20 cases; 95% CI= 0.32-0.76%). There was also a minimal percentage rate of patients who had death certificate only (DCO), unknown routes, and routes that were not classified.

Some of 2WW referrals led to GP referrals where the percentage rate of patients who were scheduled was 29.07% (2890 cases; 95% CI=28.18-29.97%) for all cancers. The percentage rate of malignant brain cancer patients was 20.67% (983 cases; 95% CI= 19.55-21.85%) whereas, for non-malignant tumours it was 35.21% (1429 cases; 95% CI=33.75-36.69%).

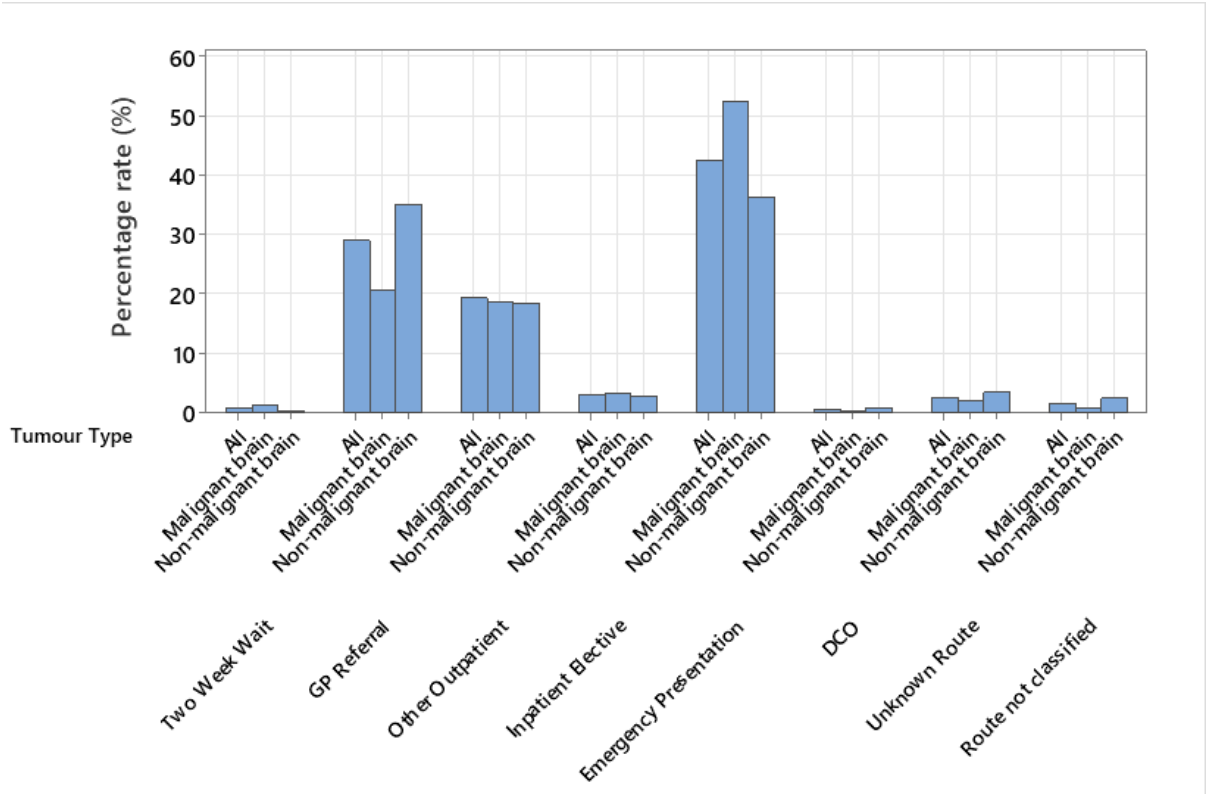
The subsequent step in the cancer diagnosis route is an outpatient appointment with a consultant to discuss the treatment care plan and monitoring tests. The percentage rate for outpatients for all brain cancers was 19.362% (1925; 95% CI = 18.597-20.15%). There was a minimal percentage between the two types of brain cancers investigated. Patients with malignant brain cancer had a percentage rate of 18.759% (892 cases; 95% CI= 17.68-19.89%) whereas, patients with non-malignant tumours had a percentage rate of 18.38 (746 cases; 17.22-19.6%). Possible reasons for lack of attendance could be speculated with psychological status, cancers by either party, opting for private healthcare, admission to hospital, or dying before the appointment (Sheridan *et al.* 2019). This may explain why the number of patients decreased in subsequent diagnosis steps for further analysis. For example, patients admitted to the hospital

and have been diagnosed with cancer through tests such as radiological examination are referred to as inpatient electives (Redhead, 2015). The proportion of patients with all types of brain cancers at this stage had a percentage rate of 2.99% (297 cases; 2.67-3.34%). This is subdivided into malignant cancers with 3.45% (164 cases; 95% CI= 2.97-4.01%) whereas, patients with non-malignant tumours had a percentage rate of 2.81% (114 cases; 95% CI= 2.34-3.36%).

However, patients who underwent one of the later routes of diagnosis known as emergency presentation where the cancer is diagnosed after when a patient is seen as an emergency, had the highest proportion of patients than any other route of diagnosis. This is largely possible due to the high volumes and urgency for results. Patients with all types of brain cancers had a percentage rate of 42.64% (4239 cases; 95% CI=41.6743.61%). The percentage rate of malignant tumours was 52.47% (2495 cases; 95% CI=51.05-53.89%) was higher than the percentage rate of non-malignant tumours 36.27% (1472 cases; 95% CI = 34.8-37.76%).

Figure 10: The percentage rate of brain cancer patients accessing the routes of diagnosis across England in 2013

These data were obtained from Get Data Out from the National Health Service.



To determine the psychological impact of malignant and non-malignant patients that are at most risk of brain cancer, 50-69 years and 70 years and above, the aim was to focus on socio-demographic factors (gender, region) for the first step of the cancer diagnosis route: Two-week wait. The heat map presented in Figure 11 is for malignant cancers whilst Figure 12 is for non-malignant brain cancers.

In Figure 11, the highest proportion of patients who underwent the two-week wait was males aged 50-69 years in the North of England with a percentage rate of 3.195% (10 cases; 95% CI =1.744-5.78). The highest incidence for male patients aged 70 years and above was in South of England with a percentage rate 2.23% (6 cases; 95% CI = 1.026-4.78).

Simultaneous results were for the female patient population. The highest proportion of female patients was in the North of England aged 50-69 years with a percentage rate of 1.82% (4 cases; 95% CI=0.71-4.58). This was followed by South of England with a percentage rate of 1.42% (3 cases; 95% CI= 0.49-4.096) and then Midlands and East of England with an incidence rate of 0.85% (2 cases; 95% CI=0.23-3.05).

For both sexes (persons), the number of cases was concentrated in the North of England aged 50 to 69 years for the two-week wait with a percentage rate of 2.63% (14 cases; 95% CI= 1.57-4.36), Similar levels were found in London and Midlands and East of England aged 50-69 years with a percentage rate of 1.49% (3 cases; 95% CI= 0.51 – 4.28) and 1.49% (9 cases; 95% CI=0.79-2.81) respectively. The upper and lower limits of confidence intervals are between 2 and 4 which reflects the degree of precision of these values.

On the other hand, the heatmap in Figure 11 illustrated that male and female patients aged 70 years above that resides in the North of England were more prone to partaking in the 2WW stage where they had a percentage rate of 2.23% (6 cases; 95% CI= 1.026-4.78) and 1.35% (7 cases; 95% CI= 0.46-3.88) respectively than other regions across England.

The heatmap for patients with non-malignant brain tumours presented in Figure 12 suggest that the highest number of patients who underwent the two-week wait in 2013 were amongst males aged 50-69 years in North of England. The percentage rate was 1.15% (2 cases; 95% CI=0.32-4.09). This was followed by 70+ in the same area that had a percentage rate of 0.83 (1 cases; 95% CI= 0.15-4.53).

The highest female percentage rate for 2WW was also found in the North of England in the 50-69 age group with 1.13% (3 cases; 95% CI = 0.38-3.26). This was subsequently followed by the South of England for the same age group with 1.03% (3 cases; 95% CI = 0.35-2.99). For

both sexes combined, North of England 50-69 years was the highest with a percentage rate of 1.14% (5 cases; 95% CI=0.49-2.63) followed by 70+ with 0.535 (2 cases; 95% CI=0.15-1.93) in the same region.

Two-way ANOVA statistical analysis was performed using the general linear model to compare the factors: of age, region, and gender on routes population incidence for the different routes of cancer diagnosis in 2013. In the analysis of 2WW, there was a moderate significant difference for age (0.053; $p < 0.05$). However, there was a higher significance for the region (0.004; $p < 0.05$) and gender (0.025; $p < 0.05$). The Coefficient p values for female patients (0.013; $p < 0.05$) were more significant than male patients (0.022; $p < 0.05$).

For GP referral, there was a significant variation in the age factor (0.004; $p < 0.05$) and region (0.007; $p < 0.05$) for malignant brain cancer patients except gender (0.255; $p > 0.05$). The coefficient values for the London region (0.085; $p > 0.05$), and North of England (0.260; $p > 0.05$) suggest no substantial difference. The p-value for the Midlands and East of England (0.001; $p < 0.05$) was below the significance level at 0.05. The coefficient values for females and males were 0.139 and 0.175 respectively.

Patients with malignant brain cancer who are receiving an outpatient appointment have significant age differences (0.000; $p < 0.05$) and region (0.001; $p < 0.05$). In opposition, there was no significant difference for gender, and was not parallel for men and women (0.977; $p > 0.05$). The coefficient values for regions suggest there was a significant difference for regions except London. London had a p-value of 0.471 ($p > 0.05$) but for the Midlands and East of England and North of England, the p-value was 0.001 and 0.022 respectively. The coefficient values for female and male patients were 0.845 and 0.864 respectively.

Furthermore, in 2013, for inpatient elective surgery and emergency presentation, malignant brain tumours patients presented significant differences for age (0.000; $p < 0.05$) but not for region and gender ($p > 0.05$). For the inpatient elective, the p-value for the region was 0.167 whereas gender had a p-value of 0.909. The coefficient value suggests no significant difference amongst those that reside in the Midlands and East of England (0.562; $p > 0.05$) and North of England (0.575; $p > 0.05$). There was a moderate significant variation in London (0.055; $p > 0.05$). The female and male patients had a p-value of 0.703 and 0.718 respectively.

Similar p-values were obtained for malignant brain cancer patients in emergency presentation. The p-value for the region was 0.166 and gender was 0.575 ($p > 0.05$). The coefficient value implies no significant difference for the

North of England (0.842; $p > 0.05$) and London (0.564; $p > 0.05$). In contrast, there was a significant difference in the Midlands and East of England (0.042; $p < 0.05$). The p-value for gender was 0.347 for females and 0.396 for male patients ($p > 0.05$).

In the Two-way ANOVA analysis for non-malignant cancer patients, for the two-week wait, there was no significant difference for age (0.158; $p > 0.05$) and gender (0.463; $p > 0.05$). The p-value for the region was 0.022 ($p < 0.05$). The coefficient values suggest London (0.177; $p > 0.05$), Midland, and East of England (0.458; $p > 0.05$) show no significance but there was a substantial difference for North of England (0.003; $p < 0.05$). The coefficient p-value for female and male patients was 0.254 and 0.328 respectively.

For the GP referral of patients with non-malignant melanoma, there was no significant difference for the region (0.639; $p > 0.05$) and gender (0.991; $p > 0.05$). There was a significant variation for age (0.000; $p < 0.05$). The coefficient values for London (0.553; $p > 0.05$), Midlands and East of England (0.235; $p > 0.05$), and North of England (0.808; $p > 0.05$). The coefficient values for females and males respectively were 0.949 and 0.894.

Moreover, gender (0.275; $p > 0.05$) had minimal significance in comparison to region and age (0.000; $p < 0.05$). The coefficient value for London was 0.825 ($p > 0.05$) whereas for the Midlands and East of England (0.000; $p < 0.05$) and North of England (0.003; $p < 0.05$). The p-values for the coefficients female and male were 0.204 and 0.139 respectively. This emphasizes there was little patterning between the variables.

In addition, there was no significant difference in region and gender for inpatient elective and emergency presentation but there was a significant age difference (0.000; $p > 0.05$). For inpatient elective, the p-value for the region was 0.720 ($p > 0.05$) and the coefficient values support this per region: London (0.543), Midlands and East of England (0.669), and North of England (0.359). The p-value for gender was 0.627 and the coefficients per gender were 0.437 and 0.380 for female and male patients respectively.

Similar outcomes of significance were established for emergency presentation, the p-values for region, gender, and age are 0.656, 0.957, and 0.000 respectively. The coefficient values for London (0.557), Midlands and East of England (0.224) and North of England (0.756). The female and male patients had a p-value of 0.792 and 0.809 respectively.

The routes of diagnosis results are vital as the key events within the healthcare system leading to cancer diagnosis within the healthcare system are dichotomized to shed light on which route of diagnosis could be improved to increase survival

rates. There is a hampering difference between NHS England and the average cancer survival rates in Europe. This could be partially associated with the late diagnosis and progression to advanced stages where the efficacy of drugs used is limited (National Disease Registration Service, 2025).

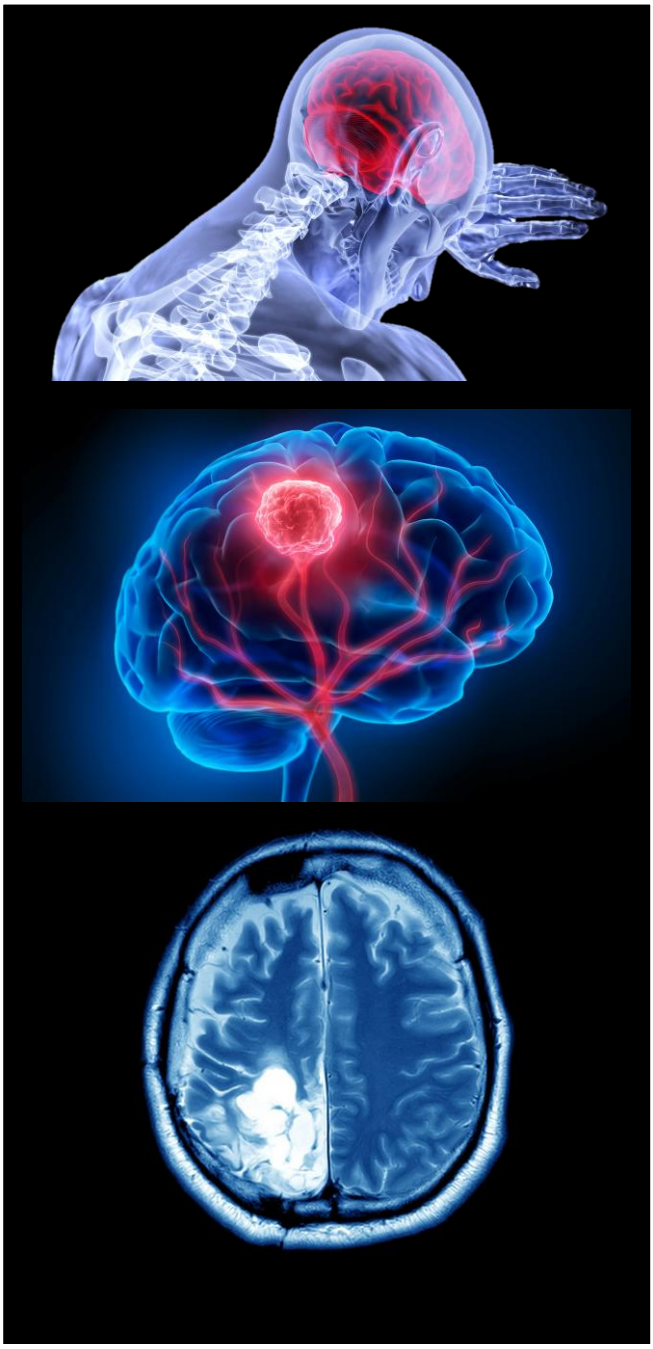


Figure 11: The trends in incidence of patients with malignant brain cancer by regions in England and by sex during the two-week wait, 2013

The heatmap and clustering reflects the proportion and percentage rate of patients that apply the two-week wait and is relative to the total route population. Dark and warm colours imply there is a high number of patients. The cooler objects indicate low number of cases. White blocks refer to very low numbers. Axes are reflective of the sociodemographic factors investigated in the heatmap. These data were obtained from Get Out Data from the National Health Service.

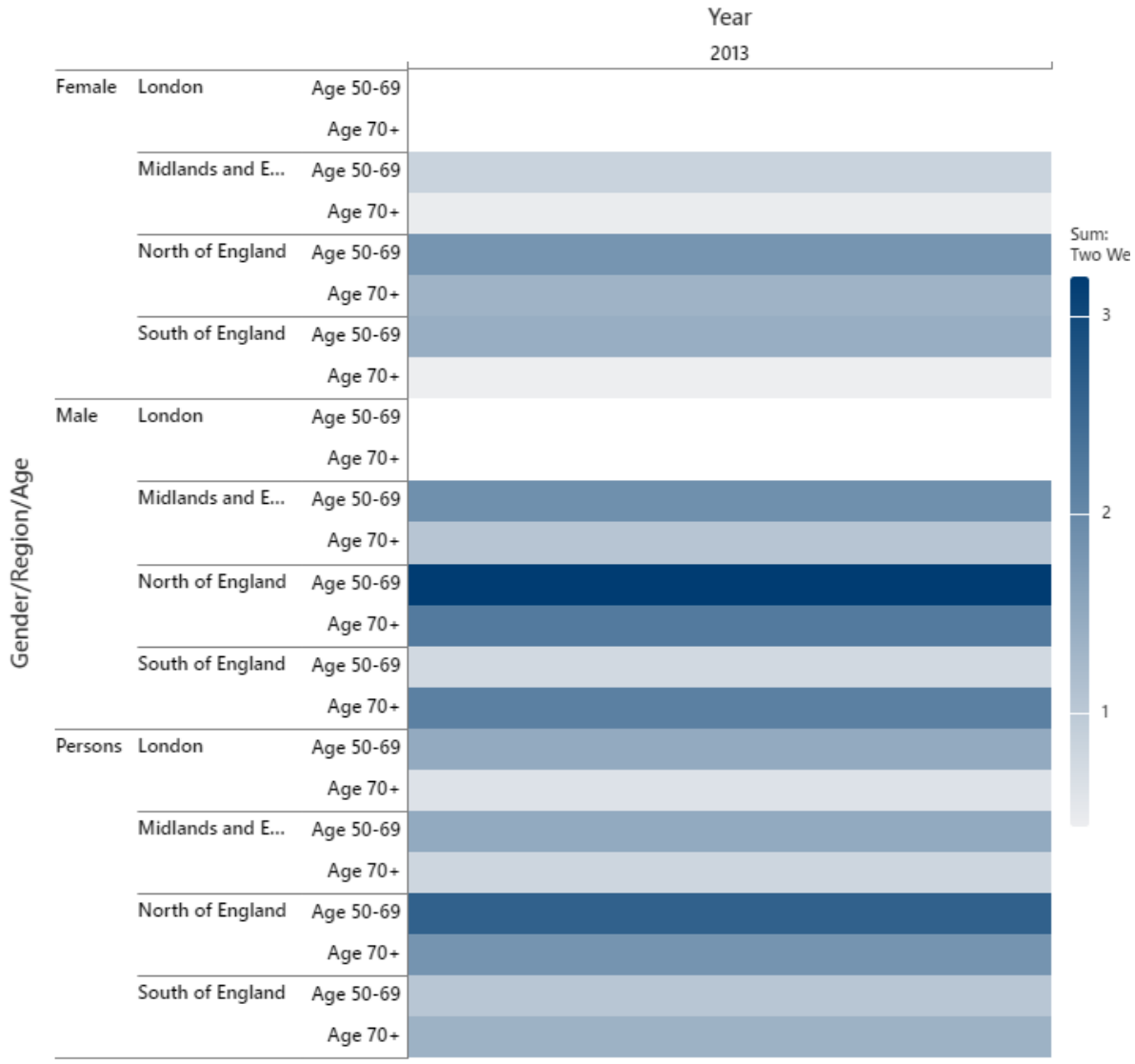
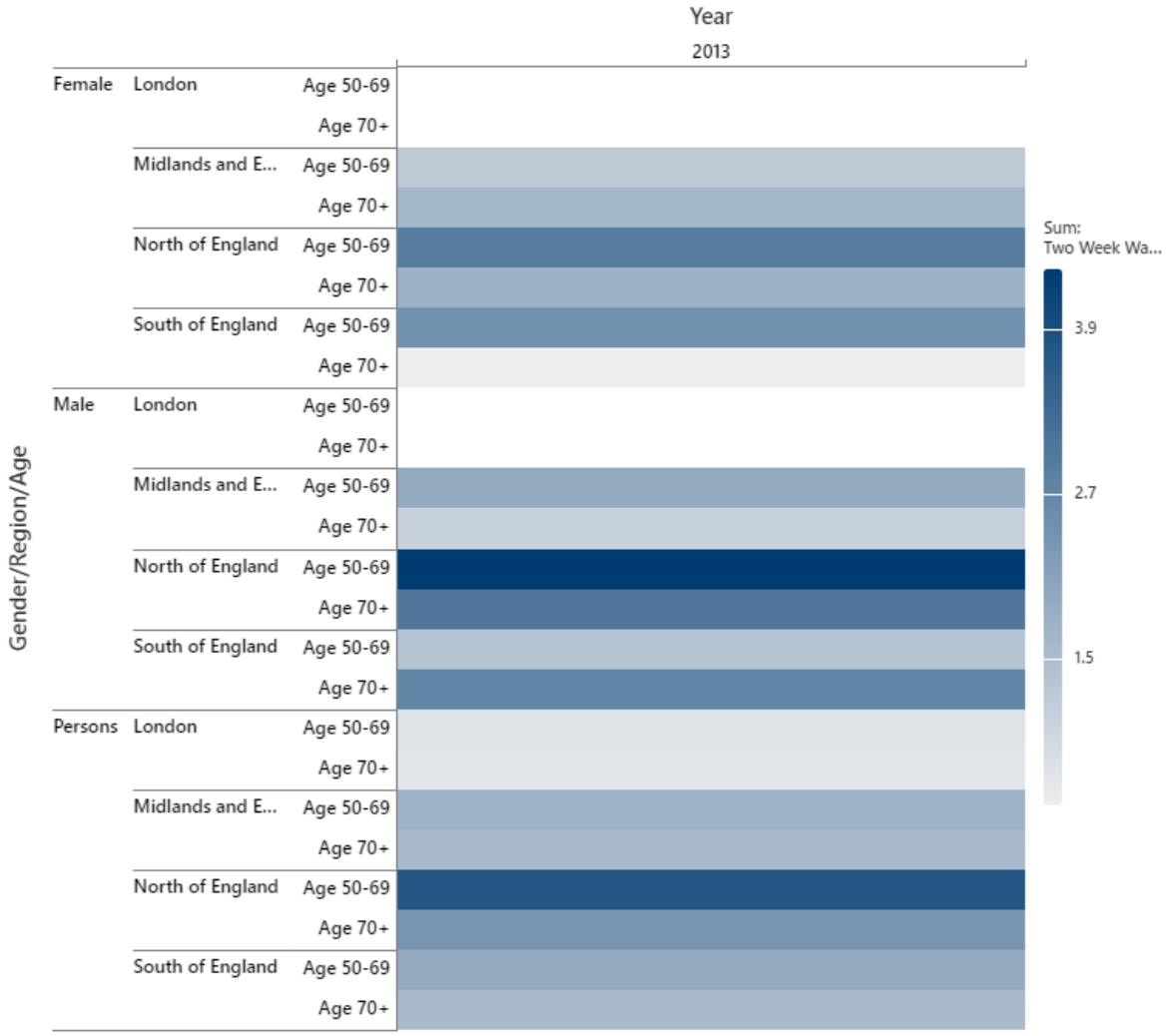


Figure 12: The trends in incidence of patients with non-malignant brain cancer by regions in England and by sex during the two-week wait, 2013

The heatmap and clustering reflects the proportion and percentage rate of patients that apply the two-week wait and is relative to the total route population. Dark and warm colours imply there is a high number of patients. The cooler objects indicate low number of cases. White blocks refer to very low numbers. Axes are reflective of the sociodemographic factors investigated in the heatmap. These data were obtained from Get Out Data from the National Health Service.



5. DISCUSSION

5.1 The rate of brain cancer incidence has decreased

This study explores patients residing in England who were diagnosed with a brain tumour between the years 2013 and 2020. The cancer registration data in England has been greatly improved in recent years as presented in Figure 1. The latest published Get Data Out (GDO) data in 2020 suggests there were 9247 new cases of brain cancer identified from a population of 56550138 (IR, 16.35) in England. In descending order, 4585 patients were diagnosed with malignant brain tumours (IR, 8.12), 3866 for non-malignant tumours (IR, 6.84), 640 for benign endocrine tumours (IR, 1.13), and 156 for non-benign endocrine tumours (IR, 0.28). This is a significant difference from the number of patient cases in 2013 when the GDO team first collated patient data. There were 9979 patients from a total population of 53865817 (IR, 18.53). These research findings correlate with NHS England Digital (2023a) where all cancers including the brain fell by 12% from 327,174 new diagnoses registered in 2019 to 288,753 new cancer diagnoses registered in 2020. Another study conducted by Cioffi *et al*., (2024) discovered that the monthly incidence of malignant and non-malignant tumours was lower in March, April, and May 2020 than in 2019.

There is cumulative evidence that investment in the NHS Long Term plan has significantly developed more effective preventative methods, highly personalized cutting-edge treatments, screening programmes, technological equipment, and faster diagnostic methods (National Health Service, 2019). Introducing the new Rapid Diagnostic Centres and Faster Diagnosis Standards within the 28-day intervals increased survival rates (Wedekind, 2022; National Health Service, n.d). The aim of the NHS Long Term plan is by 2028 55,000 people annually will survive five years or more post-cancer diagnosis. The governmental intervention to ban smoking in public places in 2007 helped reduce cancer incidence and improve the lifestyle of the public.

Furthermore, the GDO data suggests the largest rise in brain cancer incidence between 2013 to 2020 for all types was recorded in 2017 (n=10738). This connects with the discoveries of the Office for National Statistics (2019) where there was a significant increase in all types of cancer diagnoses in England from 303,135 in 2016 to 305,683 in 2017. The ONS data also indicated that males were more at risk in 2017 with 156,444 attributed to them in comparison to female patients 149239 cases. Of these cancers, there were 4769 registrations (1.6%) related to CNS tumours. The 55.59% variation in the report findings from ONS and GDO in 2017 could be possibly related to the type of cancer that has been recorded. The ONS focused on CNS tumours only whereas GDO collated Brain, meningeal, and other primary CNS tumours. Another explanation could be the time interval in which the data was collated and whether there were late diagnoses due to the complexity of the symptoms in suspected brain

cancer cases predominantly headaches, seizures, and focal neurological deficits (National Cancer Research Institute, 2023).

The results from GDO further indicated that the year with the largest rise in incidence varied per type of tumour, for example, patients with malignant tumours were found in 2015 (n=4858), and the non-malignant tumour was observed in 2017 (n=4678). The highest number of patient cases for benign and non-benign neuroendocrine tumours was 1029 in 2014 and 208 in 2013 respectively. This elevation could be explained by the rarity of the tumours and exposure to hereditary and lifestyle factors that contribute towards brain cancer incidence. For example, neuroendocrine tumours are rare and affect the cells that cause hormonal release into the blood (National Health Service, 2020). They are commonly classified as grade 1 or two tumours (NHS Inform, 2024a).

In contrast, malignant tumours are commonly graded three or four due to their aggressive behaviour, high proliferation rate, and the likelihood of a relapse post-treatment (NHS Inform, 2024a). Most malignant tumours are secondary cancers where cancer cells grew out of the primary site such as the colorectal, breast, lung, and skin, and spread to the brain via the blood and lymphatic system (NHS Inform, 2024a). This suggests the differences in the year of highest incidence could be exhibited in more than 100 histologically distinct subtypes of brain tumours that vary in occurrence by age, sex, ethnicity, clinical characteristics, and outcomes (Miller *et al.* 2021).

5.2 Malignant tumours have the highest brain cancer incidence in England.

The GDO data suggest malignant tumours are the most diagnosed solid tumours between 2013 and 2020 despite they account for a small proportion of invasive cancer cases (Miller *et al.,* 2021). McKinney (2004) estimates that 2% of all cancers in adults are associated with brain cancer highlighting its rare occurrence. There was a 2.55-fold difference between the number of patients diagnosed with non-malignant brain tumours in 2013 (n= 131) and malignant brain tumours (n= 334). In 2020, there was a 2.82-fold difference between non-malignant (n= 126) and malignant (n= 355).

Most of the literature is predominantly focused on glioma cases due to the rarity of the alternative subtypes of brain cancer. The pathogenesis of glioma remains unknown (Weller *et al.,* 2017). Gliomas are heterogeneous primary brain tumour that originates from the neuroglial precursor cellular tissue. It supports the nerve cells and is subdivided into three forms: astrocytes, oligodendroglioma, and ependymoma (NHS Inform, 2024a; Schwartzbaum *et al*., 2017; Weller *et al.,* 2017). The locations of where these cancers arise are illustrated in Supplementary Material 4. Astrocytoma develops in star-shaped glial cells that facilitate the brain framework, whilst oligodendroglioma is responsible for the fat covering of the nerves

known as the myelin sheath which helps absorb electric shock and maintains insulation. Ependymoma develops in the brain cavities, however, some tumours have a combination of these types but there is seldom evidence (NHS Inform, 2024a).

It is estimated that 80% of gliomas are histologically classified as glioblastoma (Sehmer *et al.,*2014). Glioblastoma is a WHO grade 4 tumours characterized by astrocytic morphology, microvascular proliferation, and necrosis (Lerner *et al.,*2024). It is the most aggressive form of brain cancer and patients are estimated to die within two years of diagnosis despite the use of multimodal therapies (Aldape *et al.* 2019; Kim *et al.,* 2021).

Another study revealed that the survival rate is for 14 months where symptoms are experienced three months before the diagnosis (Schwartzbaum *et al.*, 2017). This indicates the importance of identifying the preclinical tumour before the appearance of the symptoms (Schawartzbaum *et al.,* 2017). The symptoms experienced by a malignant brain cancer patient are dependent on the location and size of the cancer in the brain (The Brain Tumour Charity, 2024). The main affected lobes are the frontal and parietal and there is no dominant laterality (Sehmer *et al.*, 2014; The Brain Tumour Charity, 2024). Please see Figure 13-15.

The primitive function of the frontal lobe is thought, attention, memory, learning, behaviour, and emotional and impulse control (The Brain Tumour Charity, 2024). Thus, a tumour in this location can halt these roles and influence communication, concentration, social cognition, and executive functions (The Brain Tumour Charity, 2024). The sensory coordination and perceptive function of the parietal lobe will also be affected and cause difficulty in recognizing faces, movements, spatial awareness, and numbness (The Brain Tumour Charity, 2024).

Wanis *et al*. (2023) estimated that the number of patients diagnosed in England between 2012-2017 was 14768 for glioblastoma (60.7%) where there were 13.619 deaths. In descending order, there were 2707 cases of malignant glioma (11.1%) with 2386 deaths. 1709 patients were diagnosed with Unclassified malignant brain cancer (7.0%) and there were 1585 attributed deaths. There were 1492 cases of primary CNS lymphoma (PCNSL) (6.1%) and 1124 deaths. PCNSL is a rare type of lymphoma that arises in the CNS but does not affect the lymph nodes. However, it can affect the eye where it is referred to as intraocular lymphoma or vitreoretinal lymphoma (Macmillan Cancer Support, 2024). There were 1306 cases of astrocytoma (5.4%) and 557 deaths. Oligodendroglioma had 1279 patient cases (5.3%) and 321 deaths. Anaplastic astrocytoma had 1058 cases (4.4%) and 675 deaths.

The cause of malignant neurological tumours is unknown but researchers have hypothesized that exposure to ionizing radiation is the sole environmental risk factor strongly associated with meningioma (Ostrom *et al.,* 2019). Patients with acute lymphocytic leukaemia treated with

cranial radiation were at risk of primary malignant tumours (Davis *et al.,* 2011). Cancer Research UK (2023) reported that less than 1% of brain tumours are caused by ionizing radiation from radiotherapy treatment rather than CT scans.

Conversely, other risk factors have not shown a consistent association with neurological cancers: pesticides, low-frequency magnetic fields, diets, and occupational exposure to chemicals used in the industry (Ostrom *et al*., 2014). Rare hereditary syndromes such as familial adenomatous polyposis (FAP) and Turcot genetic syndrome type 1 and 2 characterized by small growths (polyps) in the small intestines elevate the risk of colorectal, brain, and spinal cord cancers especially gliomas, and medulloblastoma carrying the worst prognosis (Wrensch *et al.* 1997; Cleveland Clinic, 2024; Johnson *et al*., 2016; Jones, 2015). Germline mutations were commonly found in older patients with European descendants increasing the risk of neurological tumours (Ostrom *et al.* 2019; Rice *et al.* 2016).

Other mutations of malignant brain cancers are Wild-type isocitrate dehydrogenase (IDH1/2), TP53, and ATRX genes that commonly harbour astrocytoma (Lerner *et al.,* 2024; Weller *et al*., 2017). Oligodendrogliomas are IDH-mutant gliomas classified as grade 2 or 3 tumours based on proliferation and anaplasia (Lerner *et al*. 2024).

Moreover, there is epidemiological evidence that diabetes mellitus 1 (TDM1) and 2 (TDM2) can upsurge the risk of most malignant cancers (Zhu and Qu, 2022; Schwartzbaum *et al.* 2017). Obesity, inflammatory mediators, oxidative stress and genes, and hypoglycaemic drugs are involved in the crosstalk between both conditions (Zhu and Qu, 2022). On the contrary, in the case of malignant neurological tumours, several meta-analysis studies have discovered there is an inverse association between patients with comorbidities such as diabetes and glioma and brain cancers in general (Kitahara *et al*., 2014; Schwartzbaum *et al*., 2005; Seliger *et al*., 2015; Zhao, Zheng and Huan, 2016). This has been observed in patients with T2DM for more than a decade (Harding *et al*., 2015).

Cancer cells rely on oxidative phosphorylation to generate more glucose and 36 adenosine triphosphates (ATP); a source of energy supply for growth than non-proliferating cells (Schwartzbaum *et al.* 2017). This is known as the Warburg effect. This excessive glucose consumption creates a protective effect lowering glioma risk by promoting apoptosis which prevents neural stem cell growth (Chen *et al.,*2013)

Another potential mechanism is the anti-diabetic drug metformin which prevents glioblastoma proliferation, migration, and invasion. However, other researchers have discovered no clear link between the two diseases (Seliger *et al*., 2015; Seliger *et al.,* 2016). A decline in testosterone levels induced by diabetes can lower glioma risk (Seliger *et al*., 2015). On a genetic level, the telomeres at the

end of chromosomes are shortened per cellular replication in diabetic patients because patients with glioma commonly have long telomeres (Masi *et al.,* 2016; Walsh, Ohgaki, and Wrensch, 2016). Additional proposed theories of the link between glioma and diabetes are the low levels of insulin-like growth factor 1 (IGF-1) whose increased presence can cause glioma progression (Quail *et al*, 2016). This illustrated the significant impact of molecular and genetic signatures in the pathogenesis of brain cancer.

Though the strength of the evidence provided by Schwartzbaum *et al.,* (2017) is durable, several limitations were addressed by the authors. There are confounding variables that may influence the association between diabetes and glioma: blood pressure, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and body mass index were not collated from the subjects. The difference in the type of glucose was also noted where two types of glucose were utilized in the study: serum and plasma which may influence the levels of glucose measured in the body (Edlinger *et al.,* 2012).

Similarly, the GDO data had insufficient data on the grading and histological type of tumour other than whether it is either malignant, non-malignant, benign endocrine or non-benign endocrine tumours. On the other hand, these measures were put in place to maintain patient confidentiality. Nevertheless, the GDO data coincides with other researchers that malignant tumours are the most common form of neurological tumours and there is a moral obligation to face the fortuitous event with coercion, positivity, conceit, and luck which are central to the ethic of survivorship (Broom and Kenny, 2023).

5.3 Patients aged 70 years and above are at most risk of brain cancers.

The GDO data in this study indicated that the age group that is at most risk of malignant brain cancer are patients aged 70 years and above with an annual incidence rate within the range of 22.81 and 26.08 per 100,000. Similarly, they were also the age group with the highest yearly incidence rate ranging from 19.92 to 23.797 per 100,000 for non-malignant tumours. This highlights that increasing age is a poor prognostic factor for patients with a malignant brain tumour (Wanis *et al.,* 2023). This correlates with current findings where the older the patient, the more at risk of developing cancer particularly brain tumours where the greatest risk is presented in those aged between 85 and 89 years of age (Jones, 2015).

The age group with the least potential risk is patients aged 10- 19 years with an annual incidence rate between 1.83 and 2.58 per 100,000. They were also the lowest age group attributed to non-malignant brain tumours 0.9 – 1.162 per 100,000. Aldape *et al*., (2019) reported that children diagnosed with glioblastoma survived to face long-term consequences when entering adulthood due to exposure to medical treatments namely chemotherapy, radiotherapy, and/or surgery. Other reports revealed that brain cancer is

among the several cancers that occur in 56.4% of children aged 0-14 years (Office of National Statistics, 2019).

The ageing population is also at risk of benign endocrine tumours particularly those aged 70 years and over. The GDO data implied the lowest incidence was 0-39 years between 2013 and 2020. There is evidence that individuals aged 20-39 years (young adults) are at risk of glioblastoma and oligodendroglioma (Montessero *et al.,* 2022). Alternatively, children are at risk of brain tumours arising from embryonal origin such as medulloblastoma (Montessero *et al.,* 2022; Johnson *et al.* 2014). Other common histologies in children are ependymoma, brainstem, germ-cell tumours, and astrocytoma. All these tumours are collectively associated with substantial morbidity that is preventable using comprehensive treatment (Johnson *et al.,* 2014). The NHS England Digital (2024) revealed that patients aged 0 to 14 years are at risk of blood, brain, and soft tissue sarcoma accounting for 77% and 70% for males and females respectively. 26% for males and 28% for females were for brain cancers. This indicates how the type of brain tumours is distinctive per age group.

Further studies by Wanis *et al.* (2023) discovered that malignant brain tumour patients diagnosed in England between 2012 and 2017 with follow-up in 2018 were mostly between 65 and 74 years of age (6667 cases; 27.4%) where the mortality cases were 6184. There were 4993 cases of patients aged 55-64 (20.5%) and 4285 deaths. This was followed by 4738 patients aged 75 and 84 years (19.5%) and 4635 people were deceased. The least group was patients aged less than 34 with 1549 cases (6.4%) and 538 deaths. This indicates that increased age is a focal factor amongst the socio-demographic elements that are interdependent and interrelated within the health and social gradient of health.

A similar age range was also discovered by Sehmer *et al*. (2014) who conducted a study on gliomas between 2006-2010 in Lancashire and South Cumbria where they revealed that 60-79 years of age were at most risk followed by 40-59 years then 80 years and above. Patients aged less than 40 had the least risk of histologically confirmed glioma. In addition, the National Cancer Research Institute (2016) reported that 34% of tumours in patients 70 years are above were attributed to brain cancer where there were 3700 cases and 2400 deaths.

Epidemiological studies and the GDO data in this study provided consistency in the increasing incidence and prevalence of cancer amongst the elderly. This is primarily due to the duration of carcinogenesis and how they are more prone to producing DNA errors per cellular replication leading to cancer (Prathap *et al.,*2024; Dabrowski and Grondecka, 2017; Hyde, 2018). The aging population and life expectancy have increased due to lifestyle factors, supportive care, and improvement in early detection methods (Prathap *et al.,* 2024).

Antagonistic pleiotropy refers to how a gene initially exhibited positive outcomes but due to

prolonged adverse effects, it renders the elderly to be more susceptive to carcinogenesis and progression (Hosokawa, 2011). Other key drivers in biological mechanisms, lifestyle factors, and environmental stress that contribute towards the observed increase in incidence rates amongst the elderly have been elucidated but are underexplored and yet to improve for personalized treatments axiomatically (Battisti, Sehovic, and Extermann, 2017; Kim *et al.,* 2021). This presents the precarious status within neuro-oncological research where there are notable discrepancies.

It is estimated that 90% of adult glioblastoma diagnoses are related to wild-type IDH glioblastoma with a median age of diagnosis of 68-70 years (Kim *et al.,* 2021). Decreased immune function, chronic neuroinflammation, and oxidative stress in CNS regions namely, spinal cord, hippocampus, and substantia nigra contribute to the rising incidence (Pandya and Patani, 2021). Impaired cerebral circulation especially in the cingulate, prefrontal gyri, and insular in aged patients results in cognitive deficits with neurodegenerative conditions; stroke (69 years), Alzheimer's disease (75-84 years), and Parkinson's disease (72 years) (Kim *et al.,* 2021).

Rodent model studies discovered that the microglia facilitate immunosuppressive factors via the upregulation of macrophages and the secretion of matrix metalloproteinases. Indoleamine 2,3 dioxygenase 1 (IDO1) increases the function of the non-cancerous brain of mice but halts the immunotherapeutic efficacy in older adult mice with glioma (Ladomersky *et al.,* 2016; Ladomersky *et al*., 2018). It explicates the importance of xenograft models in *vivo* studies to evaluate the biological processes involved in cancer progression. They are more reliable than *in vitro* studies as mice possess an internal living environment.

Other researchers consider cellular senescence the root cause and hallmark of aging-related cancer (Prathap *et a*l., 2024). Genotypic stress triggers cells to become senescent, it is a mechanism against oncogenic potential and releases pro-inflammatory mediators. Secretory associated senescent phenotype factors e.g. matrix metalloproteinase-2 and 9, interleukin 6 (IL-6) and 8 (IL-8), and Tumour Growth Factor-beta (TGF-β) are released. This increases invasion by altering DNA methylation and expression (Fraga *et al.* 2005). Attempts have been made to target cellular senescence using xenograft models where current results suggest that combined Dasatinib and Quercetin alleviates aging-related phenotypes, and improves cardiovascular and neurocognitive effects and long-term survival (Kim *et al.,* 2021). This form of synergy helps patients with brain cancer and physicians alike to be more optimistic about clinical outcomes.

The ageing population has a growing heterogeneity of challenges such as the frailty index, and low immune system due to the thymic involution that depresses the synthesis of T cells. It is estimated *that ca.* 20% of T cells

are produced in young individuals and decreases to <1% by age 50 (Bains *et al.*, 2009). There are also relatively low levels of CD4+ and CD8+ T cells. This promotes inflammation, proliferation and evading apoptosis.

Amongst the standardized treatment options for patients with glioblastoma is the complete resection of the cancer, if possible, radiation therapy, and/or chemotherapy (Cancer Connect, 2021). Innovative techniques to help guide during surgery have been developed for the treatment of gliomas. For example, ultrasound and intra-operative MRI, confocal laser microscopy, and 5-ALA or sodium fluorescence (Lerner *et al.,* 2024; Hadjipanayis and Stummer, 2019). Despite these technological advancements, histopathological analysis remains the gold standard method for definitive diagnosis where a frozen section rapidly aids differential diagnosis (Restelli *et al.,* 2022).

Conversely, histopathology provides limited evidence in real-time and does not help with diagnosis when there is mechanical tissue destruction caused by the resection and/or if there is a high-grade cellular population within a low-grade cell population as seen in glioma patients. This is overcome using confocal laser microscopy due to wavelength and fluorescent dye to view pathological margins and intraoperatively identify tumours at the periphery (Plesec and Prayson, 2007; Restelli *et al.,* 2022). However, the CONVIVO confocal microscopic system is limited in yielding high-quality images and can produce false positive and false negative results limiting its diagnostic accuracy (Restelli *et al.,* 2022).

Other imaging modalities are used for pre-surgical and pre-radiotherapy planning such as functional MRI (fMRI) and Tractography (Lerner *et al.* 2024). The difference between the classic form of MRI and fMRI is the latter aids in mapping parts of the brain where there is high activity by tracking the blood flow and structures are vividly shown when combined with gadolinium-based contrast (Cleveland Clinic, 2023; National Cancer Research Institute, 2023). Tractography is a computational reconstruction method where it aims to reveal the fibre tracts within the white matter using *in-vivo* to reveal the neuro-structural connectome using voxels when combined with Diffusion MRI (DMRI) (Maier-Hein *et al.*, 2017; Annavarapu, Kathi and Vadla, 2019).

Safe resection of gliomas can also be further successfully done through intraoperative mapping e.g. of the cortical area for the motor and sensory evoked potential caused by external stimuli (Lerner *et al.* 2024). They are recorded electrical signals that assess the ascending sensory and descending motor pathways from the target areas (Korupulu *et al.,*2022). This helps to define safe surgical limits in neural structures (MacDonald, Dong, and Uribe, 2022).

Moreover, early holistic rehabilitation and MRI post-surgery help during the recovery period. Nonetheless, 50% of patients reported that rehabilitation is more focused than their

emotional distress which highlights the importance of psychoncology which aims to promote patients' well-being during the treatment process (Caponnetto *et al.,* 2024).

Besides, neurotoxicity reports post-treatment in patients with pre-existing medications which can promote cancer cell migration and invasion into the non-cancerous brain parenchyma (Cancer Connect, 2021). This has a profound impact on developing an optimal treatment to gain progression-free survival and overall survival due to the limitations of candidates for neurosurgical procedures where there is a risk of using anticoagulants which increases complications during surgery and many would opt for biopsy.

This highlights the acknowledgment and importance of a thorough geriatric assessment for optimal supportive care designed to tailor individual patient needs based on their respective comorbidity to alleviate side effects. Symptomatic management, psychological support, nutritional counselling, and physical rehabilitation programs to improve health and well-being. It will overcome limitations such as gaps in knowledge, patient-related barriers, and age discrimination when accessing healthcare resources and treatment decisions and promote long-term survival (Prathap *et al.*,2024).

Temozolomide is a DNA alkylating agent that delivers a methyl group (CH_3) to a purine base of DNA (O_6-guanine; N_7-guanine and N_3-adenine) (Zhang, Stevens and Bradshaw, 2012). The chemotherapeutic regimen has poor efficacy due to its inability to penetrate the blood-brain barrier of tight junctions and transport proteins. This allows selective molecules to pass through as a protective measure for delicate neural tissue. This has particularly been experienced in patients with medulloblastoma when they have not responded to the first-line chemotherapy (Aldape *et al.,* 2019; Phoenix *et al.*, 2016). It is also used in patients with glioblastoma multiforme (GBM) (Zhang, Stevens, and Bradshaw, 2012). This emphasizes some of the challenges faced when exposed to systemic chemotherapy. Multidrug resistance could also be caused by the genetic and microenvironmental features of the brain (Aldape *et al.,*2019).

Alternatively, several reports stated that *ca.* 50% of patients see an advantage when combined with conventional radiation therapy lowering the risk of progression in patients aged 70 years and over with glioblastoma multiform and astrocytoma (Cancer Connect, 2021). Stupp *et al.,* (2005) conducted a study where patients were treated with temozolomide during radiotherapy and this was followed by an additional 6 cycles of temozolomide treatment. It was compared with the control group that was treated with radiotherapy alone. There was a two-month difference in progression-free survival where patients with temozolomide/radiotherapy had seven months compared to patients with radiotherapy alone (two months) (Stupp *et al.,* 2005; Cancer Connect, 2021). There was a 2.55-fold difference in overall survival at two years when

patients were treated with combined therapy (26.5%) in comparison to patients treated with radiation alone (10.4%) (Stupp *et al.,* 2005; Cancer Connect, 2021).

A molecular test was developed to determine the suitability for the combined treatment of temozolomide and radiotherapy rather than alone (Cancer Connect, 2021). It involves identifying the methylated-DNA--protein-cysteine methyltransferase (MGMT) that is fundamental for genetic stability. Results revealed patients with MGMT have a better response and survival rate. Bernhardt *et al.,* (2020) and Tambuyzer *et al.,* (2023) also agree that Temozolomide should not be given as adjuvant treatment in unmethylated MGMT patients. MGMT can remove the cytotoxic lesion, O6-methyl guanine, and deficiency of MGMT confers resistance to temozolomide (Zhang, Stevens, and Bradshaw, 2012). This suggests how increased cytotoxicity of anticancer drugs is mediated with combined chemotherapy, the obstacles of acquired or inherent resistance, and the importance of research in developing novel therapeutic modalities.

5.4 Regional differences in brain cancer incidence.

The results in 5.2 and 5.3 led to the following nationwide analysis of the GDO data by comparing female and male patients aged 50-69 and 70 years in different regions across England in 2013 and 2020. There was geographical variation in the age-sex-standardized rate of brain cancer incidence. These age groups were also selected in other studies for analysis. Shelton *et al.* (2024) revealed that diagnostic accuracy is better among patients aged 35-69 years than older patients with co-morbidities and low proportion of brain tumours verified microscopically and helps to identify trends in the older populations.

In 2013, male and female patients aged 50-69 years had the highest incidence in the Midlands. However, in 2020, male and female patients of this age range had the highest incidence in South of England. This is similar to the research findings by Wanis *et al*., (2023) where the South East of England had the highest incidence of brain cancer with 3318 cases (13.6%) and 2747 deaths.

Conversely, Sehmer *et al*. (2014) discovered that the North West region of England predominantly in Lancashire and South Cumbria between 2006 and 2010 revealed males were more at risk of glioma with 281 cases (65%) than females with 154 cases (35%) (Sehmer *et al.,* 2014).

Moreover, Wanis *et al*., (2023) revealed that the lowest incidence was found in the North West of England with 1414 cases (5.8%) and 1212 deaths. This contradicts GDO findings where Midlands and East of England had the lowest incidence rate. Wanis *et al*., (2023) further compared the level of deprivation where the most deprived area (5) had 3804 cases (15.6%) and 3121 deaths whereas the least deprived area had 5615 cases (23.1%) and 4705 deaths (Wanis *et al*., 2023). Therefore, this may lead to

a hypothesis that South East of England is amongst the areas where people with low socio-economic status reside. London is where people who are least deprived live. This may also provide reasoning for the low incidence rate discovered in combined sexes in London.

Other published findings presented London in the light of having the lowest brain cancer incidence. The Office of National Statistics (2019) reported London having a general cancer diagnosis rate of 567.6 patients per 100,000 people. On the contrary, the North East region had the highest rate of cancer incidence at 646.1 patients. In relevance to brain cancer, the Office of National Statistics (2019) proclaimed London had the lowest brain cancer incidence with 7.3 per 100,000 people. Higher incidences were found in South West with 9.7 per 100,000 people. The equivocal outcome was found in patients residing in East of England and South East of England with 9.2 per 100,000 people. Thus, there is some agreement that London is the lowest region of cancer incidence but the region with the highest incidence varies. Thus, there is a growing sense that the level of deprivation and region influence the frequency of brain cancer cases.

A similarity between the GDO data and research findings by Scot and Hoskin (2024) discovered London had the lowest cancer mortality rates. Nevertheless, Rashid *et al.* (2023) reported that this is irrespective of socioeconomic status because a woman demised from cancer in London is one in ten chances compared to one in six if the same patient resided in Manchester. Similarly, the probability of someone residing in Harrow with cancer is one in eight compared to one in five in Manchester.

The regional difference in brain cancer incidence suggests that health inequalities still exist in cancer care in England amongst the marginalized and deprived populations despite progress has been made in developing faster methods of diagnosis, continuous free access to the National Health Service and training made on Equality and Diversity that bounds every health and social care profession (Scott and Hoskin, 2024; Rashid *et al.*, 2023; Nelson, 2023). Key examples of marginalized populations are those involved in the justice system, substance abuse, disabilities, ethnic minorities, migrants, homeless, and rough sleepers (Scot and Hoskin, 2024). Armes *et al.*, (2024) revealed how incarcerated individuals faced restrictions in communication where precise language was used to schedule appointments and minimal conversations were performed with cancer specialists. Improper safety protocols, patient autonomy, and medical confidentiality were also reported (Armes *et al.*, 2024). This emphasizes some of the challenges encountered by marginalized populations.

There are additional policy movements that further helped to necessitate and improve the efficiency of cancer care and remove social disparities that are broadly displayed. The NHS Cancer Plan 2000 increased expenditure for the specialization of cancer services and multidisciplinary teams (Rashid *et al.*, 2023).

The National Awareness and Early Diagnostic Initiative established in 2008 aimed to reduce stigma around patient-centred care and ethical cosmology through the optimization of referral pathways and screening programmes in primary and secondary care services. Nonetheless, neither of these initiatives has presented a direct impact on one-year survival which further coerced the NHS to invest in technological, vaccine, and drug development (Exarchakou *et al.,* 2018; National Health Service, 2023; National Health Service, 2019). However, the heterogeneous trends in incidence and mortality rates suggest there is a lag phase where the inequitable access to novel diagnostics and advanced treatments is limited leading to delayed diagnosis and inferior clinical outcomes regionally and nationally that are comparable with other developed nations with simultaneous healthcare systems (Rashid *et al*., 2023; Scot and Hoskin, 2024).

Rashid *et al*. (2023) performed a spatiotemporal analysis of the cancer registration data published by the ONS on cancer mortality rates between 2002 and 2019. There were 314 districts in England whose socioeconomic status measured the English Indices of Deprivation. They recruited people below 80 to prevent confounding variables such as multimorbidity conditions that occur in patient's post-80 years. Results revealed that 70% of cancer diagnoses were amongst the poorly deprived areas compared to those who reside in the least deprived areas (Nelson, 2023). Amongst the highly deprived areas that had high mortality rates were in the Northern region: Manchester, Hull, Liverpool, Newcastle, East of London, and coastal and rural areas. However, the high mortality rate in the districts of East London was related to endometrial cancer in patients of Afro-Caribbean origin than other ethnicities (Delon *et al*., 2022).

Reasons for the regional differences were explored and were exposed to be associated with inequities that stem from a complex interplay of modifiable lifestyle risk factors, for instance, smoking, excessive consumption of alcohol, unbalanced diet, and obesity that were commonly found in cancer patients in the Northern region of England (Office for Health Improvement and Disparities, 2023a; Office for Health Improvement and Disparities, 2023b, NHS Digital, 2023).

However, this is dependent on the type of tumour because blood cancers had less geographic variation and were not integrated with these risk factors. Lung, colorectal, oesophageal, and bladder cancer are strongly associated with these aspects (Nelson, 2023). Therefore, this suggests a stronger positive correlation between the individual or household with cancer risk than per region.

Hospitals situated in rural and coastal areas are under-resourced and have poor medical care infrastructure is another possible cause for the regional difference. Some areas have one regional cancer centre or a specialist centre for specific cancers where late-stage cancers are treated there. Specialist Children's Hospitals is where children and adolescents are treated. Thus, the patient's choice of where to receive

care varies and depends on age and stage of cancer (Rashid *et al.,* 2023).

Minimal access to transportation for appointments, awareness of public health programmes, and health literacy are other possible causes for the conflicting trends in the uptake of vaccinations, screening for precancerous lesions, and other preventative measures which affect clinical health outcomes (Nelson, 2023).

Nonetheless, there is a limitation to Rashid *et al*. (2023) study where information on where the patient was born or grew up could influence their chance of cancer diagnosis. The population of a region can vary due to migration inside and from overseas which attributes to changes in the health and well-being of the population living there. However, most migration occurs within the same district (van Dijk, Lansley, and Longley, 2021).

Another explanation for the lowest cancer prevalence in London than other regions in England could be conceivably due to the cultural diversity that is found within London where smoking rates are profoundly low in comparison to other regions. For instance, the UK Government (2024) revealed that in 2022, the percentage of adults who smoked in England from Afro-Caribbean origin (4.7%) was lower than people who were Asians (7.4%), Chinese (8.4%), Caucasian (13.2%), mixed ethnic origin (17%), other ethnicities (13.6%) and unknown (12.5%). The rates have decreased in comparison to previous years. Furthermore, London has a higher density of hospitals and cancer specialist centres where advanced treatment options, for instance, immunotherapies are more readily available (Delon *et al*., 2022). This suggests how there is spanning access to patient care services across England which is reflected significantly in the cancer incidence rates (Scot and Hoskin, 2024).

Qualitative studies shed light on how cultural beliefs can also shape perceptions and behaviours toward cancer care (Licqurish *et al*., 2017). Thus, the concept of intersectionality developed by renowned sociologist Kimberley Crenshaw could explain the health disparities through the lens of how power can collide due to a combination of social identities: age, gender, ethnicity, religion, sexuality, and socioeconomic status. This poses a social discourse and health disadvantage in cancer incidence and access to quality healthcare in a deprived area (Martins *et al.,*2022; Crenshaw, 1991). The UK Government (2020) reported that ethnic minority groups that reside in the most deprived decile in England have limited access in comparison to people who are White British. This excludes patients from Indian, Chinese, White Irish, and White other groups (UK Government, 2020). However, differences in statistical model systems and lack of granularity of the diversity of the population can influence the entry and interpretation of ethnicity data and effective interventions (Martins *et al*., 2022; Scot and Hoskin, 2024).

Further reports suggest the population of ethnic minorities will increase from 8% to 20% by 2051

(Scot and Hoskin, 2024). Thus, there is a critical need to improve the methodology in how data is collated to identify the ethnic minority and marginalized groups that face cancer care disparities and develop effective interventions and comprehensive targeted standards of care. This centralization embraces how there are delineating differences in social empowerment within the intrinsic frameworks of healthcare which contribute to a spasm of preventable hatred and unnecessary tension within groups amongst groups as seen in the recent vandalism and hostile protests towards vulnerable service users at refugee centres in provincial cities across the UK (Edwards, 2024).

The aging population also faces health disparities in deprived areas which is compounded by their recognition and understanding of symptom characteristics, cognitive decline, mobility, frailty, and transportation to medical appointments which influences their attitudes toward the healthcare system (Sorensen *et al*., 2015). On the other hand, despite the challenges of health literacy, it remains underscored by the National Cancer Control Plans (NCCPs) whose focal existence is to lower cancer incidence and collaborate with the NHS to achieve the Long Term Plan (World Health Organisation, 2024). Nevertheless, Scott and Hoskin (2024) revealed that the NCCP and Regional Cancer Alliance aim to collaborate to create a movement for health literacy.

Similarly, the Lesbian, Gay, Bisexual, Transgender, Queer\Questioning (LGBTQ+) community also faces gaps in understanding cancer. It has developed negative attitudes such as phobia, stigma, and confidentiality concerns in the realm of cancer care (Connolly *et al.,* 2020). This highlights how various social identities are facing health disparities and require sensitive care in medical practice.

In contrast, the NHS aims to overturn these limitations through the establishment of the Core20PLUS5 initiative that focuses on the most deprived 20% of the population identified by the National Index of Multiple Deprivation (IMD) based on social determinants of health (NHS England, n.d.). PLUS, groups who are the marginalized populations from ethnic minorities, and various disabilities, and who share protected characteristics as stated by the Equality Act 2010 (NHS England, n.d.). The 5 is connected to the clinical areas in which Governance hopes to improve: maternity, severe mental health (SMI), chronic respiratory disease, early cancer diagnosis where 75% of cases are diagnosed at stage 1 or 2 by 2028 and optimal management of hypertension and lipid profiling to minimize myocardial infarction and stroke (NHS England, n.d.). This suggests the continuation of the NHS in developing strategies for equitable cancer outcomes through timely screenings and therapies.

5.5 Males are more at risk of brain cancer

Furthermore, the GDO data in this study suggests males are more at risk of cancer than females. This is concurrent with reports by NHS England Digital (2023b) which discovered a three percent change in male patients with brain cancer where the number of cases in 2019 (2684) cases was higher than in 2021 with 2603 patients. However, for female patients, there were 1901 cases in 2019 which was reduced to 1826 in 2021. Similarly, Wanis *et al.,* (2023) discovered that there were more male patients (14094; 58.1%) diagnosed with brain cancer than female patients (10225; 42.1%).

Researchers from the Washington University School of Medicine in St. Louis (2014) have exposed why the presence of symptoms differs with sex in malignant brain cancer incidence irrespective of age and response to treatment (National Cancer Institute, 2019). There were 40 male and 23 female patients with glioblastoma post-surgical intervention who underwent cycles of temozolomide and radiotherapy. Upon the analysis of their MRI data and tumour genomic profiling for the assessment of growth and spread of tumours known as tumour growth velocity. Female subjects who expressed low levels of integrin-signalling components had a *ca.* survival of three years post-diagnosis in comparison to one-year survival with alternative molecular profiles (National Cancer Institute, 2019).

On the contrary, male participants who expressed low levels of components involved in the cell cycle survived for *ca.* a minimum of 18 months in contrast to one-year survival with alternative profiles. This correlated with the genetic and protein expression of the following proteins that normally function as tumour suppressors: neurofibromin, retinoblastoma, and the guardian of the genome (p53). Conversely, their mutated phenotype causes carcinogenesis and progression. Amongst all three proteins, retinoblastoma is more inactive in neural cells in male participants than in females. The disabling mode of this protein in both sexes equalizes the susceptibility towards brain cancer. IDH1 mutations are also associated with better survival in female patients with glioblastoma, whereas, male participants had a distribution of IDH1-mutant tumours (National Cancer Institute, 2019). These research findings replaced the common biological explanation of how sex differences in brain cancer are related to circulating sex hormonal production, for instance, testosterone and oestrogen (National Cancer Institute, 2019).

Arney (2009) reported that men in the UK tend to have poor lifestyle factors namely excessive alcohol consumption, overweight, and physical inactivity than females. The psychological input is also distinctive between both sexes. Female patients have frequent communication with healthcare professionals on symptoms, attend screening programs, and seek information about cancer prevention through magazines, social media, and other media avenues. The

saturation level has not been reached amongst the male population when gaining knowledge from health and fitness magazines and other publications. Scott and Hoskin (2024) revealed that males from deprived backgrounds have poor awareness of the risk factors of cancer. The National Awareness and Early Detection Initiative (NAEDI) seeks to improve diagnosis, particularly in men (Arney, 2009).

5.6 Socio-demographic factors influence routes of brain cancer diagnosis

Two-week wait pathway

The stage in the diagnostic pathway where there was the lowest proportion of patients was the two weeks wait referral. A total of 87 patients from the route's population (9942) in the GDO data attended their index two week wait (2WW) referral where there are 63 malignant cancer (1.33%) and 20 non-malignant cancer (0.49%). Male and female patients aged 50-69 years and 70 years and above with malignant cancers were profoundly in the North of England who underwent 2WW. South of England was highest for male patients alone aged 70 years and above. The region with the lowest attendance for female patients aged 50-69 years alone was Midlands and East of England. Combined sexes aged 50 to 69 years had the highest attendance in North of England but lowest in London and Midlands of England. Similarly, male, and female patients with non-malignant tumours had the highest population in North of England that underwent 2WW. These results are similar to the research findings of Wanis *et al.,* (2023) where the least number of malignant brain cancer patients underwent 2WW. There were 428 cases (1.8%) and 355 deaths (Wanis *et al*. 2023).

Sheridan *et al.* (2024) discovered reasons for the low proportion at 2WW referral. In their study, they revealed 108,166 patients did not attend and were commonly patients amongst the young and the elderly populations, male and lived in the most deprived areas (Campbell *et al.*, 2015; Sheridan *et al.* 2024). Amongst the causes for non-attendance was transport difficulties where they lived at a further distance from the hospital, passed away or experienced a hospital admission between the GP and hospital appointment (Nelson, 2023, Campbell *et al.*, 2015; Sheridan *et al.* 2024). However, there was a small number of patients who had cancer from those who did not attend but had poor clinical outcomes (Sheridan *et al.,* 2024).

Non-attendance rates has also been observed nationally which suggests it is a significant concern because reports propose 5-7% of patients did not attend because of transport difficulties, finance, short-notice appointment and contact details are not up to date (Scott and Hoskin, 2024). Psychological factors such as fear of tests, anxiety for potential cancer diagnosis and therefore, ignoring the symptoms they experienced. Patients with multiple health conditions or have mental health problems could also cause patients to not attend. This highlights the importance of effective

communication and reasoning when care-planning with the patient and during discussion in multidisciplinary team (MDT) meetings (Scott and Hoskin, 2024).

GP referral

The next stage in the diagnostic pathway is the GP referral where the GP determines which specialty the patient should be referred to depending on the signs and symptoms at presentation (Sheridan *et al.,* 2024). The referral is completed by the GP and received by the hospital within 24 hours and this is where the 'referral period' initiates. Ozawa *et al*., (2018) reported that some patients were transferred to neurology (24%), general medicine (22%), emergency, ophthalmology, and neurosurgery (8%). The percentage number of patients who were referred to stroke services and paediatrics was 4% and the remainder was unknown (Ozawa *et al*., 2018). Patients with a past medical history of cancer have a referral to oncology because of the increased likelihood of CNS symptoms being related to a brain tumour at a metastatic stage. This demonstrates the variability in the secondary care services that suspected brain tumour patients may be referred to. In contrast, the GP referral can be terminated if the patient has been seen by the Trust or was referred to the GP (Sheridan *et al.,* 2024).

The GDO data suggests that 2890 patients underwent GP referral. There were 983 malignant (20.67%) and 1429 non-malignant brain cancers (35.21%). Midlands and East of England showed significant differences whereas London and Northern England had no significance for patients with malignant cancers. No substantial difference was observed by region in patients with non-malignant cancers. There is a close similarity in the percentage number of malignant brain tumours patients who underwent GP referral (19.9%) in the Wanis *et al*., (2023) study where there were 4833 patients and 3669 deaths.

Researchers have developed a structural framework that aids in the cancer diagnosis pathway called the Andersen Model (Walter *et al.,* 2012). There are five key precepts: appraisal delay, illness delay, behavioural delay, scheduling delay, and treatment delay. Appraisal delay refers to the time interval where symptoms are recognized as serious and could contribute to delayed diagnosis due to health literacy, social support, and cultural beliefs (Scott and Hoskin, 2204). A study discovered that over 7000 individuals were interviewed via the telephone in six countries including the UK. Results suggest there was minimal understanding of cancer symptoms which lowers chances for patients to report them (Quaife *et al.*, 2014). Social support is also a factor where family intervention varies

per culture. Patients from Asian origin are commonly surrounded by extended families whereas patients from White British have nuclear families (Wanis *et al.,* 2023). This increases the likelihood of earlier diagnosis because extended families tend to notice neurocognitive changes which may be suspected brain tumour (Wanis *et al.,* 2023).

Illness delay refers to the time point when the patient decides to contact the GP. Amongst the factors that influence their decision are personal beliefs and trust in the healthcare system could be declined if the patient experiences negative scenarios previously. Other factors are stigma, finance, fear, and caregiving responsibilities which cause the patient to evade seeking support and misattribute symptoms (Walter *et al.,* 2012).

Behavioural delay refers to when the patient aims to perform an action and seek support. This is dependent on the severity of the symptoms and is compounded with negative thoughts on trust and cultural nuances where the disease is seen possibly bringing shame to the family due to the condition or symptom deemed inappropriate. Other possible explanations are prioritization and the personality of the patient. Some patients have language barriers, and transport difficulties or consider the use of traditional medicine.

Scheduling delay refers to the time point to seek an appointment. The treatment delay is the time from the first consultation to the start of the treatment (Scott and Hoskin, 2024). Scot and Hoskin (2024) found no differences between significant appraisals and treatment delays. Illness delay was unrecognizable from appraisal delay (Scot and Hoskin, 2024). Further studies discovered definitive comparative methods are needed.

Moreover, there are several different referrals conducted by GP practice for brain cancer. Zhou *et al.*, (2018) implied that brain cancers have the least likelihood to be fast-tracked for referral from a total of 35 primary cancer sites. The GP direct-referral imaging pathway is where there is a small proportion of GPs who have access to an MRI and can receive results within two weeks (National Cancer Research Institute, 2023). It is estimated that 3.3% of brain tumours are detected via this route and considered a definitive diagnostic method for brain cancer due to its sensitivity (National Cancer Research Institute, 2023; Zienius *et al.*, 2019). There were also successive outcomes to detect incidental tumours.

The GP may organize a CT referral, especially in acute settings if the patient's previous scan showed intracranial metastases in multiple secondary sites notably the pelvis, chest, and abdomen (Lerner *et al.*, 2024). GPs have limited

access to CT compared to MRI (National Cancer Research Institute, 2023). Other reasons for a CT referral are if the patient has head and subacute cognitive presentations (Zienius *et al.,* 2019).

Additional advantages of the CT scan are its wide availability, inexpensive procedure that has shorter waiting time intervals, and has little to no chance of gaining false negative scans (Zienius *et al.,* 2019; National Cancer Research Institute). Positron Emission Tomography (PET is another imaging technique that helps detect hot spots that have high metabolic activity which signifies higher grade malignancy and sites for biopsy (Weller *et al.,* 2017). Other investigations organized by the GP are routine blood tests, ophthalmological evaluation, and clinical examination of the skin and breast (Lerner *et al.*, 2024).

However, according to the clinical radiology census report published by the Royal College of Radiologists (2023), there remains a backlog of image reporting despite the radiology workforce growing by 6.3%. There is a 30% decrease in clinical radiology consultants (1962) and 75% of patients in England (745290) are pending test results for more than four weeks, particularly CT and MRI reports, and have initiated lifesaving treatments while waiting for the outcome of the reports. It is predicted to increase if further action is not taken by 2028. The NHS has attempted to overcome these limitations by increasing expenditure (£276 million) on ad-hoc locums, outsourcing, and in-sourcing where 2690 consultants are recruited to meet the demand. This suggests there are still outstanding challenges to be addressed as in 2020, the Royal College of Radiologists announced one hospital met their imaging reporting requirement despite CT being more widely available than MRI (National Cancer Research Institute, 2023).

Additional preventative measures have been applied by the UK Government and the NHS who aim to open 160 community diagnostic centres by 2024 because of the pressure experienced at hospital radiology services and low staffing (National Cancer Research Institute, 2023). The introduction of the iRefer clinical decision support tool may help ensure the right scans are done in time. New-generation CT can give high quality images to detect tumours with mass, haemorrhage, infiltrative patterns, and hydrocephalus. This will low costs for GP but further studies are needed to confirm these findings (Keeney *et al.* 2020).

It is agreed upon that the first neurological symptoms experienced amongst patients with brain tumours are: severe, persistent headaches, seizures, cognitive deficits, dizziness, and unsteadiness (National Cancer Research Institute, 2023).

Nausea, behavioural change, visual deficits, focal neurological deficits, and paralysis are common (NHS Inform, 2024b). The estimated median time from first symptom to neurosurgery was 43.5 days (National Cancer Research Institute, 2023). Conversely, some patients have symptom complexity, especially among teenagers and adults where there require multiple GP consultations before a referral is then made to secondary care (Dommett *et al.*, 2013). There is a median time of two months for diagnosis where the GP felt delay could have been avoided in a third of cases due to the complex symptom presentation (Ozawa *et al.*, 2018).

Nall (2023) defined a seizure as an electrical surge in the brain that can arise in one area (focal onset seizures) where it can affect your consciousness (focal impaired-awareness seizure) or it can affect both hemispheres of the brain influencing muscles and movement of the limbs (generalized onset seizures). Seizure activity ranges between 35-70% of brain cancer patient cases but is dependent on the type of tumour (Newton and Wojkowski, 2024). Low-grade glial tumours and extrinsic tumours of the meninges or pituitary region are slowly present with this symptom (National Cancer Research Institute, 2023). On the other hand, it can be accompanied by cognitive decline, focal deficits, and visual defects (National Cancer Research Institute, 2023). Nevertheless, it can occur in any grade of neurological tumours. Other causes of seizure are stroke, infection, dementia, hypoglycaemia, side effects of drugs, and electrolytic disturbance (National Cancer Research Institute, 2023).

The onset of seizures in patients above the age of 18 is uncommon and requires emergency hospital attention. The National Cancer Research Institute (2023) discovered 10% of patients have their first seizures and confirmed brain cancer diagnosis in such cases. Alternatively, seizures commonly occur in 20-25% of brain tumour cases. Other researchers discovered patients who experience seizures and go to see their GP survive longer than those who experience speech impairment, weakness, and confusion (National Cancer Institute, 2024). High intracranial pressure, tumours in the cerebellum, and deeper neural tissues have poor survival. Seizures are commonly treated with Levetiracetam alone which has high efficacy and does not influence the chemotherapy's mechanism of action (Roth *et al*., 2021). Other epileptic drugs work better when combined with corticosteroids and have shown to decrease the frequency of the first seizure within 6 months post-diagnosis (Lerner *et al.,* 2024).

The second most common symptom in brain cancer patients is headaches where there are less than 50% of cases at hospitals (National Cancer Research Institute, 2023). Headaches are caused by pain receptors in the blood vessels, ependyma, and meninges and can cause other symptoms. Structurally, there is no underlying cause for most headaches, and they are classified as primary headaches. Headaches caused by tumours are termed secondary tumours. People who are at most risk are those with a historical presentation of headache, Human Immunodeficiency Virus (HIV), papilledema, pregnancy, exercise, the elderly, and a rare phenotype of headache National Cancer Research Institute, 2023). Headaches were worse after undergoing the Valsalva maneuver. The Valsalva maneuver is a breathing technique used to help diagnose the autonomic nervous system and restore heart rate to normal range (Roland, 2019). Progressive headaches commonly occur during the night and early morning or when reflexes namely coughing, sneezing, or bending are performed. The NICE guidelines for (CG150) for headaches and when scanning referral is required.

Patients with intracerebral tumours experience neuropathic pain frontally or to the vertex (National Cancer Research Institute, 2023). Frontal headache or orbital pain is also felt if tumours are near the cranial nerve and/or pituitary fossa (National Cancer Research Institute, 2023).

The neuropathic pain is sharp, burning, and stabbing pain that continues to occur if the patient has cranial nerve deficit insufficiency or overproduction of the pituitary hormone. However, tumours in the pons, medulla or cerebellar posterior fossa, meninges, vessels, and low cranial nerves (VII – XII) experience pain in the mastoid, occiput, or neck (National Cancer Research Institute, 2023). The anatomical presentation of these neural structures is illustrated in Figure 13 to 15.

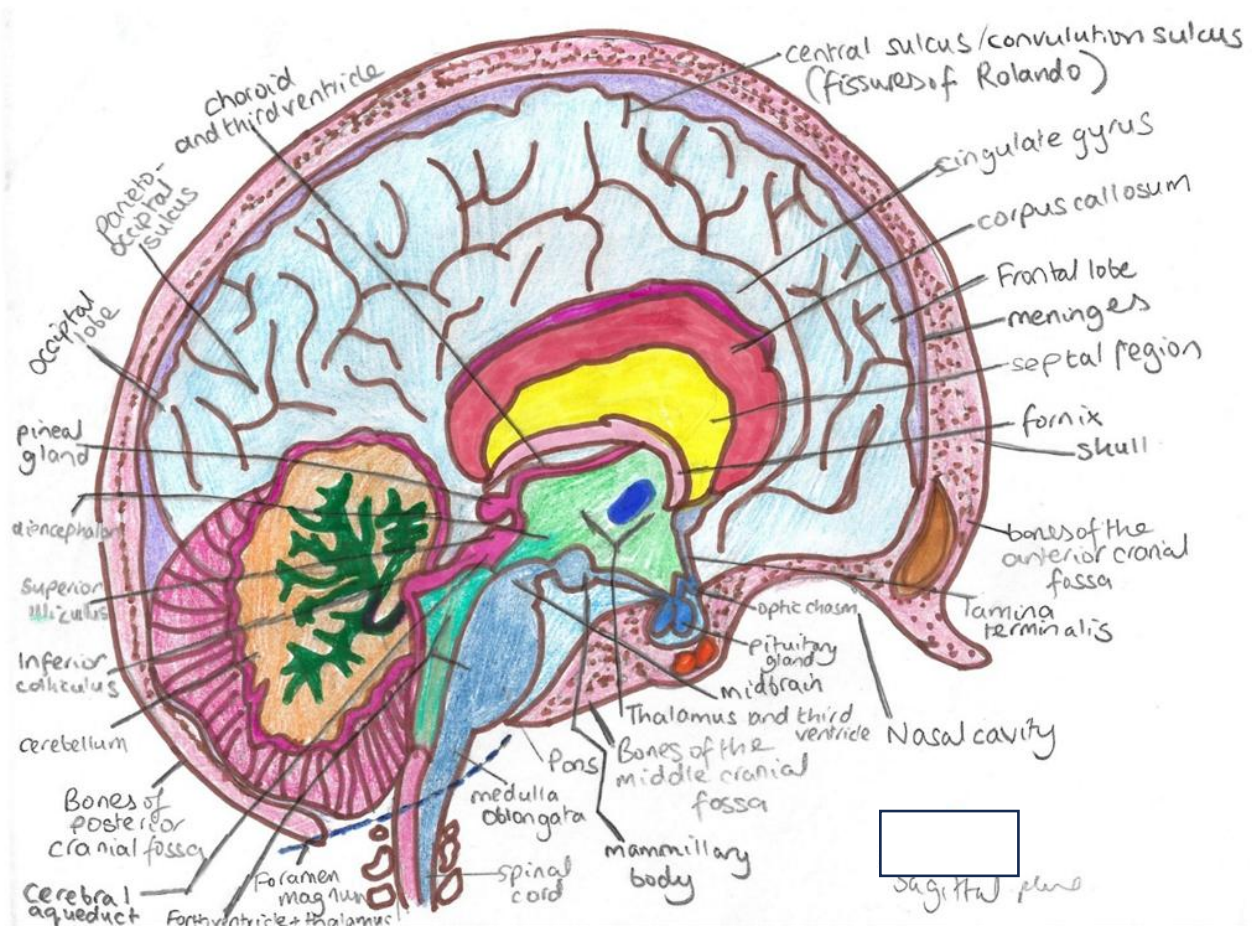


Figure 13 Schematic diagram of the neuroanatomical plane of the brain (Sagittal view).

There are three divisions in the brain: the forebrain, cerebellum, and brain stem. The forebrain is subdivided into diencephalon and cerebrum. The cerebrum consists of the right and left cerebral hemispheres. The hemispheres are disconnected by a longitudinal division that associated with a bundle of neural fibers called corpus callosum. The cerebral cortex forms the outer layer of the cerebrum where the occipital and frontal lobes (illustrated) are among the lobes, and the parietal and temporal lobes are the other lobes. The cerebrum contains raised ridges called gyrus and deep grooves between the gyrus called sulcus. The choroid plexus is a vascular epithelial structure that surrounds the cerebral ventricles and functions in producing the cerebrospinal fluid (CSF) that fills these ventricles and the subarachnoid space that surrounds the brain and spinal cord. The brain is protected by a membrane called the meninges followed by the skull. The cranial fossa (anterior, middle, and posterior) help keep the brain and vital structures in position. The diencephalon contains the thalamus and hypothalamus. The thalamus is involved in most cases of soft cerebral cortex and focused attention. The hypothalamus regulates the internal environment using a homeostatic mechanism. The thalamus and hypothalamus are part of the limbic system regulating emotions and learning. The mamillary bodies form part of the hypothalamus and function in memory, learning, anxiety, and spatial information processing. It is subdivided into medial and lateral mamillary nuclei. The cerebellum functions in voluntary movements, posture, and memory. The midbrain, pons, and medulla oblongata constitute the brain stem and contain reticular formation (Widmaier, Raff and Strang, 2008).

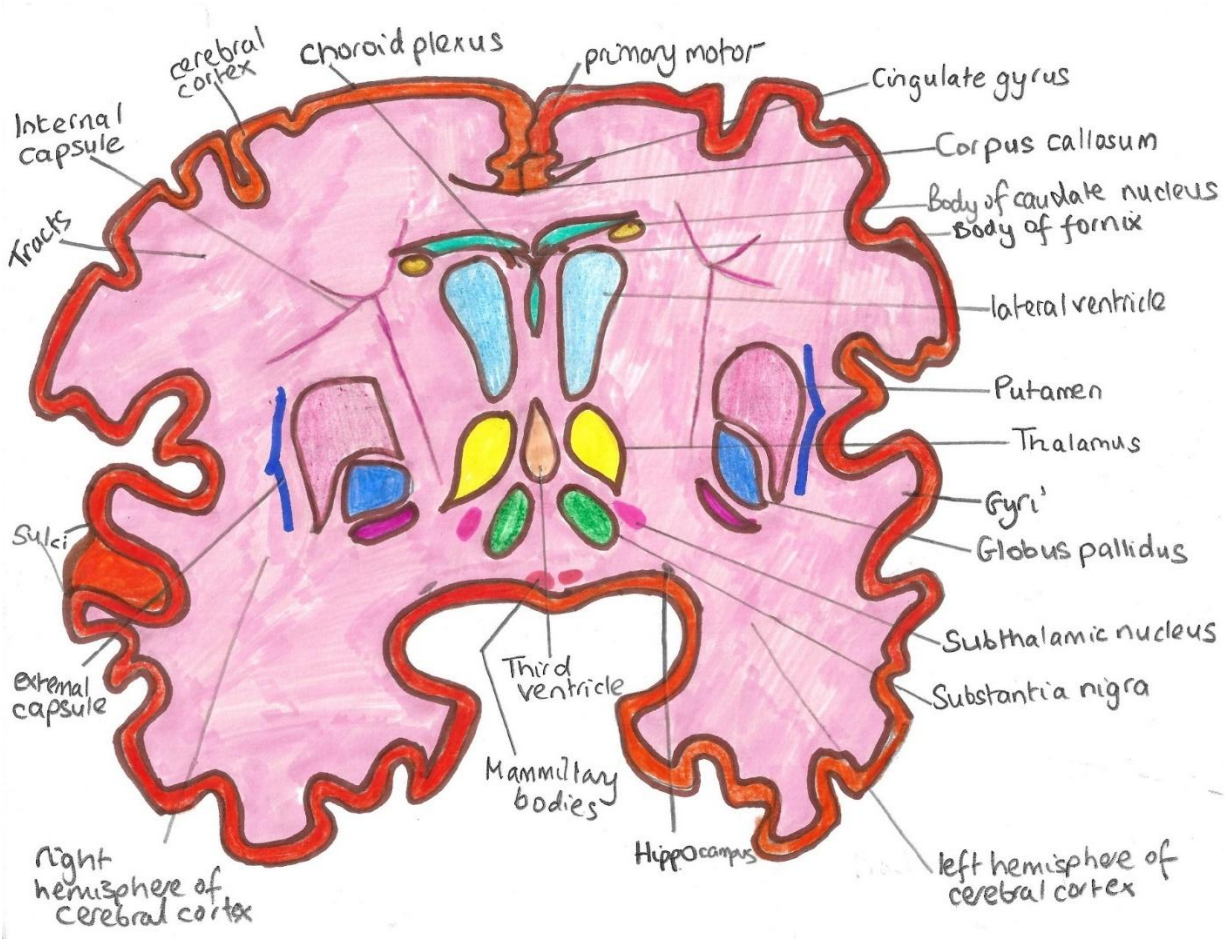


Figure 14 Schematic diagram of the neuroanatomical plane of the brain (Coronal/Frontal view).

This is the frontal section of the brain presenting additional internal structures. The hippocampus is part of the limbic system that regulates emotions and learning. The substantial nigra is a subcortical nucleus that contains neurons that releases dopamine and suppress muscle action (Widmaier, Raff and Strang, 2008). The putamen is a subcortical nucleus that maintains learning, language, and motor control. The putamen in combination with the globus pallidus creates a lentiform nucleus. The lentiform and caudate nucleus forms the basal ganglia (Ghandili and Munakomi, 2023). The fornix consists of neural fibers called fimbria that surround the thalamus and connect with the hippocampus (Vandera and Gould, 2016).

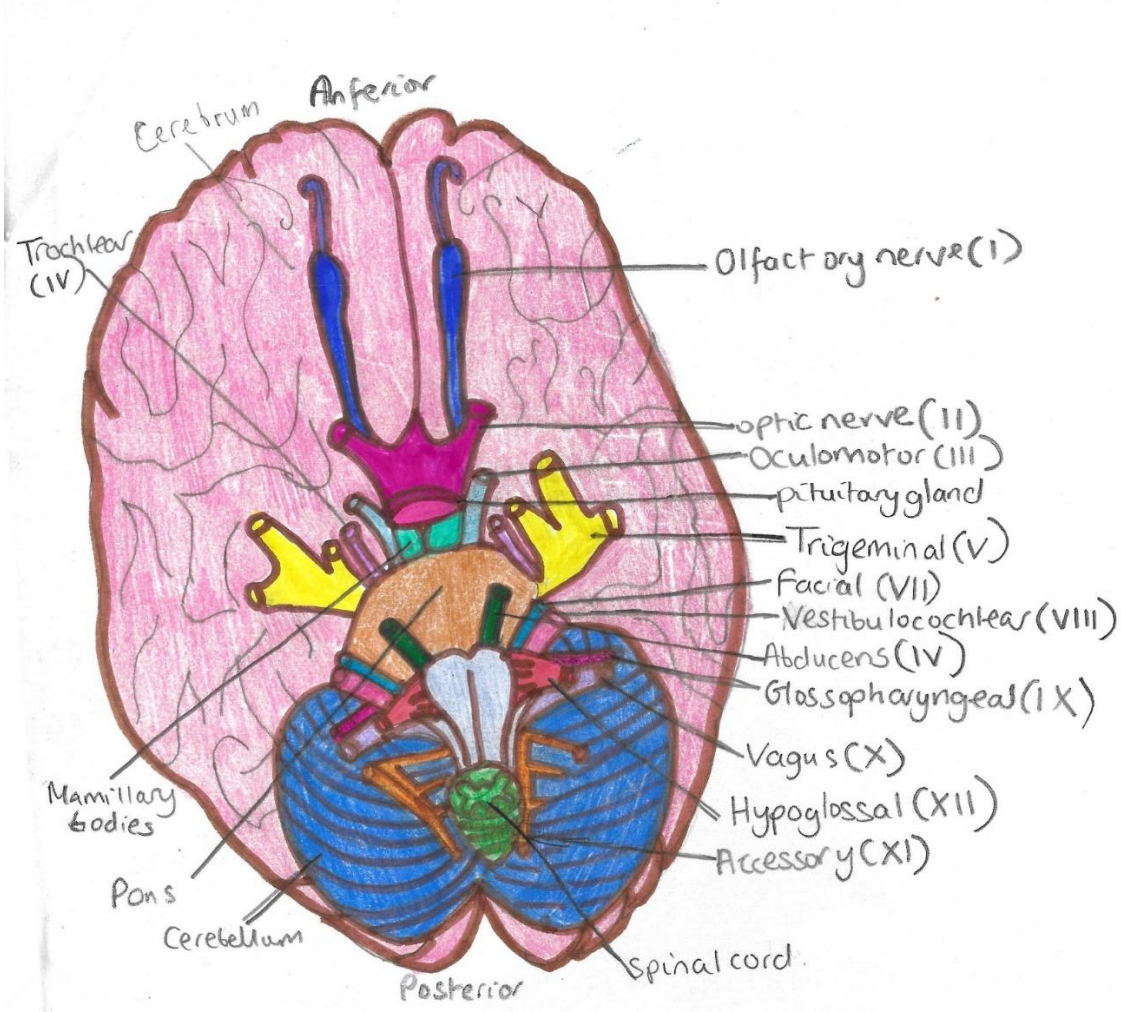


Figure 15 Schematic diagram of the neuroanatomical plane of the cranial nerves in the brain (Inferior view).

Twelve pairs of cranial nerves form the peripheral nervous system and connect with the brain stem and forebrain with structures externally particularly in the organs in the thoracic and abdominal cavities. They can be subdivided into afferent and efferent fibers. Afferent fibers transmit information from the sensory receptors to the central nervous system whereas, the efferent fibers transmit information from the central nervous system to the effector which is a muscle or gland. Olfactory (I) is an afferent fiber that is considered not a true nerve but carries impulses from the receptors situated in the olfactory neuroepithelium (smell) (Widmaier, Raff, and Strang, 2008). The optic (II) is an afferent fiber considered not a true nerve but carries input from the eye receptors. Oculomotor (II) has a dual role where efferently it contracts the skeletal muscles that help move the eye and eyelid. It also helps the smooth muscles to contract which constricts or dilate the pupils and alters the shape of the lens in the eye for near and far vision. However, Ocululmotor can also transmit information from receptors in muscles afferently. Trochlear (IV) can help move the eye downwards and laterally. It can also transmit information from receptors within the muscles. Trigeminal (V) can control muscles while someone chews and can transmit information from receptors in the skin, muscles in the face, and teeth sockets. Abducens (VI) can help move the eyeball laterally and transmit information from receptors in muscles. Facial (VII) innervates skeletal muscle within the face, particularly the nose, palate, lacrimal, and salivary glands. It can also help transmit information from taste buds within the tongue. Vestibulocochlear (VII) contains afferent fibers that transmit information from receptors within the ear for sound and balance. Glossopharyngeal (IX) can efferently innervate skeletal muscles that are involved in swallowing and producing saliva in the parotid salivary glands. However, it can afferently transmit information from taste buds found at the back of the tongue/posterior third of the tongue, tonsils, and pharynx (voicebox). The vagus (X) can help guide the muscles of the pharynx and larynx. Smooth muscle thorax and stomach for breathing, heart rate, and digestion. It also helps transmit information from receptors in the thorax and abdomen. Accessory (XI) supports neck skeletal muscles. Hypoglossal (XII) can efferently help with strengthening the tongue movement (Widmaier, Raff, and Strang, 2008).

Tumours in the meninges and cranial nerves have slow-growing masses and low cerebrospinal fluid (CSF) blood volume (National Cancer Research Institute, 2023). This is caused by having access to compensatory mechanisms where there is low intracranial pressure and has not blocked the CSF pathway. On the other hand, patients with glioblastoma can sojourn the flow rate of cerebrospinal fluid and this causes hydrocephalus, a build-up of fluid in the brain caused by headaches and elevated intracranial pressure (National Cancer Research Institute, 2023). Lack of concentration, seizures, and neurological deficits commonly occur together increasing the likelihood of brain cancer (Ceronie *et al.* 2021). Suspected arachnoid haemorrhage infection or giant cell arteritis in patients with headaches are triaged to urgent appointments or scans (National Cancer Research Institute, 2023).

Papilledema is the optic disc swelling in response to high intracranial pressure. It is estimated that 12-15% of cases of brain cancer upon admission (National Cancer Research Institute, 2023). Some studies suggest that 12.6% of patients with seizures also have Optic fundi. Multiple symptoms alongside headache require urgent medical attention. One of the limitations is the GP and hospital lack confidence when identifying this condition hence why they do not check optic fundi using fundoscopy (Dixon *et al*. 2015). Other potential causes of papilledema are haemorrhage, head trauma, thrombosis, hydrocephalus, and meningitis (National Cancer Research Institute, 2023).

Dizziness, unsteadiness, numbness, unilateral weakness, and visual field defects are key examples of focal neurological deficits and rarely occur initially. In 20-30% of cases, focal neurological deficits are the first symptom at a hospital or GP appointment (National Cancer Research Institute, 2023). The median time for brain cancer diagnosis was 21 days (Ozawa *et al.*2018).

The initial presentation of cognitive deficits is common but progressively occurs more at the point when the diagnosis is confirmed. Poor concentration, memory, and attention are caused by lack of sleep, seizures, headaches, anxiety, and focal neurological deficits (National Cancer Research Institute, 2023). This increases the likelihood of neurological conditions like dementia, multiple sclerosis, or brain tumour (National Cancer Research Institute, 2023).

Additional symptoms may appear in patients with neurological, pulmonary, psychiatric, or cardiac conditions or other comorbidities who experience longer diagnostic intervals and more advanced stages of cancer (Renzi *et al*., 2019). There is also a form of stereotypical bias

where doctors dismiss symptoms amongst marginalized groups or delay tests because of ethnicity, gender, or socioeconomic status. Cultural and linguistic barriers may also be among the limitations (Scott and Hoskin, 2024).

Alternative referral pathways organized by the GP: urgent suspected cancer pathway occurs within two weeks. 0.9% of patients were diagnosed with brain cancer compared with 6.6% of all cancers via this pathway (National Cancer Research Institute, 2023). Blacks were more frequently diagnosed through elective GP referral (31.1%) than Caucasians 22.9% (Scott and Hoskin, 2024).

Univariate analysis of patient experience in NHS primary care between 2011 and 2017 discovered young patients from ethnic minorities and resided in the most deprived areas had fewer positive experiences due to difficulty in accessing GP this was particularly noted in London despite their low brain cancer incidence (Scott and Hoskin, 2024; Lyratzopoulos *et al*. 2012; Saunders *et al*. 2021). However, there is limited evidence of longitudinal trends when evaluating inequalities in patient experience using primary care services (Cookson *et al*., 2016). Possible explanations for these results are caused by poorly performing GP practices or differences in patient care at the same practice despite the establishment of the GP Access Fund that aimed to decrease disparities in care by providing a financial commitment to alleviate difficulties faced by GPs through innovative solutions (NHS England, 2018b; Saunders *et al*. 2021).

Similar research findings were also revealed by Scot and Hoskin (2024) and Fraulob and Davies (2019) where communication halted the doctor-patient relationship and 20% of brain cancer patients were unsatisfied with the care received from their respective GPs. This led them to change their practice post-diagnosis due to psychological stress (Fraulob and Davies, 2019).

Patient care is influenced by the dual proxies of well-being: objective and subjective. Socio-economic status, literacy, and rates of life expectancy are aligned with objective measures. On the other hand, subjective well-being is delved into the perceptions of patients on life and their experiences, especially after a confirmed cancer diagnosis (Durand, 2015; Diener, 2009). Communication with patients can largely influence cancer patients through two views of subjective well-being. Hedonic well-being adheres to how a cancer patient feels and senses their well-being whilst the eudemonic view reflects on the patient's potential and chances to overcome challenges that comprise internal personal and external social factors during their cancer journey fulfilling their desire to be cancer-free (Das

et al., 2020; Kahneman *et al*., 1999; Vanhoutte and Nazroo, 2014).

Prominent research works of Wilson (2015) defined happiness and pain because of satisfaction of needs and psychological engagement. Through the functionalist lens, Parson's (1951) system theory considered illness as a social concern that requires a patient to seek help and cooperate with the doctor. The patient must increase efforts to heal while the doctor aims to support the patient by applying the method of Verstehen and giving advice by putting themselves in the places of their patients. This helps understand the sentiments the patient and their respective family may undergo.

Conflict theorists consider illness a key element that has conceptualized the diagnosis and treatment of patients, health power in society, and resources (Svensson, 2001). A key example is the Foucauldian work on the clinical gaze where the oracle of the doctor-patient communication is vital due to linguistic and epistemological construct, the archaeology of knowledge shared, and gazing action (Foucault, 1973). A physician might observe a neurological sign during the consultation and they will use their medical knowledge and exercise their professional power to interpret what the patient has using the clinical gaze approach. This will progress with the linguistic construct where questions will be asked to the patient to gain information that might guide additional inspections of symptoms seen and the use of the stethoscope that contribute towards clinical gaze (Suijker, 2023). The patient also possesses invisible power where they have individual responsibility for making decisions and their behaviour during consultations (Canter, 2001).

Further investigations may be required to determine the pathology and rule out other possible conditions because each disease embeds itself differently. Osborne (1992) considers this an objective entity but the localization of the disease can be subjectifying especially as they encounter GPs and hospitals where they feel cancer has invaded all their lives (Suijker *et al.,* 2021).

Recent years have shown a positive shift in primary care as evidenced by the recently published outcomes of the National Cancer Patient Experience Survey 2023. It was completed by 63438 cancer patients where 242 had brain tumours (0.4%). 78.3% of the participants contacted their GP practice once or twice before their cancer diagnosis. This is an increase in comparison to 77.7% in 2022. 13.9% of respondents saw their GP three times or more and 7.8% consulted five times or more (NHS England, 2024). These statistics were also slightly higher than the previous year suggesting there are still missed opportunities for earlier

diagnosis (NHS England, 2024). 66.5% of participants in 2023 stated their GP explained their diagnosis in a way they could understand compared to 65.4% in 2022 (NHS England, 2024). Sensitive care and compassion were also applied as 84% of respondents were told their physician informed them, they could return for further information after digesting their confirmed diagnosis compared to 83.6% in 2022 (NHS England, 2024). This highlights significant improvements in patient care in the NHS primary services.

Outpatient appointments.

The GDO data in this study revealed that 19.36% (1925) of subjects progressed to communicating with a consultant in an outpatient appointment following a GP referral. There were 892 (19.76%) and 746 (18.38%) cases of patients with malignant and non-malignant brain cancers respectively. This is similar to the percentage number of patients who underwent outpatients by Wanis *et al.* (2023) where there were 19.7% (4791) cases and 3569 deaths. It has been reported that inadequate investigation of symptoms faced by suspected brain cancer patients can delay the initiation of treatment after their first outpatient appointment. Other causes of treatment delay are lack of follow-up, referral delays caused by systemic and patient factors, and delays in receiving pathology reports and other test results (Walter *et al*., 2012; Scott and Hoskin, 2024).

Additional challenges were particularly notable in geriatric patients with cancer in secondary care services. Limited access to modern diagnostic methods and therapeutic interventions results in longer waiting times. Conditions such as hearing impairment and dementia affected their communication with their consultant during the consent process and discussion of the treatment plan. Other symptoms experienced are disorientation and distress at the hospital (Harrington, 2016). Further reports revealed physicians may hold stereotypical views and lack of understanding about aging mechanisms and as a result, prescribe alternative treatments to alleviate neuropathic pain and prolong survival (Prathap *et al.*, 2024). According to Freidson (1970) conflict theory, differences in social and cultural elements can shape the concepts and knowledge on cancer.

However, Stewart *et al*., (2009) revealed elderly patients are susceptible to complications post-treatment due to the cytotoxic levels, inability to metabolize drugs, and low degree of functional tissue. This elevates the likelihood of conditions induced by myelosuppression such as anaemia and thrombocytopenia. Other conditions such as enterocolitis and microsites are also affected (Stewart *et*

al., 2009). Elderly patients are also excluded from clinical trials because of a lack of understanding of the effects of these cancer treatments. They also experience unsupportive care to prevent side effects due to limitations in the healthcare system. To overcome such challenges, milder diagnostic approaches will help elderly patients unable to recognize symptoms and the need for an individualized care plan to cooperate with geriatric medicine for a holistic plan that involves psychosocial, dietary, cognitive, and physical support (McKenna, 1994). Patients aged 70 years and older required scans to determine survival, the position of the tumour, and if there are multiple tumours and to assess pressure on the brain (National Cancer Research Institute, 2016).

The diagnostic pathway was also influenced by the COVID-19 pandemic that was initiated in December 2019. There were affected measures, especially during the UK governmental lockdown and restrictions between March 2020 and December 2021 (Institute for Government, 2022). For instance, there was a transition from face-to-face consultations to telephone and video consultations. Delays in scanning and surgical procedures, minimal hospital admissions, lack of screening, and capacity of conventional care were reduced due to deviating the available resources and efforts toward COVID-19 patients. This deteriorated neurological function and dramatically impacted brain cancer incidence and survival and cancer in general due to the poor clinical management system in place (National Cancer Research Institute, 2023; Cioffi *et al.,* 2024).

Furthermore, this could explain why there are data limitations within the GDO because lockdowns in 2020 influenced the trends of cancer diagnosis lowering numbers than the previous year (Jeffrey, 2024). Registration of 2019 tumours was done during covid-19 pandemic which decreased access to data sources (Jeffrey, 2024). Delayed or avoided medical care was also seen from a patient's perspective because of the fear or risk of contracting COVID-19 or being unable to receive care (Cioffi *et al*. 2024). There is a dire need for policymakers to create effective measures to be implemented during future disease outbreaks (Tambuyzer *et al.,* 2023).

Emergency presentations

The GDO data in this study revealed the highest proportion of patients underwent emergency presentation. There were 4239 (42.64%) patients where there were 2495 cases of patients with malignant cancers (52.47%) and 1472 cases of non-malignant (36.27%). There was no significant difference by region and gender. This percentage rate was lower than the research findings of Wanis *et al*.

(2023). There was 12926 malignant cancer cases (53.2%) and 11.622 deaths with emergency presentation (Wanis *et al*. 2023). There was 743 (3.1%) and 595 deaths for inpatient elective (Wanis *et al*. 2023).

There are other reports that 50.1% of cancer presentations occur via emergency pathways where a third of patients visited their GP prior to this. The remainder of patients are referred to optometry or undergo self-referral after experiencing seizure or stroke (National Cancer Research Institute, 2023). 20-33% of patients have ophthalmic symptoms prior to diagnosis such as headaches, the need of new glasses due to refractive error and other ocular symptoms. Suspected papilledema is referred to emergency or ophthalmology departments (National Cancer Research Institute, 2023).

However, despite the high proportion of patients undergoing emergency presentations, it also has poor survival rates due to missed diagnosis and is associated with the extensive of disease and level of deprivation where more deprived areas are at risk (Abraham *et al.,* 2022;). Similar results were also found by the National Cancer Intelligence Network (2015). People from other ethnicities had the highest likelihood of emergency department diagnosis (28.1%). Patients from Black, Asian, and mixed ethnic backgrounds have lower diagnosis rates compared to whites (Scotts and Hoskin, 2024). This highlights how socio-demographic factors influences incidence, diagnosis, and survival rates.

The GDO data contrasted with findings of the Clinical Practice Research Datalink that evaluated 240,000 patients. Most patients were diagnosed through 2WW (36.4%), followed by elective GP referral 23.2%, emergency presentations (18.2%), hospital outpatients (10.3%) and screening (8.6%) (Martins *et al.,* 2022).

6. CONCLUSION

The GDO data in this comprehensive study and current literature revealed the positive outcomes and areas of improvement that harness the delivery of care to patients at the NHS. Please see Supplementary Material 5. There are biological and non-biological explanations for the incidence and routes to diagnosis of brain cancer patients. The NHS aims to interconnect concepts of individual and collective wellbeing through statutory and policy measures. This increases the patients' potential towards their wellbeing and improve survival rates to meet the ambitious objectives of the NHS Long Term plan by 2028.

Charities such as the Brain Tumour Charity, Cancer Research UK, and MacMillan Cancer Support as well as British Neuro-Oncological Society

(BNOS) have taken various measures to create an equilibrating healthcare system that develops research, training, resources, and awareness campaigns that are culturally sensitive such as the Be Clear on Cancer campaign. This helps improve communication and the mental health and wellbeing of patients and their families (Scott and Hoskin, 2024).

Moreover, health promotion on the different types of brain cancer is vital. Triage symptoms of outpatient referral using advice and guidance from NICE guidelines also helped direct primary and secondary care physicians to optimize their care planning process. This articulates reasoning as to why the trends in brain cancer incidence have decreased.

However, this is inhibited by the inequities and inequalities that have been postulated by the neoliberal ideologies that pressure the social, political, and economic power structures that shape and influence how society views those afflicted with cancer (Tulip *et al.* 2020; Ostry, Loungani and Furceri, 2016; Bunton and Macdonald, 2003; Kemp and Fisher, 2022). The young, the elderly, males and those who live in deprived areas have increased prevalence. The wielder of power and control is laid in the doctor and patient understanding the importance of the investigative procedures to test, monitor, and treat in the best interests of the patient. It is socially constructed where patients come to understand how to adapt and live with the illness and face reality (Conrad and Barker, 2010)

The imbalance in the incidence rates and routes of diagnosis by region, age, and type of tumour signifies the necessity to invest in research, particularly in recognizing the complexity of symptoms in suspected brain cancer cases.

In general, Crosby *et al*. (2020) have outlined the UK's capacity to thrive in the early detection and diagnosis industry due to the solidified data infrastructure, scientific base, and vast NHS. However, its magnetism towards global investment in the delivery of early detection and diagnosis has been 'largely unexploited' and 'scant' as it is a comparatively novel field with complex biology, there are challenges to obtain quality samples, and lack of funding for translation and the expense for longitudinal studies are contributing factors. A proactive and holistic approach is needed from the initial stages to its implementation to surpass the trials faced in diagnosis and treatment.

Cancer Research UK is a prime example that actively consulted multiple stakeholders across multidisciplinary and multisectional networks to help overcome challenges in healthcare by uniting specialists with a shared vision to enhance research development and improve health system delivery and governmental policy (Crosby *et al*., 2020).

There has been considerable efforts in improving our understanding of neurological cancer since the Ancient medical texts to date – a summary of key events are summarised in Supplementary Material 1-3.

Collaborative initiatives in a stepwise manner with local authorities and multidisciplinary contributions will help raise awareness of cancer beyond the individual through school establishments, universities, workplaces, and community health clinics, particularly in deprived areas to help lower the incidence rates and meet the basic psychological need for connection and develop nurturing environments to overcome the burden of cancer driven by vagal function (Kemp and Fisher, 2022).

Telemedicine, community health clinics, and financial assistance for travel increase the accessibility of quality patient care in the most deprived and remote areas (Scott and Hoskin, 2024). Educational material in multiple languages will help improve communication with the community.

This compiling evidence demonstrates the importance of the social-ecological model in understanding the relationship between social determinants of health with health behaviour and clinical outcomes. The quintet model has the following sectors: individual, interpersonal, organizational, community, and policy. A collective movement of personal knowledge, attitudes, perceptions, social connections, support, and social cohesion on an organizational level can have a significant impact on cancer incidence and clinical outcomes (Stadeli *et al*., 2020).

Furthermore, one of the key research areas needed for improvement is to determine which radiological technique is best for headaches: CT or MRI. The evolution of Artificial Intelligence (AI) is increasingly encouraged for the rapid reporting of symptoms within the intracranial tissue particularly in symptom combinations (National Cancer Research Institute, 2023; Wood *et al.* 2022). Safety netting could be used during face-to-face consultations and simple cognitive testing such as the semantic verbal fluency test (SVFT) will facilitate the diagnosis of neurological conditions (National Cancer Research Institute, 2024; National Cancer Research Institute, 2023). Headache management pathways could also help increase certainty when distinguishing primary and secondary headaches and other neurological combinations. This will decrease the number of scans and upsurge the predictive value. Improving diagnosis and survival in geriatric patients with glioblastoma can be achieved by identifying targeted proteins and surface markers as biomarkers of aging (Kim *et al.* 2021). This will help in increasing the number of studies that compare patients

before and after a confirmed diagnosis of brain cancer (Grant *et al*., 2020).

Ultimately, there is a multitude of ways to further decrease brain cancer incidence. It is an interdisciplinary challenge that unlocks doors and carves pathways with relevant tools for established experts and early cancer researchers to explore and evaluate further. This will improve the dual practices of research and medicine.

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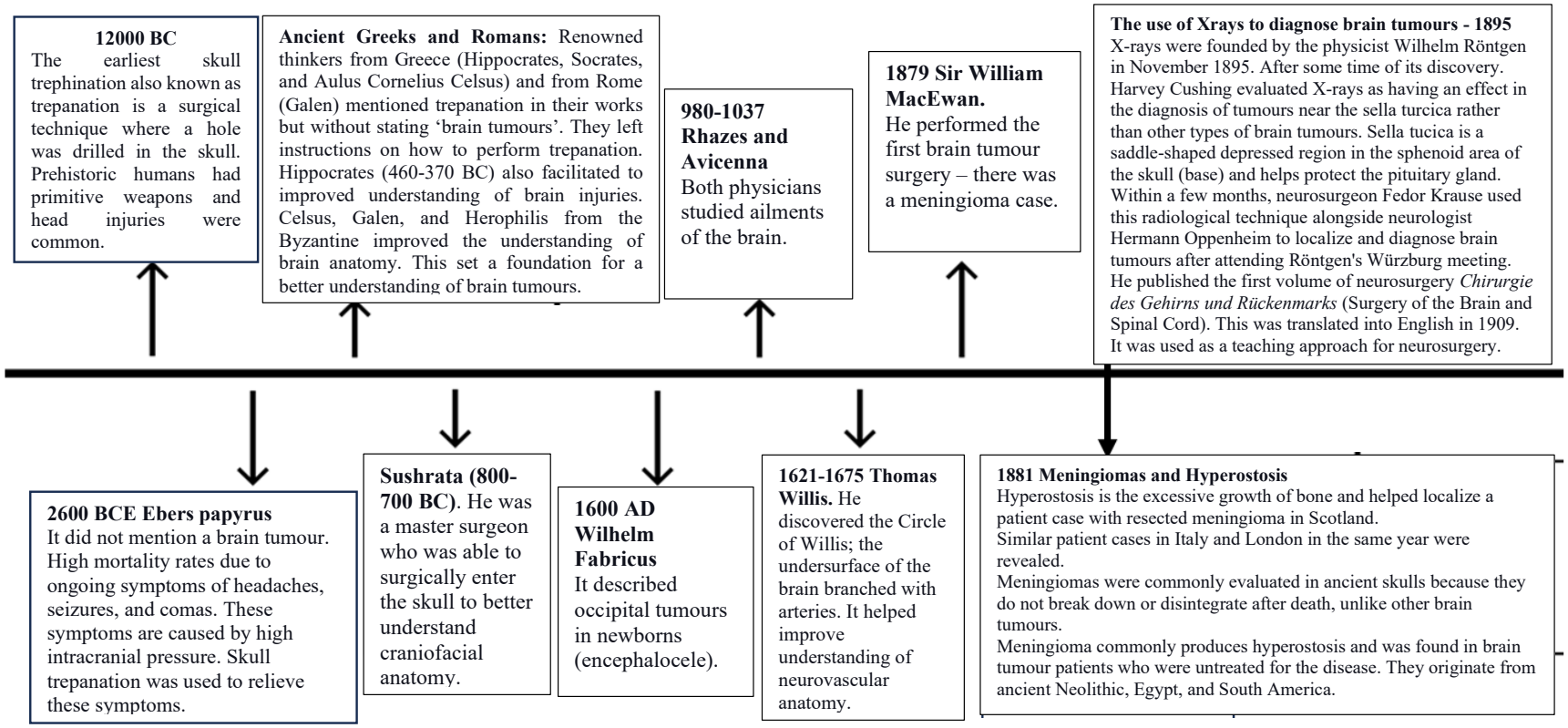
Supplementary Material 1

Some of the groundbreaking events in the detection of brain tumours from Pre-historic times to the 19th Century (1800s)



(Castillo, 2014; Elhadi *et al*., 2012; National Today, 2025; Shreykumar *et al*., 2021)

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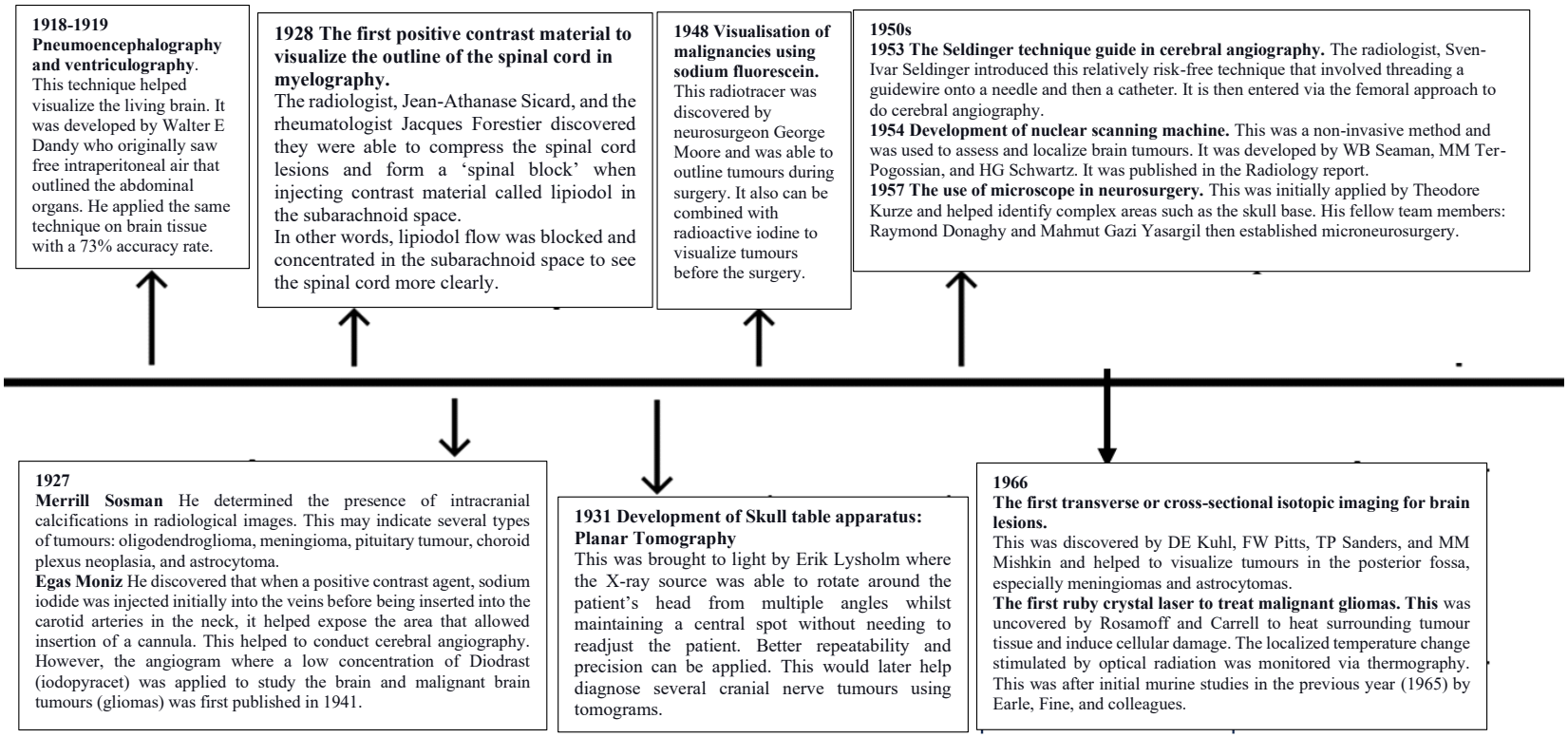
Supplementary Material 2

Some of the groundbreaking events in the detection of brain tumours in the 20th century (1900s)



(Castillo, 2014; Catalyst Medtech, n.d.; Lagman *et al*., 2017; National Today, 2025; Seaman, Ter-Pogossian and Schwartz, 1954; Shreykumar *et al*., 2021)

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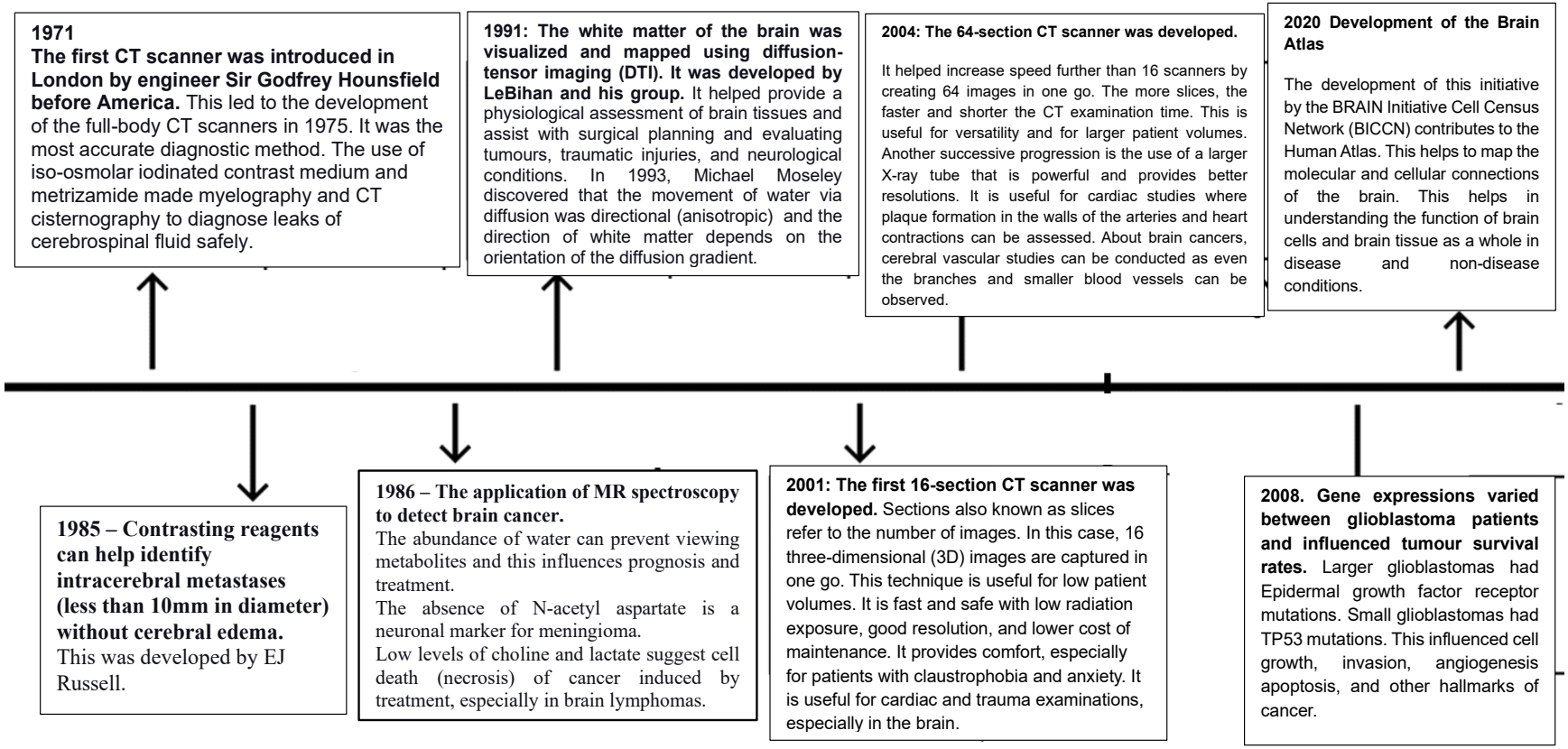
Supplementary Material 3

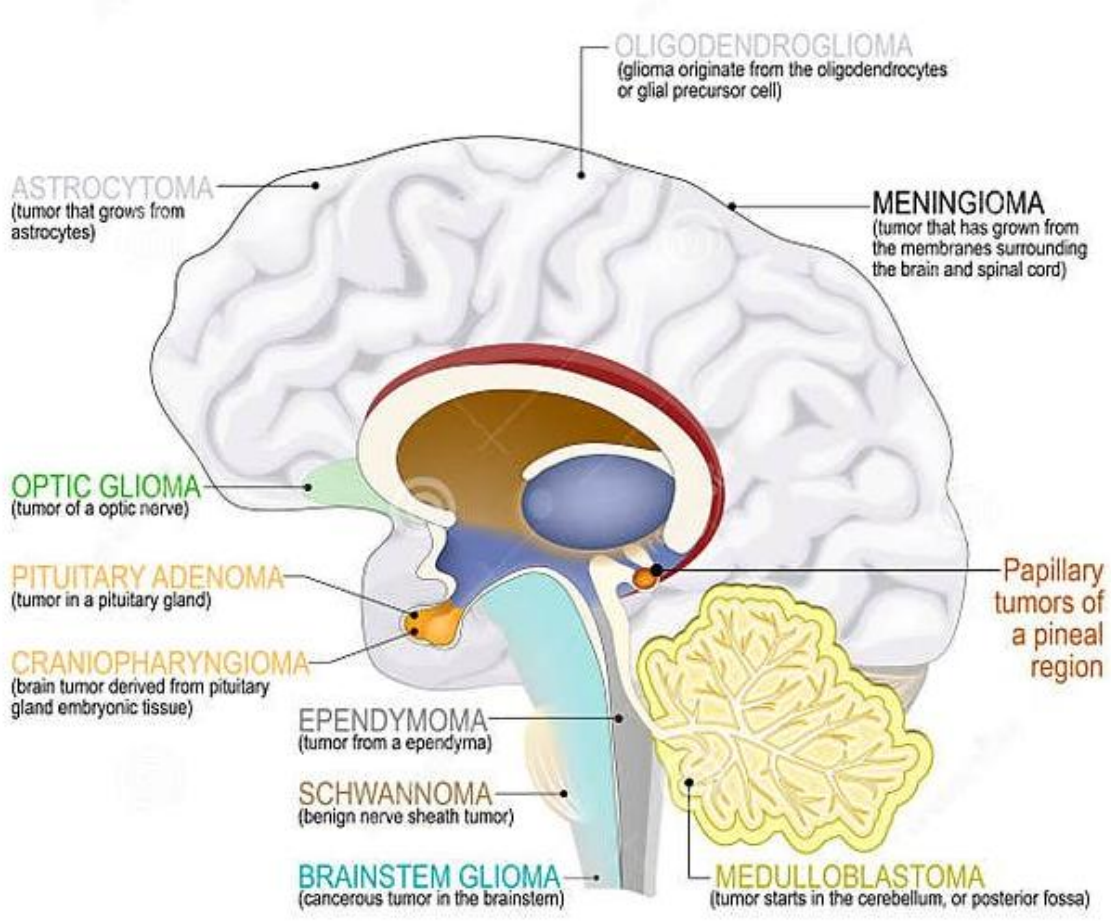
Some of the groundbreaking events in the detection of brain tumours in the 1970s till the 21st century (2000s)



(Castillo, 2014; Human Cell Atlas, 2023; LBN Medical, 2025; Shreykumar *et al*., 2021)

Supplementary Material 4

A schematic diagram of the various forms of primary brain tumours that affects distinctive areas of the brain.



Supplementary Material 5

Take Home Message – Why is this study important?

Neurological tumours are the ninth most common cancer in the UK.

It is the leading cause of death in the UK with estimates of a rising incidence of *ca.* half a million cases annually by 2035 (Crosby *et al*., 2020).

The ongoing changes made over the past four decades in the NHS, governmental policy, and societal awareness of cancer have transformed prospects in the incidence and survival rates of cancer. In this case, brain cancer varies in the type of cancer as presented in the results of this study project.

Revealing the baseline demographics (gender, region, and age) of the study population in the GDO data alongside their clinical characteristics (type of tumour) provides transparent descriptions. It highlights the contributing factors that influence cancer incidence and survival rates of neurological tumours.

The results of this study provide evidence of World Cancer Day's latest initiative on the importance of people-centered care and equity in the healthcare system. This influences patient experience, understanding, clinical outcomes, and heterogeneity of therapeutic modalities.

Investigation into sociodemographic factors within this study assesses the inclusive practice and representation of participants by the National Institute of Health Revitalization Act 1993.

The results from this study bridge biological and non-biological explanations in the notable variability in outcomes and the importance of medical sociology and its associated models in medicine.

Nevertheless, not all sociodemographic factors have been evaluated within the NHS's GDO data particularly ethnicity and socioeconomic status. Research by Wanis *et al.* (2021) noted comparable incidence and survival rates between different races. Nevertheless, the impact of socioeconomic status could be evaluated based on region. Many studies verified the correlation between cancer incidence and regions in England.

Further improvements are needed to detect brain cancer and improve cancer awareness to increase survival rates.

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